and gene expression in plants.* The knowledge generated from investigations of DNA sequences and their functions will be essential to the use of biotechnology in crop improvement, although the initial contributions of biotechnology will not be in crop improvement but in acquiring a better understanding of the basic biology of plants.

It is unlikely that results from laboratory "model" species can be extrapolated to agriculturally important crop plants. Therefore, research is needed for improving and understanding the laboratory culture conditions for cells from these important plants. These plants must be able to be regenerated from single cells on a routine basis before many experiments using novel biological techniques can be performed. Much more work needs to be done before any plant cell vector can be used routinely. Additionally, a continued search for vectors for monocots is necessary if rDNA technology is to have an impact on some of the most important crop species.

It also is important to develop better selection methods. For instance, it is essential to be able to determine rapidly which cells carry specific genes and whether or not those genes are acting appropriately.

Both basic and applied research efforts in improved plant characteristics are quite active. The economic impact of finding disease or environmental resistances in the near term are potentially great enough that this research area is the primary thrust of many of the new plant genetics companies in the United States. Considerable effort continues in universities, as well, although overall funding for the university effort probably is much less than that represented by the current industrial effort. For many desirable traits, the actual protein product of the gene is not known. Cloning and genetic analysis of such genes would greatly increase the knowledge of what kinds of proteins are involved in disease and other resistances. Other improvements in specific plant characteristics may be made by modifying genes in major crop plants or by the introduction of novel traits from other plants. Both approaches warrant investigation.

Plants are known to produce a variety of secondary metabolites that have either pharmaceutical or agricultural uses, yet little is known about the genetic regulation of their production or the development of culture systems for optimal production. Better understanding of these areas could lead to the production of new, improved, or less expensive drugs and compounds that attract or repel insects for controlling weeds and pests.

Goals for improved biological nitrogen fixation include extending nitrogen-fixing bacterial systems to a wider variety of plants, transferring the bacterial nitrogen-fixing genes to plants, and making existing nitrogen-fixing systems more efficient. Genetic studies will reveal how nitrogen-fixing genes are regulated, including how they respond to environmental levels of nitrogen and oxygen.

The extension of any of the nitrogen-fixing sysems depends partly on understanding more about survival and competition of nitrogen-fixing bacteria in field conditions. Temperature extremes, nutrient and pH status of soils, and presence of other micro-organisms are factors that influence colonization of host plants. Reliable, analytical descriptions of the field ecology and physiology of nitrogen-fixing organisms are needed.

Much basic biology of microbial insecticides is yet to be understood. In order to determine the appropriate strategy for their use, it is necessary to study the influence of such factors as sunlight, temperature, rain, and relative humidity on the micro-organisms. Additionally, little is known about the mode and schedule of application and dose required for effective use of micro-organisms in the field. Criteria established by EPA require an analysis of the pathogen's possible effect on human and animal health and the environment.

Even with the lack of biological knowledge currently, it is possible to apply the techniques of biotechnology to the field of microbial insecticides. Approaches include the development of more potent strains, an increase in their tolerance

*These priorities only cover the techniques discussed in this report. It should be noted, though, that genetic advances and applications are dependent on concurrent research in plant biochemistry and physiology.

to environmental stresses, and an extension of their host ranges. The cloning of the *Bacillus* toxin gene, for example, opens up possibilities for the genetic manipulation of this gene to produce a more potent toxin and for the transfer of the gene to other micro-organisms.

The virus AcNPV currently is well enough characterized that its use as a vector is now possible. Some ideas for genetic manipulation include the introduction of insect-specific toxins and broadening the host range of the virus. The use of fungal insecticides requires a better understanding of the physiology, genetics, and pathogenicity of the genes that code for these insecticides. This understanding should lead to the development of strains with increased virulence and greater ease of production in culture (81).

Plants are capable of producing insecticides, yet little is known about their biosynthesis or mode of action. Further research on this topic would allow for more specific, effective, and environmentally sound insecticides.

Because of the complexity of the photosynthetic system, more basic research is needed on the enzymatic processes of photosynthesis and their regulation and compartmentalization. Photosynthesis is used for the production of carbohydrates, and understanding how these compounds are partitioned throughout the plant may allow the ability to direct them into the harvestable parts of the plant.

Finally, knowledge concerning the ecological results of growing plants more densely or of growing plants on marginal land is scant. More research is needed on soil and water use and mineral cycling plants.

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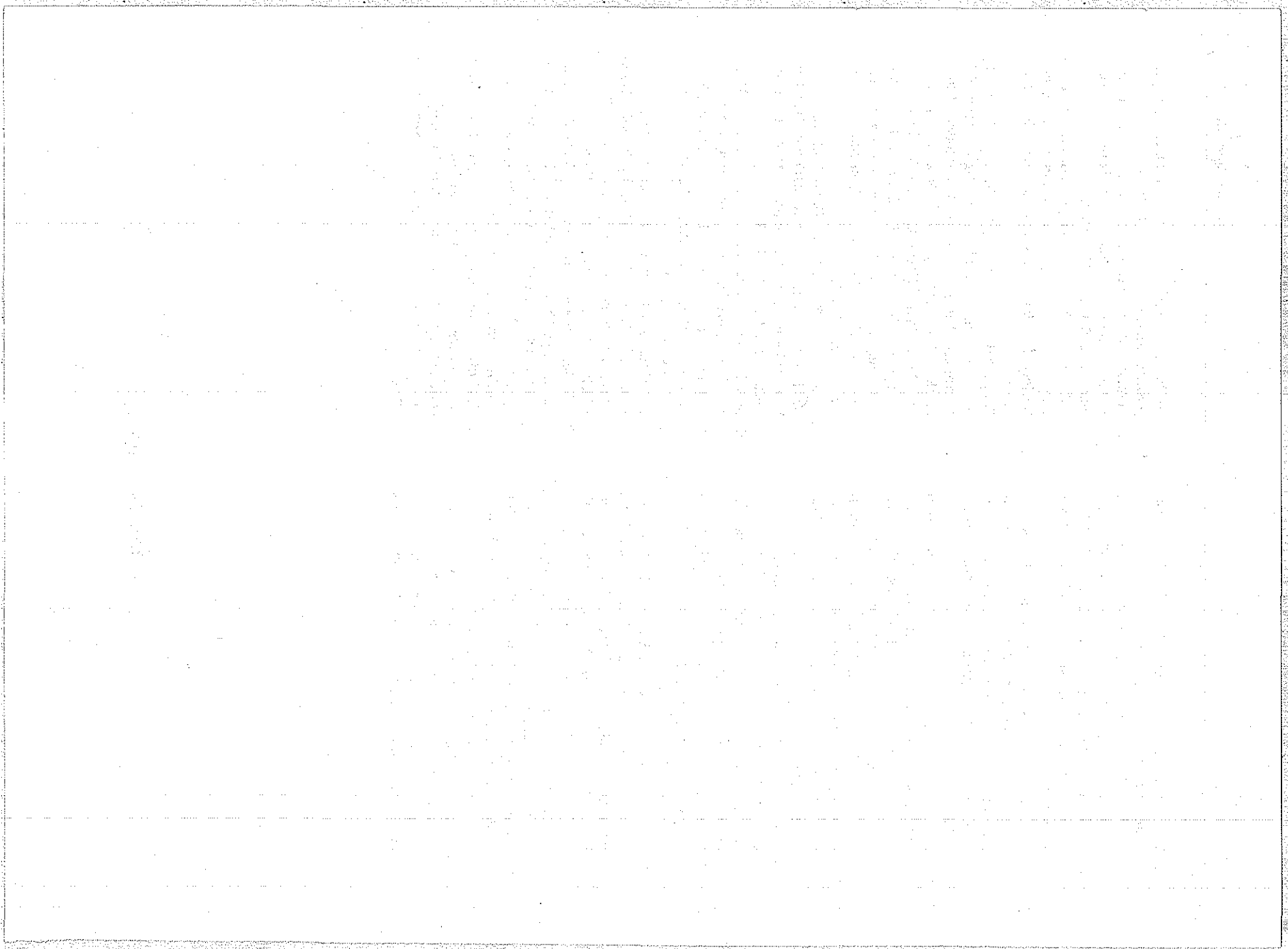


Chapter 7

Specialty Chemicals and Food Additives

Contents

Table

Figures

Chapter 7

Specialty Chemicals and Food Additives

Introduction

In the production of specialty chemicals, defined in this report as chemicals whose price exceeds $1/lb (50¢/kg) in cost, there are many potential applications of biotechnology.* The nearest term applications are in the production of specialty chemicals that are already produced by processes using micro-organisms, e.g., amino acids and enzymes. Enzymes are the direct products of genes, so their production is particularly accessible with new genetic technologies.

A number of specialty chemicals are chemically synthesized. Some, including some vitamins, are synthesized chemically from petrochemicals. Others, including fatty acids and steroids, are synthesized chemically from naturally occurring compounds. Current chemical synthesis production processes often require large energy inputs, have complicated synthesis steps, and yield many byproducts. Potentially, some of the steps in current chemical synthesis processes could be replaced by biological steps catalyzed by enzymes. Enzymes that perform some of the necessary conversions in a very specific manner and with small energy inputs are already known. If appropriate microbial enzymes (or higher organism enzymes) were identified and characterized, the appropriate genetic information could be cloned and expressed fairly rapidly in well-studied micro-organisms to produce or modify compounds such as vitamins, lipids, steroids, and aromatic chemicals. Alternatively, a chemical synthesis production process might be replaced entirely by a biological process if a micro-organism were identified that performed the synthesis. Both individual enzymes and biosynthetic pathways consisting of several enzymes can be manipulated genetically to increase production.

Finally, it should be noted that there are some specialty chemicals synthesized in nature, such as complex polysaccharides, for which chemical synthesis is not feasible. Improving the syntheses of these specialty chemicals in controlled microbial processes is beginning to be investigated.

This chapter discusses the applications of biotechnology to the production of specialty chemicals. It also discusses applications to the production of animal feed and human food additives, because many of the genetic techniques applicable to the production of specialty chemicals also apply to the production of such additives. Since the main difference between specialty chemicals and food additives is in the Food and Drug Administration's (FDA's) regulatory approval process for food and food additives, food additives are discussed here as a subset of specialty chemicals.**

The several kinds of products that could be produced using biotechnology, which are discussed in this chapter, are only representative of the large range of products that could be synthesized using biotechnology. The specialty chemicals and food additives market is extremely broad, and many other applications of biotechnology to the production of such products may be evident in the future.

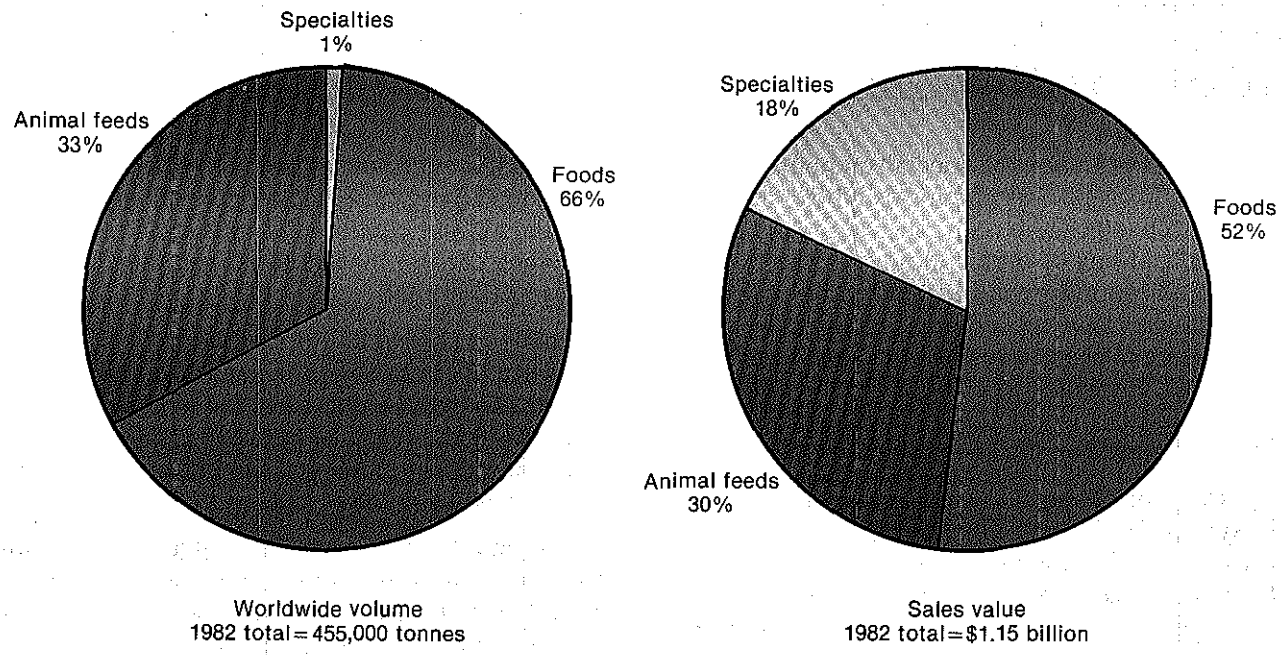
*The application of biotechnology to the production of commodity chemicals, defined in this report as chemicals that sell for less than $1 per pound, is discussed in *Chapter 9: Commodity Chemicals and Energy Production.*

**FDA's regulatory approval processes are discussed in *Chapter 15: Health, Safety, and Environmental Regulation.*

Amino acids

In 1982, the worldwide sales volume of amino acids was 455,000 metric tons (tonnes) valued at $1.15 billion (see fig. 17), and an annual growth rate of 7 to 10 percent is expected during the remainder of this decade. The world markets for amino acids are currently dominated by Japanese

Figure 17.—Uses of Amino Acids



SOURCE: Office of Technology Assessment, adapted from P. L. Layman, "Capacity Jumps for Amino Acids," *Chem. & Eng. News*, Jan. 3, 1983.

producers, the largest of which is Ajinomoto. Amino acid production in the United States, however, is beginning to expand. W. R. Grace is planning to use a new plant in Maryland to produce pharmaceutical-grade amino acids, and two Japanese producers, Ajinomoto and Kyowa Hakko, are opening plants in the United States (47).

Amino acids have traditionally been used as animal feed and human food additives, and their use as animal feed additives may increase as other proteinaceous feedstuffs become more expensive. Recently, there has been increased use of pharmaceutical-grade amino acids for enteral and intravenous feeding solutions. Important constituents of these feeding solutions are the essential amino acids, those that the human body cannot make. Leading U.S. manufacturers of such solutions are Abbott Labs, Baxter Travenol, and American Hospital Supply (30). As shown in figure 17, the specialty market accounts for only 1 percent of world volume of amino acid production, but amounts to 18 percent of the sales value. The production of pharmaceutical-grade amino acids using biotechnology is receiving attention from both U.S. and Japanese companies (28,47).

Glutamic acid

The largest world market for an amino acid is the market for glutamic acid; the sodium salt of glutamic acid, monosodium glutamate (MSG), is used as a food additive. On the order of 300,000 tonnes of glutamic acid are produced annually worldwide (23,25). Approximately 30,000 tonnes are used in the United States, and about one-half of U.S. needs are met through imports at a price of about $2/kg (10).

MSG is produced by an efficient bioprocess using a strain of *Corynebacterium*. This strain was first isolated, on the basis of the microorganism's ability to synthesize and excrete glutamic acid, by the Japanese in the late 1950's. Reports through the Japanese patent literature indicate that Ajinomoto, the world's leading MSG manufacturer, is applying recombinant DNA (rDNA) techniques to *Corynebacterium* strains in an effort to improve glutamic acid production.*

*Strains of *Corynebacterium* are used extensively in Japan for synthesis of several amino acids, but the Japanese bioprocess industry did not do basic research with these bacteria until recently. However, patents and reports in the literature indicate that Japanese amino acid producing firms have begun application of rDNA tech-

Methionine

Another large market for amino acids is in animal feeds (47). Typical corn/soybean animal feeds have low concentrations of the amino acids methionine and lysine, so their nutritive value in animal diets is limited. Methionine and lysine (see below), therefore, are widely used as animal feed additives. Two companies in the United States, Monsanto and the U.S. affiliate of the West German firm Degussa, produce feed-grade methionine using a chemical process (9). Because this process is quite inexpensive, it is not likely that competitive biological routes to methionine production will be developed in the near future.

Lysine

The production of the amino acid lysine is dominated by three Japanese producers, Ajinomoto, Kyowa Hakko, and Toray Industries (11), which together account for 90 percent of the world market. Manufacturers' prices are variable, generally in the range of $3 to $4/kg for feed-grade lysine (43). The United States imports all its lysine (67) and in 1981 imported approximately 11,000 tonnes (68). A plant for lysine production is being built in Cape Girardeau, Mo., by the Japanese manufacturer Kyowa Hakko, and it is projected that the plant's initial production of lysine will be 7,500 tonnes per year (40).

Most lysine is produced in a bioprocess using mutant strains of *Corynebacterium*. A substantial increase in lysine production and a corresponding decrease in cost can be expected to result from applying rDNA techniques to these bacteria (30). In production processes, *Corynebacterium* mutants already yield large amounts of lysine from a crude carbon source such as molasses (45). Amplification of lysine biosynthetic enzymes in these bacteria through gene cloning should result in an increased synthesis rate and amount.

Tryptophan

The amino acid tryptophan is the second limiting essential amino acid in corn and the third limiting essential amino acid in combination feeds for swine and poultry (58). Although tryptophan would seem to be a prime candidate for the animal feed supplement business, marketing analyses have shown that the cost of tryptophan would have to be reduced to the $10/kg range (i.e., about three times the cost of lysine) in order to interest feed formulators in its use (47). The current cost of tryptophan, $95/kg, makes its addition to animal feeds out of the question at this time.

The development of efficient bioprocesses for tryptophan production using either modified *Corynebacterium* or enterobacteria (intestinal bacteria) such as *Escherichia coli* could potentially lower tryptophan costs. The current level of understanding of the *E. coli* aromatic amino acid pathway and sophisticated rDNA techniques that are available should facilitate strain construction in the enterobacteria. As for constructing a tryptophan-producing *Corynebacterium,* basic understanding of the synthetic pathway and development of a vector system remain to be achieved. Manipulating any micro-organism to produce tryptophan efficiently may be difficult, however, because the synthesis of tryptophan requires a greater expenditure of energy than does that of any other amino acid (1). The yield of tryptophan from a given carbon source, therefore, will be lower than the yield for other amino acids. The yield of product from glucose is an important factor in determining production cost in a bioprocess. Information concerning production cost improvements made by the Japanese companies now manufacturing tryptophan is not available.

Progress has been made in developing a two-step enzymatic process for tryptophan production (32). This approach requires three substrates: glycine, formaldehyde, and indole. The high levels of the two enzymes required for this process are obtained by cloning and amplifying each of the genes for these enzymes. This process has not yet been commercialized, but is being investigated by the new biotechnology firm (NBF)* Genex (U.S.). Commercialization requires that the three substrates be priced low enough to meet the target price for tryptophan. Another enzymatic process for the production of tryptophan has been devel-

niques to *Corynebacterium*. Genex and W. R. Grace also have research programs to develop genetic techniques for these bacteria (30).

*NBFs, as defined in *Chapter 4: Firms Commercializing Biotechnology,* are firms that have been started up specifically to capitalize on new biotechnology.

oped by Mitsui Toatsu Chemicals. Commercial production of tryptophan by this Japanese firm was due to begin in January 1983 (7,12).

The relative costs of corn and soybean meal influence the use of these products as animal feed additives. As the price of soybean meal, the main source of protein, and thus amino acids, in poultry and swine feeds rises relative to feed-corn prices, as is expected during the 1980's, there will be a tendency to use less soybean meal in animal diets if less expensive feedstuffs are available. A reduction in lysine production cost and a substantial reduction in tryptophan cost could result in increased incorporation of these amino acids in animal diets as a substitute for proteinaceous soybean meal.

Aspartic acid

Innovative processes for amino acid production that involve immobilization of whole cells or enzymes for bioconversion of precursors to amino acids are being developed (30). In the case of aspartic acid, a constituent of the sugar substitute aspartame, an immobilized process has reduced the costs of production. An early process for aspartic acid production involved the enzyme aspartase in a one-step batch reaction. The life of the catalyst in this process was, at most, a few days. When the enzyme aspartase was immobilized and a continuous-flow process was developed, a 40-percent saving in aspartic acid production cost was realized (14). The life of enzymes in immobilized systems can be increased many fold, up to several months. Cost savings are due to reductions in the amount of catalyst required, in the size of equipment used, and in the labor needed to operate the system.

Phenylalanine

The demand for the amino acids aspartic acid and phenylalanine as components of the sugar substitute aspartame has spurred process development. Aspartic acid is already available at an attractive price, and the research described below will make reasonably priced phenylalanine available soon (30). Phenylalanine, like tryptophan, requires large amounts of energy for the microbial cell to make. However, it should be possible to genetically manipulate enterobacteria or *Corynebacterium* strains to overproduce phenylalanine, thereby making the process economic.

A group of Australian scientists at the University of New South Wales, Kensington, is constructing *E. coli* mutants to overproduce phenylalanine in either a batch or continuous-flow bioprocess (15). No report of the commercialization of their process has been made. Amino acid producers in Japan (Ajinomoto and Kyowa Hakko) may also be applying rDNA techniques to improve phenylalanine production by their *Corynebacterium* strains in order to reduce phenylalanine costs.

A single-step enzymatic process to produce phenylalanine for use in aspartame is being developed in the United States by Genex and in Japan by Tanabe Seiyaku (31,73). In this process, yeast cells that contain the enzyme phenylalanine ammonia lyase (PAL) are utilized. Under the appropriate conditions, PAL will catalyze the formation of phenylalanine from cinnamic acid and ammonia. The economics of the PAL process are very sensitive to the cost of the major raw material, cinnamic acid, which is currently rather expensive. Recovery of phenylalanine from the PAL process, however, will be much more straightforward than recovery from the complex broth that results from a batch bioprocess. High recovery yields in the PAL process may offset the disadvantage of a more expensive raw material.

Enzymes

Enzymes are proteins whose function in living systems is to catalyze the making and breaking of chemical bonds. They have been used commercially since the 1890's, when fungal cell extracts were first added to brewing vats to facilitate the breakdown of starch into sugar. The size of the

world industrial enzyme market for 1981 was estimated to be 65,000 tonnes at a value of $400 million. A growth rate resulting in 75,000 tonnes valued at $600 million has been predicted for the end of 1985. Fewer than 20 enzymes comprise the large majority of this market. Economic sources of enzymes include a limited number of plants and animals and a few species of microorganisms (33).

The enzyme industry is dominated by two European companies, Novo Industri (Denmark) and Gist-Brocades NV (Netherlands), which together have about 65 percent of the current world market (25). Other companies marketing or planning to market large volume enzymes include CPC International (U.S.), ADM (a division of Clinton, U.S.), Miles (U.S.), Pfizer (U.S.), Dawi Kasi (Japan), Alko (Finland), Finnish Sugar (Finland), and Rohm (a division of Henkel, F.R.G.).

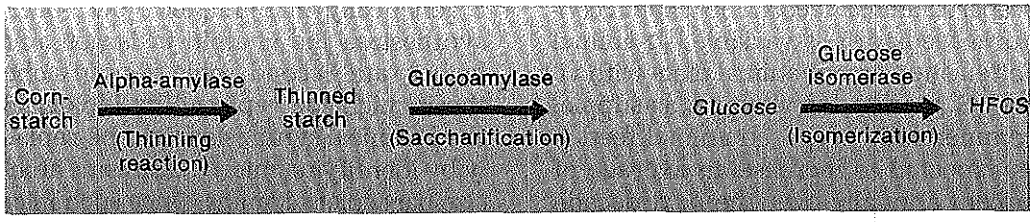
The leading enzymes on the world market in terms of volume are the proteases, amylases, and glucose isomerase (25). Alkaline protease is added to detergents as a cleaning aid and is widely used in Western Europe. Trypsin, another type of protease, is important in the leather industry. Two amylases, alpha-amylase and glucoamylase, and glucose isomerase are corn-processing enzymes. The reactions catalyzed by these three enzymes represent the three steps by which starch is converted into high-fructose corn syrup (see fig. 18). Fructose is sweeter than glucose and can be used in place of table sugar (sucrose) in preparation of candy, bread, carbonated beverages, and in canning. Historically, the United States imported sugar, but with the commercial development of an economic process for converting glucose to fructose in the late 1960's, corn sweeteners have decreased the amount of sugar imported. About $1.3 billion in U.S. payments for sugar imports was saved in 1980 because of the domestic use of corn sweeteners (17).

The process for converting glucose to fructose is catalyzed by the enzyme glucose isomerase. Initially, the conversion was done using a batch reaction; in 1972, however, a continuous system using immobilized glucose isomerase was initiated (36). The immobilized glucose isomerase process represents the largest immobilized enzyme process used in production in the world. A large processing plant can convert 2 million pounds of corn starch into high-fructose corn syrup per day (19).

Because of expanded sales in, for example, the detergent and high-fructose corn syrup markets, demand for enzymes will increase. The application of rDNA techniques to microbial enzyme production is expected to facilitate the expansion of the enzyme industry (25). Additionally, enzymatic activities of higher organisms could be cloned into micro-organisms, also expanding the enzyme industry. The fact that enzymes are direct gene products makes them good candidates for improved production through rDNA technology. For example, a 500-fold increase in the yield of a ligase, used for connecting DNA strands in rDNA research, was obtained by cloning the gene for that enzyme on an *E. coli* plasmid vector (25). Several research enzymes now on the market are produced by micro-organisms modified using rDNA techniques. Some are restriction endonucleases used for cutting DNA, and others are DNA-modifying enzymes. Companies that market these enzymes include Bethesda Research Laboratories (U.S.), New England Biolabs (U.S.), P-L Biochemicals (U.S.), and Boehringer Mannheim (F.R.G.) (30).

Recombinant DNA technology could potentially be used to increase glucose isomerase produc-

Figure 18.—Conversion of Starch Into High Fructose Corn Syrup (HFCS)



SOURCE: Office of Technology Assessment.

tion in micro-organisms and to improve the enzyme's properties. An improved glucose isomerase would have the following properties:

- a lower pH optimum to decrease the browning reaction caused by the alkaline pH now required;
- thermostability so that the reaction temperature can be raised, thus pushing the equilibrium of isomerization to a higher percentage fructose; and
- improved reaction rates to decrease production time.

Improvements in glucose isomerase will first come from the cloning of its gene into vectors and micro-organisms that have been developed for high production. It is also possible that screening a broad range of micro-organisms will yield enzymes with some improved properties. Finally, it will be possible in the future to identify the regions of the enzyme that are responsible for its various properties, such as pH optimum, and to direct changes in the gene structure to modify these properties.

Rennet is an enzyme that is essential to the cheese industry because of its milk-clotting properties. The world market for rennet from various sources is valued at approximately $64 million, over half of which is the more valuable calf rennet (25). The increasing scarcity of calf rennet has made this enzyme a very attractive candidate for gene cloning and subsequent production in a microbial bioprocess. The first announcement of the cloning of the rennet gene came from a Japanese scientist (53). Since then, it also has been cloned by four NBFs: the U.S. firms Genex, Collaborative Research (29), and Genencor (56), and the British firm Celltech (24,35). The first marketing of calf rennet produced by genetically manipulated bacteria is likely to occur in 1984 (30).

Enzymes, such as urokinase and streptokinase, are being used increasingly for treatment of human disorders. Their use and importance are discussed in *Chapter 5: Pharmaceuticals*. Many other enzymes are used for research and medical purposes in small quantities. Because rDNA technology potentially allows the construction of enzymes with improved stability and faster reaction rates, the use of enzymes industrially and medically could increase dramatically.

Vitamins

In 1981, the U.S. Department of Commerce reported that sales of vitamins for human use amounted to $1.1 billion (69). This market is expected to grow substantially over the next decade because of the current trend toward a more health- and nutrition-conscious population. A smaller but significant sector of the human vitamin market is for food processing and fortification.

Another important use of vitamins is in commercially prepared animal feeds. The vitamin content of natural feedstuffs is variable, so animal producers often supplement animal diets with vitamins. The U.S. market for vitamins as supplements in commercially prepared animal feed is large but is expected to increase an average of only 2.5 percent annually over the next decade (26) because of a decrease in the consumption of animal products.

Vitamins are either synthesized chemically or isolated from natural sources, and to date, biotechnology has had essentially no impact on vitamin production. Nevertheless, some opportunities do exist for reducing vitamin production costs using biotechnology. First, the cost of existing bioprocesses for vitamin production, such as that for vitamin B12, might be reduced by using a genetically manipulated micro-organism that synthesizes the vitamin in larger amounts at a higher rate. Second, some steps in a chemical synthesis might be replaced by biological steps, or the chemical synthesis might be replaced entirely by identifying micro-organisms able to synthesize particular vitamins. Once such microbes have

been identified, vitamin synthesis can be enhanced by various biochemical, traditional genetic, and rDNA techniques. Finally, a micro-organism might be identified that produces a vitamin precursor. Such a micro-organism might then be genetically modified so that it would produce the vitamin itself by introducing a gene (or genes) that specifies an enzyme that would convert the precursor to the vitamin.

There are technical problems that introduce risks to research programs for new process developments for vitamins. One major problem is the dearth of information concerning vitamin biosynthetic pathways, especially in micro-organisms. Another problem is that any new biotechnology-based process will have to be very efficient to compete with the established chemical production methods.

Since vitamins are naturally occurring substances, they all have the potential for biotechnological production. The discussion below concentrates on vitamins B2, B12, C, and E to illustrate the range of biosynthetic pathways and potential problems for industrial production.

Vitamin B2

Riboflavin (vitamin B2) is known to be synthesized in small quantities by micro-organisms, but is manufactured primarily by chemical synthesis. The synthesis of riboflavin by the bacterium *Bacillus subtilis* has been studied extensively by a group of Soviet scientists (13), and strains of *B. subtilis* that overproduce and excrete riboflavin have been isolated (22). Because *B. subtilis* has been the subject of extensive studies by U.S. and European scientists, techniques such as DNA transformation, protoplast fusion, and gene cloning have been developed for this bacterium (21). The availability of such techniques should facilitate the construction of a strain of *B. subtilis* for the production of riboflavin.

Vitamin B12

Vitamin B12 is currently produced by a microbial bioprocess (27). The U.S. market for vitamin B12 is supplied both by U.S. and European firms. One U.S. company (Merck) supplies the major part of the feed-grade vitamin B12 market, while imports from Europe account for the major portion of the pharmaceutical grade (30). The current manufacturers' price for vitamin B12 is approximately $8,000/kg for pure material (9).*

Reducing the cost of vitamin B12 production will require genetic modifications of bacterial strains so that the micro-organisms synthesize vitamin B12 more efficiently. Vitamin B12 is one of the most complex molecules of living systems, however, and its biosynthetic pathway has not been definitively characterized.

Vitamin C

The U.S. market for vitamin C is very large, 17,500 tonnes in 1982 (30). Approximately two-thirds of this volume is supplied by U.S. producers, while the remaining third is imported. The current price of vitamin C is approximately $12/kg (9).

Although some of the synthesis of vitamin C is done microbially, efforts to replace other steps with bioconversions have not been successful (18). The synthesis of vitamin C has been reported in a few micro-organisms (50). The first step in developing a vitamin C bioprocess, therefore, will be screening for a potential production organism. Analysis of the biosynthetic pathway must be done, because little is known about microbial pathways for vitamin C synthesis. Once the rate-limiting steps of the pathway have been identified, rDNA techniques could possibly be used to increase production. A complicating factor in a vitamin C bioprocess is the fact that this vitamin, in solution, is readily oxidized when exposed to air. Controlling dissolved oxygen and complexing vitamin C with other compounds are two potential techniques for controlling the rate of vitamin breakdown during production. The wealth of unknowns makes it impossible at this time to predict a time frame for developing an improved vitamin C production process.

*The prices in this reference are for small volumes. The purchase of large quantities of these chemicals can result in a substantial price reduction.

Vitamin E

If an approach to natural vitamin E production using biotechnology could be developed, its impact would be quite significant. In 1979, approximately 3,200 tonnes of vitamin E were used in the United States (39). Of this amount, 700 tonnes were the natural form of vitamin E. The remaining 2,500 tonnes were synthetic forms. Synthetic vitamin E is a mixture of closely related compounds that vary in biological activity, whereas the natural vitamin preparation consists of only the most active compound. Demand for vitamin E as an antioxidant could increase the market for this vitamin by as much as 1,500 tonnes per year, depending on FDA's decisions concerning continued use of chemical antioxidants. The U.S. demand for natural vitamin E is met by two U.S. manufacturers, Eastman Chemicals and Henkel, and 95 percent of synthetic vitamin E is produced in the United States (30). The May 1983 price of the synthetic vitamin mixture was $27/kg (9). The price of the natural vitamin was several times that amount, depending on the activity of the preparation.

Natural vitamin E is now purified from vegetable oil by a process that involves several steps. If a one-step fermentation process could be developed based on a high-producing microbial strain, the manufacturing cost of natural vitamin E might be lowered substantially.

Blue-green algae are the only well-characterized micro-organisms that are known to produce vitamin E (20,55). It might be possible to increase vitamin E synthesis by altering the biosynthetic pathway in blue-green algae, but the biochemistry and physiology of this pathway is poorly understood, and gene cloning in these micro-organisms is at a rudimentary stage of development.

The discovery in bacteria, such as *E. coli, B. subtilis,* and *Pseudomonas,* of a compound that is potentially a vitamin E precursor suggests another route for vitamin E production (37). These bacteria are well-characterized species for which genetic transfer techniques are developed. Construction of a vitamin E-producing strain first would involve isolating mutants that overproduce the precursor. Then the genes for the enzyme that catalyzes the conversion of the precursor to vitamin E could be isolated from blue-green algae and introduced into the potential production strain. Although the savings in production cost of vitamin E could be great, this project involves a substantial amount of risk related to the lack of information concerning the biosynthesis of this vitamin. For example, it is not known if only one enzyme is needed for the conversion of precursor to vitamin, how complex such an enzyme is, how many genes encode it, and what cofactor requirements it might have.

Summary

Biotechnological techniques for improving the efficiency of vitamin production are similar to those being used in amino acid process development. The research and development (R&D) effort for vitamins will be more extensive than that for the amino acids, because vitamin biosynthetic pathways are more complex and less understood. In some instances, screening programs to identify micro-organisms with potential for producing a particular vitamin may be required. Furthermore, for some micro-organisms that have good potential for vitamin production, it will be necessary to develop techniques of genetic manipulation. In summary, the impact of biotechnology on vitamin production will be more long range than its impact on the production of either amino acids or enzymes.

Single-cell protein

The term "single-cell protein" (SCP) refers to cells, or protein extracts, of micro-organisms grown in large quantities for use as human or animal protein supplements. Although SCP has a high protein content, it also contains fats, carbohydrates, nucleic acids, vitamins, and minerals. Interest in SCP production is not new, as evidenced by the fact that Dutch, German, and Brit-

ish patents for SCP production were issued as early as 1920 (51). Interest in SCP has waxed and waned throughout the ensuing years, but SCP production has never achieved great significance, mostly because of economic considerations (49,64). With the advent of new biotechnology and the threat of potential world food shortages, interest in SCP may once again return (49).

SCP can be used as a protein supplement for both humans and animals. In animal feed, it is a replacement for more traditional supplements, such as soybean meal and fishmeal. For humans, SCP is used either as a protein supplement or as a food additive to improve product functionality, for example, flavor, whipping action, or fat binding (49). The use of SCP in human food presents a problem: humans have a limited capacity to degrade nucleic acids. Therefore, additional processing is necessary before SCP can be used in human food. The animal feed market is more attractive for SCP, not only because there is less processing of the product, but also because the regulatory approval process is less stringent.

Relative protein content of the various commercial sources of concentrated protein is shown in table 38. Nutritionally, the amino acid composition of SCP resembles meat, fish, and shrimp meal rather than vegetable protein. It has been shown through extensive testing both in the United States and abroad to be a suitable substitute for at least part of the former high-cost protein sources. The high protein content, good storage properties in dry form, texture, and bland odor and taste of SCP suggest real potential in feed and food markets. In prepared aquaculture feeds where, for juvenile animals, protein content up to 50 percent and above is required, SCP appears to be an attractive product. Another application is as a calf, lamb, or kid starter, thus leaving more milk for human consumption.

Table 38.—Typical 1982 Selling Prices of Selected Microbial, Plant, and Animal Protein Products

Product	Protein content (%)	1982 selling price ($/kg)
Food-grade products:		
Candida utilis (tortula yeast)	50 to 55	$1.87 to $2.24
Kluyveromyces fragilis	45 to 50	2.09 to 2.29
Soy protein concentrate	72	0.88 to 1.03
Soy protein isolate	92	2.59 to 2.68
Dried skim milk	37	1.16 to 1.21
Feed-grade products:		
Saccharomyces cerevisiae	45 to 50	$0.48 to $0.66
Soybean meal	44	0.19 to 0.20
Meat and bonemeal	50	0.19 to 0.21
Fishmeal	65	0.23 to 0.40

SOURCE: J. H. Litchfield, "Single-Cell Proteins," *Science* 219:740-746, 1983.

Incentives for production of SCP are fourfold. First, some parts of the world, for example, the high rainfall, tropical areas, have agricultural feed and food products high in carbohydrates; in such places, there is a chronic shortage of protein, which results in deteriorated physical and mental health. SCP would raise the protein content of food. Second, the land in other regions, including the Middle East and Africa south of the Sahara, cannot produce sufficient food of any type to prevent hunger. Here also an SCP supplement would be an asset. Third, there is demand worldwide for very high protein ingredients for feeds in the aquaculture industry, i.e., in the production of shrimp, prawns, trout, salmon, and other finfish and shellfish. Finally, SCP does not rely on temperature, rainfall, or sun for survival. At least one of the variety of feedstocks is usually available in almost any country or region of the world. The security of having such an internal source of protein is attractive to many countries.

Economically feasible SCP production is dependent on the efficient use of an inexpensive feedstock by a micro-organism. A large variety of feedstocks have been used for SCP production over the years, including carbon dioxide, methane, methanol, ethanol, sugars, petroleum hydrocarbons, and industrial and agricultural wastes. These feedstocks have been used industrially with different micro-organisms, including algae, actinomycetes, bacteria, yeasts, molds, and higher fungi. The choice of a feedstock includes such considerations as cost, availability, efficient growth of the micro-organism, and requirements for pretreatment (49).

SCP has yet to become an important source of protein, mainly because of high production costs. Some SCP-production processes that were economical at one time have not remained so because of changes in prices of competitive sources of protein such as soybean meal or fishmeal. In comparison to SCP, these protein sources are quite

inexpensive (see table 38). In fact, the price of most SCP processes would have to be decreased one-half to one-fifth for SCP to be competitive with soybean meal and fishmeal.

Through the years, the high cost of SCP relative to that of these other sources of concentrated protein has prevented extensive utilization of SCP, primarily in animal feeds. In the case of SCP produced from methanol, for example, the methanol represents approximately 50 percent of the cost of the product. In the United States, the cost of SCP made from methanol exceeds the average cost of fishmeal by a factor of 2 to 5. A plant in the United Kingdom (ICI) is operating at a loss because of such a situation (49,52). In some parts of the world, such as the Middle East, low-cost methanol and high shipping costs for fishmeal and other natural protein sources make the cost differential considerably less. In countries without methanol, biomass presents an option as a cheap feedstock source. However, this market has not been developed yet.

It is possible that the application of biotechnology will help to reduce the cost of production of SCP. Strains of micro-organisms could be improved using rDNA techniques. Improvements could include increasing the production of proteins with a better amino acid balance* or improving the ability of the micro-organism to utilize the feedstock efficiently. Technological improvements in the process and recovery steps would also be important. The use of automated, continuous processes could improve the efficiency of production. Recovery steps could be aided by using micro-organisms that have been genetically manipulated to excrete protein. Additionally, it is possible that an enzyme that degrades cell walls could be cloned and produced in large amounts. Its use would help in the production of a protein concentrate from cells. New technologies will probably improve the production of SCP, but widespread introduction of SCP will be governed by economic and regulatory factors.

Several companies in Western and Eastern Europe, the United States, and Japan have built SCP production plants in the last 15 years (3,5,64). Many of these are no longer operating because of high production costs and regulatory approval problems. Nevertheless, there are several companies operating plants, including Shell Chemicals (Netherlands), British Petroleum (U.K.), ICI (U.K.), Rank Hovis MacDougall (U.K.), Sosa Texaco (Mexico), Finnish Pulp and Paper Institute (Finland), Amoco (U.S.), Phillips Petroleum (U.S.), Pure Culture Products (U.S.), Rhinelander Paper Corp. (U.S.), and Amber Laboratories (U.S.). In addition, there is one plant in the German Democratic Republic, and there are several in the U.S.S.R.

The center of SCP technology is in England, especially at ICI (71). The ICI process uses aerobic bacteria with methanol and ammonia as feedstocks. The bacteria are grown in the world's largest continuous bioprocess system with computerized control and monitoring of performance. The product, Pruteen®, contains 80 percent crude protein as well as a high content of essential micronutrients, especially B group vitamins. Pruteen® is used in animal feed diets (poultry, swine, fish) and as a milk replacer (calves). In 1981, ICI had scaled up its process to produce 3,000 tons of SCP per month. It is beginning research using rDNA technology to facilitate protein harvesting (49). So far, however, the production of Pruteen® has not been economic even though it is twice as nutritious as soybean meal (52).

Two of the SCP plants in the United States (Amber and Rhinelander) use wastes produced in other parts of their plants for feedstocks, assuring a constant and inexpensive source of raw materials for SCP production (49). This type of small-scale operation using internally generated wastes as feedstocks may be the most appropriate use of SCP technology in the United States and other countries where animal- and plant-derived protein sources are abundant.

The U.S.S.R. is actively pursuing the production of SCP. The Soviets consider the construction of plants to produce SCP a high priority in order to decrease their dependency on foreign sources of protein for animal feed (5). The U.S.S.R. produces about 1 million tons of SCP per year, but production has not increased since 1976 (62). About half of the Soviets' SCP feedstock is cellulose, and the balance is petroleum. The current Five-Year Plan

*As do proteins from plants, proteins from micro-organisms often lack one or more essential amino acids. Most commercial SCP products are low in methionine (51).

calls for doubling SCP production by 1985 to 2 million tons per year, but the Soviets will have to produce a total of 3 million tons per year in order to be able to stop importing soybeans for use as a protein source.

Low-cost or waste biomass feedstocks have been cited as one means to product cost reduction. Inedible biomass can serve as an indirect feedstock for SCP processes by high-temperature conversion to synthesis gas and then to methanol (2).

Engineering improvements expected include bioreactor designs for continuous operation and high cell density. High cell densities decrease cost, because at high cell densities, the cell suspension leaving the fermentor can be dried without preconcentration of the cells by centrifugation, and because extracellular nutrients are recovered in the product.

Conventional genetic and rDNA methods for SCP production are currently being directed toward the following goals: 1) broadening the range of utilizable feedstocks; 2) increasing the optimum bioprocessing temperature and achieving a concomitant decrease in cooling requirements; 3) increasing the efficiency of utilization of the feedstock with the associated benefit of decreased generation of heat; 4) optimizing the balance of the essential amino acids in the product; and 5) producing of high-value products in conjunction with the SCP (e.g., growth stimulators) which may be either left in the SCP product or isolated from the broth.

The future of SCP depends largely on reduction in cost and improvement in quality. Means to meet these requirements involve lower cost feedstocks, improved engineering of the conversion and recovery processes, and upgrading the yield and quality of the product through conventional genetic and rDNA methods. The renewed interest in all of biotechnology, in part due to rDNA technology, is leading to increased effort in developing economically competitive SCP with improved qualities.

Complex lipids

Lipids are water-insoluble compounds found in cells whose many functions include serving as the structural components of membranes and storing of metabolic fuel. The term lipid designates a general class of compounds that includes the complex lipids (saponifiable lipids) which contain fatty acid components and simple lipids (nonsaponifiable lipids) which have no fatty acid component. The simple lipids include some vitamins, steroid hormones, and other highly specialized fat-soluble biomolecules.

Complex lipids are readily available and are extracted from natural sources. Some lipids such as sophorolipids have commercial uses. By far the most valuable attributes of lipids, however, are the products that can be derived from them, including fatty acids and fatty alcohols and the potential of lipids to replace petroleum feedstocks (48). Biotechnology could be used to develop new methods for economical production of lipid-derived products.

Fatty acids

Fatty acids are important industrial chemicals used in cosmetics, plastics, lubricating greases, rubber compounding, polymer emulsifiers, specialty household cleaners, foods, paints, varnishes, and flotation reagents (46). In the United States alone, the present consumption of fatty acids is about 1.65 billion pounds annually (46). The major sources of fatty acids are the naturally occurring fats and oils of plants and animals. The major plant sources of fatty acids in the United States are tall oils and coconut oil, and the major animal source is tallow (46). Synthesizing fatty acids from petroleum feedstocks is possible, but the process requires complex reactions and is more expensive than obtaining the acids from natural sources.

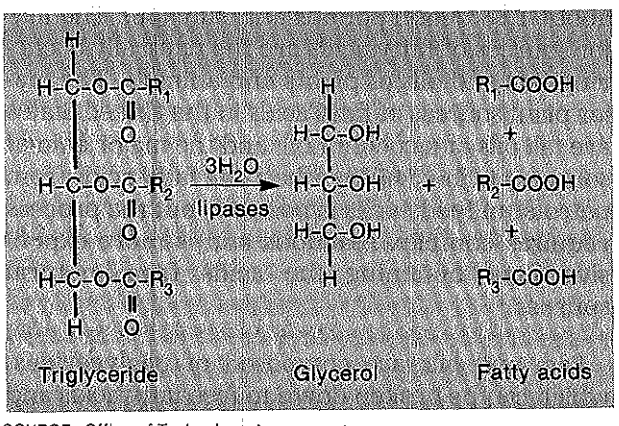
Fats and oils are composed of triglycerides, which can be broken down to free fatty acids and glycerol, a valuable coproduct. The usual decom-

position method is a chemical process whereby the triglycerides are continuously hydrolyzed (16). This chemical process is efficient; 99 percent of the available triglycerides are hydrolyzed to free fatty acids and glycerol. Because the process requires both high temperatures and high pressure, however, it is also energy-intensive.

An attractive alternative to chemical hydrolysis of triglycerides is an enzymatic process that uses lipases to split the triglycerides into free fatty acids and glycerol (see fig. 19). Such a process does not require severe reaction conditions and is therefore more energy-efficient. Two Japanese companies have begun to commercialize the production of fatty acids from natural oils and fats using lipases. Miyoshi Oil and Fat Co. has reportedly constructed two plants for the lipase-catalyzed production of fatty acids. Its initial plant reportedly is producing 300 tons of fatty acids annually. Similarily, the Nippon Oil and Fat Co. has begun trial operation of a pilot plant at its Amagaski facility. It plans to produce initially about 1,000 tons of fatty acids per month. These Japanese companies report that the lipase-based production of fatty acids is both energy- and labor-efficient (38,39).

Because of their stability and lack of cofactor requirements, lipases are good candidates for use in an immobilized enzyme process. At the present time, however, the apparent requirement of lipases for an emulsified substrate represents a barrier to an immobilized enzyme process. Research on both process design and the identification of lipases that are more amenable to immobilization should result in the development of an immobilized enzyme process for the production of fatty acids. Such process development might take several years.

Figure 19.—Hydrolysis of Triglycerides



SOURCE: Office of Technology Assessment.

The cost of obtaining sufficient quantities of lipase will have a major impact on the economic viability of such processes. The application of biotechnology to develop or improve techniques for the recovery and reuse of lipases would be desirable. Supplies of specific lipases could be increased through gene cloning and amplification.

Fatty alcohols

Fatty alcohols are important industrial chemicals. The plasticizer ester industry uses large quantities of shorter chain (6 to 10 carbons) alcohols, while alcohols of longer length (11 to 18 carbons) are used to make detergents. Fatty alcohols can be synthesized chemically from ethylene, which is derived from petroleum feedstocks. Alternatively, some Japanese companies use a chemical process to convert fatty acids obtained from coconut oil into fatty alcohols (30). Although the Japanese chemical process does not rely on nonrenewable petroleum feedstocks, it does require extreme reaction conditions and therefore high energy consumption. A number of micro-organisms are capable of converting fatty acids to fatty alcohols, but these biological conversions are also energy consumptive. Furthermore, both the substrate and product are toxic to micro-organisms. Hence, the development of a biological process would require, at best, a number of years of R&D effort.

Microbial oils

Although naturally occurring fats and oils can currently be obtained cheaply from plants and animals, there is a resurgence of interest in exploiting micro-organisms for the production of oil. Israel, for example, is actively pursuing the development of a microbial source for oil (57) to reduce its dependence on imports. A number of eukaryotic oil-producing micro-organisms have already been identified, and preliminary research in developing micro-organisms as a source of oil is underway. It is impossible to predict when such

processes will be commercial. The United States has sufficient plant and animal sources for fats and oils, but the supply is affected by climate. European countries, unless they develop a microbial source, will have to rely on imported materials to satisfy demands for vegetable oils and fats (57).

Sophorolipids

There is increasing interest in identifying and exploiting microbial biosurfactants (biologically derived emulsifying agents). One group of glycolipids, the sophorolipids, shows considerable promise for use as biosurfactants. Sophorolipids can be produced from vegetable oils by the yeast *Torulopsis*. These sophorolipids are comparable in activity to other surfactants, but are produced by the yeast in much higher yield and are easily separated from reaction broths, thus minimizing costs. Further characterization of the sophorolipids and their potential markets is required before applications of biotechnology to their production are likely to be considered.

Steroids

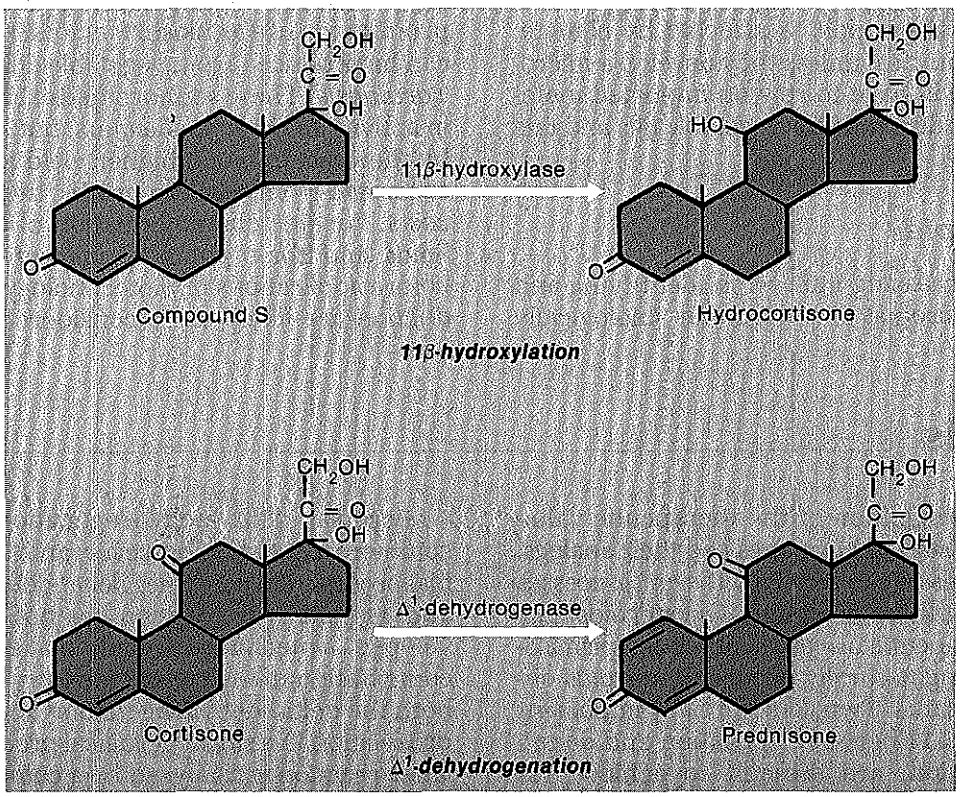
With the recognition of the therapeutic value of the natural steroid hormones and their analogs, it became necessary to develop efficient processes for producing these products. The steroids currently in therapeutic use are synthesized primarily by modifying naturally occurring steroids obtained from plants. Two commercially important modifications, 11-beta-hydroxylation and delta^1-dehydrogenation, are difficult to achieve via chemical routes, but micro-organisms have been reported to perform both reactions. Examples of a microbial 11-beta-hydroxylation and a delta^1-dehydrogenation are shown in figure 20.

Microbial reactions have been identified for the hydroxylation of virtually every position of the steroid nucleus. Because whole-cell bioconversions for introducing the 11-beta-hydroxyl group occur at low levels and are plagued by the formation of byproducts, they have not been developed for commercial use. Further study of the enzymatic process should establish whether the byproducts are the result of many steroid-metabolizing enzymes or a lack of specificity of the 11-beta-hydroxylating enzyme. If the enzyme is specific, it may be possible to obtain the desired conversion levels by cloning and expressing at high levels the genes that encode the 11-beta-hydroxylase.

Microbial delta^1-dehydrogenations are used commercially today. However, an efficient microbial process that combines delta^1-dehydrogenation and 11-beta-hydroxylation has not yet been developed. Biotechnology could make a significant contribution to the steroid industry by achieving both the delta^1-dehydrogenation and 11-beta-hydroxylation in a single biological process step. The latter reaction is catalyzed by a complex enzyme, so it is unlikely that an immobilized enzyme system could be developed for it. Therefore, the most efficient process would be to have the two reactions carried out by one cell.

The steroid market is readily accessible to biotechnology. Microbial processes are used routinely in the manufacture of steroid products. Furthermore, bioconversions with potential value to the steroid industry have been identified, and rDNA technology could be used to construct a micro-organism that more efficiently converts the steroid substrate to the desired product. The primary barriers to further biotechnological applications in the manufacture of steroids are the lack of rDNA host/vector systems for some of the micro-organisms involved and a lack of understanding of the specific enzymatic processes of steroid synthesis.

Figure 20.—Microbial Modifications of Steroid Molecules



SOURCE: Genex Corp., "Impact of Biotechnology on the Specialty Chemicals Industry," contract paper prepared for the Office of Technology Assessment, U.S. Congress, April 1983.

Aromatic specialty chemicals

Aromatic compounds occur in many household products, medicines, agricultural products, pesticides, paints, cosmetics, and dyes, and their synthesis is a major component of the specialty chemical industry (6). Aromatic compounds that contain a hydroxyl group on the aromatic ring are an important group of specialty chemicals. Examples are the parabens and their esters, which are used as preservatives; 2,4-dichlorophenoxyacetic acid (2,4-D), which is the most extensively used herbicide; and N-acetylated para-aminophenol, an aspirin substitute. The synthesis of each of these compounds requires the specific hydroxylation of the aromatic ring.

The chemical hydroxylation of the aromatic ring is generally an inherently expensive step in the synthesis of an aromatic specialty chemical. This expense often results from the nonspecificity of the hydroxylation reaction, which forms unwanted byproducts and is therefore an inefficient use of the starting material. Additional processing may be required in order to remove the byproducts and to dispose of them properly. Chemical hydroxylations also require severe reaction conditions and therefore consume a large amount of energy. In addition, chemical reactions can result in the formation of undesirable contaminants. One highly publicized case is the dioxin

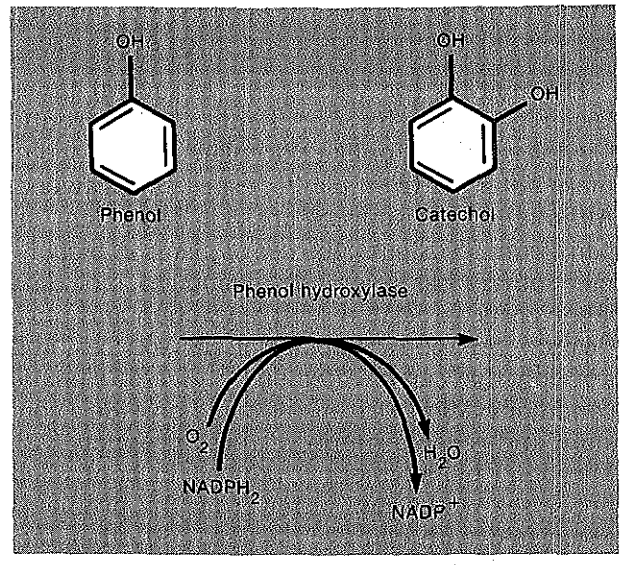
contamination that occurs during the chemical synthesis of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), an herbicide and a component of the now banned Agent Orange.

By replacing a chemical reaction with a biological process, biotechnology has the potential to decrease the manufacturing cost of aromatic specialty chemicals, especially in processes that involve aromatic hydroxylations. Many micro-organisms are able to grow on aromatic compounds, and aromatic hydroxylations are key reactions in these growth pathways. These enzymatic reactions occur under mild conditions and result in specific hydroxylations of the aromatic ring. Furthermore, using enzymatic reactions, hydroxylations can be obtained at positions not readily hydroxylated by chemical reactions. The development of bioprocesses for aromatic hydroxylation reactions represents a valuable biotechnological opportunity for the specialty chemical industry.

Microbial aromatic hydroxylations are mediated principally by oxygenases that catalyze the direct incorporation of molecular oxygen into the aromatic ring (6,54,65,66). An example of an aromatic hydroxylation mediated by a microbial oxygenase is shown in figure 21. Many oxygenases have been studied in detail; while differences do exist among the various types of oxygenases, oxygenases generally are complex enzyme systems that require cofactors for activity.

As found in nature, the conversion efficiencies of most aromatic hydroxylations are generally too low to be commercially viable (30). However, the conversion efficiency could be improved by cloning the gene(s) encoding the oxygenase and expressing the cloned gene at high levels in an appropriate production strain. Once the oxygenase gene(s) have been cloned and expressed in an appropriate production strain, more research time and effort will be required for process development. One major consideration is how to minimize the toxic effects of the aromatic compounds on micro-organisms. One solution would be to develop an immobilized enzyme process; however, because of the complexity of the hydroxylation reaction it may not be possible to apply this technology. Toxic effects in bioprocesses have been minimized by innovative process design, and it is anticipated that there will continue to be significant advances in this area of research. Another consideration in developing an effective process is that the substrates and products are not soluble in water. Again, innovative process design could minimize this problem.

Figure 21.—An Example of a Microbial Aromatic Hydroxylation



SOURCE: Office of Technology Assessment.

Polysaccharide biopolymers

Biopolymers are naturally occurring macromolecules that include proteins, nucleic acids, and polysaccharides. The discussion here will emphasize the polysaccharide biopolymers and the opportunities for the application of biotechnology to their synthesis.

The major commercially available water-soluble biopolymers are used as viscosifiers (thickening agents), flocculating agents (aggregating agents), and lubricants. Currently, there is a trend toward increased use of synthetic polymers as flocculating agents in place of natural products (70). This

trend, however, is sensitive to the availability and cost of the petroleum feedstocks required for manufacturing synthetic polymers, and biopolymers will be important if the price of oil rises.

The market for viscosifiers is several times larger than that for flocculants. The currently used viscosifiers, unlike flocculants, are biopolymers obtained from plants, especially seaweed. Although these sources are not dependent on petroleum feedstocks, the use of plants as biopolymer sources has several disadvantages, including labor costs associated with extraction and purification, limited availability of the sources, and a supply that can be affected by adverse climatic conditions. Micro-organisms could provide a constant and reliable supply of these products (72). Microbial biopolymers produced in controlled processes would not suffer from the problems associated with climate, disease, and other factors that normally affect plant products. Furthermore, microbial biopolymers have relatively uniform chemical and physical properties.

These attributes have led to increasing interest in the production of biopolymers that could be used in novel applications as well as in place of commercial biopolymers that are not now microbially produced. For example, alginate is a commercially important gum obtained from kelp. The markets for alginates demand different specific characteristics such as solution viscosities and gelling qualities. The alginates obtained from kelp can vary in composition, so they must be separated, evaluated, and categorized for the different markets. Alginate is also synthesized by *Azotobacter vinelandii* (41). Because the composition of the microbial alginate can be closely controlled by bioprocessing conditions, separate microbial bioprocesses could be developed to produce specific alginates with uniform chemical and physical properties. Another microbial biopolymer that has been developed by the Kelco Co. and has recently become commercially available is gellan. Gellan is a *Pseudomonas* polysaccharide that can be used as a solidifying agent for laboratory media or food products (44).

While a number of microbial biopolymers are being developed for commercial applications as gums, plastics, and other products, only xanthan gum, dextran, polytran, and gellan are currently being produced commercially (44,72). In terms of production volume, xanthan gum is the major microbial polysaccharide. At present, over 20,000 tons of xanthan gum are manufactured in the United States annually (30). Xanthan gum's primary use is as a food additive for stabilizing liquid suspensions and for gelling soft foods, such as ice creams and cheese spreads. More recently, it has been used in the new clear-gel toothpastes. The use of xanthan gum in enhanced oil recovery is still experimental, but this appears to be the largest potential market for this product.* Xanthan gum is commercially produced in an aerobic batch bioprocess using the bacterium *Xanthomonas campestris* (30).

The importance of polysaccharide biopolymers is likely to grow. For example, the microbial polysaccharide pullulan is synthesized by *Aureobasidium pullulans* from a number of substrates (42). Pullulan has potential applications in the cosmetic industry, in diet foods, and, more importantly, as a biodegradable plastic to be used in place of wraps and plastic containers. Plastic wraps and containers are now made from petroleum-based plastics which are not biodegradable and are dependent on nonrenewable feedstocks. The Japanese are already at the pilot plant stage for the microbial production of pullulan, and pullulan has the potential to develop into a significant market.

Another microbial biopolymer that is expected to be available commercially in 1983 is emulsan. A potent hydrocarbon emulsifier, emulsan is expected to gain widespread use in cleaning oil-contaminated vessels, oil spill management, and enhanced oil recovery (4).** Like many biologically produced polymers, emulsan exhibits a specificity that generally is not observed in chemically synthesized materials; the emulsifying activity of emulsan is substrate-specific, acting only on hydrocarbons that have both aliphatic and cyclic components. Emulsan was originally discovered by researchers in Israel (34,59,60,61,75).

*Enhanced oil recovery is discussed in *Chapter 8: Environmental Applications.*

**See discussion in *Chapter 8: Environmental Applications.*

Emulsan was awarded patents in the United States in 1982, and Petrofirm, USA, a subsidiary of Petroleum Fermentations, N.V., headquartered in Netherlands Antilles, is developing emulsan as a commercial product (4). To date, the development has been confined to strain improvement through mutation and selection techniques. Because of the complexity surrounding the microbial biopolymer, the feasibility of applying rDNA technology for strain improvement is uncertain.

Useful microbial biopolymers can extend beyond the polysaccharides. For example, polyhydroxybutyrate (PHB), a metabolic product of the bacterium *Alcaligenes eutrophus,* has potential commercial applications as a biodegradable thermoplastic that could be used as a surgical material. The unique electrical properties of PHB are also useful in other specialty markets (8). ICI (U.K.) soon will market a PHB product known as Biopol®, made with a bioprocess using glucose as a feedstock. ICI does not know yet what Biopol® 's first markets will be. PHB has properties similar to polypropylene but costs substantially more. Its edge is its biodegradability, and ICI believes that its customers will pay the higher price for this quality (63).

There are several inherent problems in using bacteria to produce polysaccharides (30). There are probably at least 100 enzymatic steps important in the production of these biopolymers, very few if any of which have been identified. Therefore, it is much more likely that classical genetic selection techniques will be more useful than rDNA techniques initially for improving the charactertistics of the compounds. Before it is possible to predict the role that rDNA technology will play in microbial biopolymer production, the producing micro-organism will have to be characterized genetically and physiologically. It will also be important to have an understanding of the complex biochemical pathways for the production of the biopolymer and its regulation. Most biotechnology advances will only appear several years into the future, if at all.

More immediate improvements in the production of microbial biopolymers might be realized by the development of novel bioreactor designs. The polysaccharides have very large molecular weights and are viscous, two characteristics that preclude the use of most standard bioreactors. One way to generate a large quantity of polysaccharides is to maintain live cells in an immobilized cell bioreactor. The cells cannot be microencapsulated, because the product is too large to be washed away. Therefore, they need to be attached to a solid surface by a procedure that does not damage the cells. Another critical research area is improved product recovery from the broth. Current methods for the recovery of xanthan gum, for example, often result in preparations that contain water-insoluble solids such as nonviable cells and residual medium constituents. For xanthan gums to be used in enhanced oil recovery, it is important to have a product free of cells and other fine particulates because the fluid must be able to flow through porous rocks.

Another area of research is the identification of thermophilic polysaccharide producers. Development of a thermophilic micro-organism could result in substantial gains in productivity and lower process costs due to energy conservation. Screening thermophiles for polysaccharide production is an active area of research (74). To date, no thermophilic xanthan gum producers have been identified. Thermophilic *Bacillus* and *Clostridium* bacteria are being screened for the production of polymers that would be useful as biosurfactants (74).

Commercial aspects of biotechnology in specialty chemicals

Some specialty chemicals are currently made using bioprocesses, most notably amino acids and enzymes. The amino acid markets are dominated by Japanese companies, especially Ajinomoto and Kyowa Hakko, whereas the enzyme markets are dominated by two European firms, Novo and Gist-

Brocades. Japan also leads the world in the biotechnological production of fatty acids, a relatively new process.

Most of the opportunities for the use of biotechnology in the production of specialty chemicals are still in planning or early development stages. Many potential bioprocesses would replace chemical processes, necessitating a large investment in new plants. Thus, the potential of a process using biotechnology must justify this investment. On the other hand, enzymes that could withstand high temperatures and pressures could be used to replace existing chemical steps without having to change the basic chemical process. Enzymes with these characteristics are beginning to be studied.

U.S. companies are beginning to enter some specialty chemical markets with biotechnology products. Corn sweetener companies are planning to market enzymes that they have produced for in-house use for some time. Other established firms, such as W. R. Grace, are entering markets with biotechnologically derived specialty chemicals. Several U.S. NBFs, such as Genex, Genentech, Chiron, Amgen, Ingene, Enzo, and Industrial Genetics, have stated interests in specialty chemical markets. Although 20 percent of U.S. companies using biotechnology say they are working in the specialty chemicals field, their interests are not well known and most of their research is highly proprietary.

Priorities for future research

The most glaring lack of knowledge for the successful application of biotechnology to the production of specialty chemicals is in the identification and characterization of micro-organisms that perform particular chemical conversions. Often when industrially useful reactions in micro-organisms have been identified, the micro-organism is so poorly understood that the application of new biotechnology is not possible. There are many opportunities for the specialty chemical industry to expand and improve its production capabilities using biotechnology, but before it can take advantage of these opportunities, useful micro-organisms, especially those that function at high temperature and pressure, will have to be screened and identified.

For the specialty chemical industry to take full advantage of biotechnology, sharing of information between industrial chemists and biologists is needed. The sharing of information has to proceed beyond identification of specific steps in a chemical synthesis that are inherently expensive to discussion of the total process for the manufacture of a specialty chemical. Broad discussion could suggest a bioconversion that uses a less expensive starting material and that would replace several steps of the chemical process. Processes for the manufacture of many specialty chemicals could ultimately combine chemical and biological steps, thereby resulting in more economic and energy-efficient manufacturing.

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Chapter 8

Environmental Applications

Contents

Figures

Chapter 8

Environmental Applications

Introduction

Micro-organisms have several uses in the environment, and new biotechnology can potentially be used to improve these micro-organisms. One application is in the control of pollution and treatment of toxic wastes. As discussed in this chapter, micro-organisms are currently used in pollution control, and the potential applications of biotechnology to treat liquid and solid wastes are numerous. Additionally, techniques are beginning to be used to select micro-organisms that can degrade extremely toxic compounds. In the mining industry, microbes are used to leach metals from mine dumps and concentrate metals from dilute solutions, and there are possibilities for using biotechnology to improve the efficiencies of these processes. A third environmental application of biotechnology is in enhanced oil recovery. About 50 percent of the world's subterranean oil is either reserves trapped in rock or is too viscous to pump. It is possible that either micro-organisms themselves or microbially produced compounds could be injected into oil wells to release the trapped oil.

None of the environmental applications of new biotechnology are ready to be marketed, and there are still many technological problems to be overcome. Nevertheless, several companies are pursuing research and development (R&D) in these environmental applications, and their development will progress over the next several years.

Pollution control and toxic waste treatment

Waste products and the pollution problems associated with such products have been part of human existence since the dawn of civilization. Troublesome wastes are of three types: those in the atmosphere, those in aqueous systems, and solids. In the treatment of both liquid and solid wastes, there are significant opportunities for the use of biotechnology. Indeed, most liquid and solid wastes have been dealt with for millennia by natural biological processes. Moreover, humans in their initial attempts to control such wastes have generally resorted to contained biological systems, particularly for the treatment of liquid wastes. The possibilities for using biological systems to control atmospheric pollution, in contrast, are rather limited. The discussion here, therefore, focuses on the applications of biotechnology in the treatment of liquid and solid wastes.

Treatment of nontoxic liquid and solid wastes

Of the conventional microbiological systems for the treatment of liquid wastes now in use, the most complex is that found in publicly owned water treatment plants. As shown in figure 22, there are four basic unit operations in a wastewater treatment plant:

- primary processing;
- secondary processing;
- tertiary processing; and
- digestion.

The primary treatment step removes solids from the wastewater. These solids (sludge) are then either disposed of or sent to a sludge digester, and the wastewater is forwarded to second-

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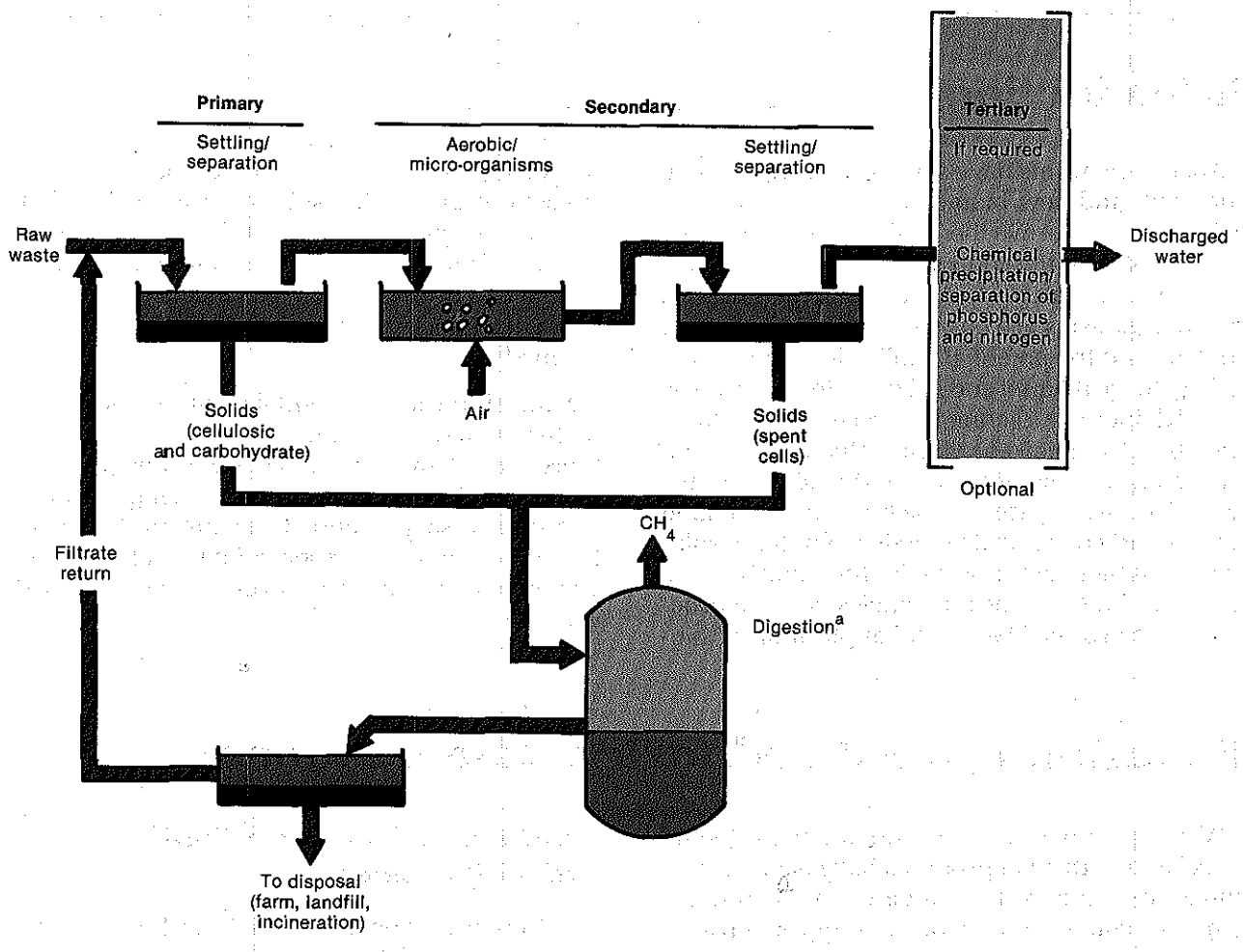
Figure 22.—Steps in Waste Treatment



NOTE: [a]May be aerobic.

SOURCE: Office of Technology Assessment.

ary treatment. The secondary treatment system generally consists of natural aerobic microbes in a large open basin with some type of forced aeration. The purpose of this processing step is to degrade the dissolved organic compounds. The sludge resulting from this operation is primarily composed of microbial cells and is either disposed of or sent to a digester. The liquid from the secondary operation is sometimes subjected to tertiary processing, which can involve precipitation and separation of phosphorous and nitrogen, sand filtration, detention ponds, or biological filters. The water from the tertiary unit (or, in the absence of tertiary treatment, from the secondary unit) is returned to the environment.

The sludge digestion process used to treat the sludge resulting from the primary and secondary treatments is conventionally an anaerobic bioprocess. Its purpose is threefold: to reduce the total volume of solids requiring disposal, to reduce the odor, and to reduce the number of pathogenic organisms. Another potential objective of solid waste treatment can be to recover useful methane from the anaerobic bioprocess. Although the effective anaerobic treatment of solid wastes is

more a problem of engineering than of biotechnology, there is a possibility that enzymes added to the waste could improve the efficiency of this treatment. Like secondary processing, sludge digestion is a classic bioprocess open to further technological improvements.

The total cost of running publicly owned water treatment systems in the United States has been estimated to be $5 billion to $6 billion per year (12). The cost of the chemicals used in these systems represents approximately 20 percent of the total operating costs (12). The biotechnology-based improvements that could be used by these treatment systems will either:

- increase the capacity of the treatment plants and therefore reduce the need for new capital expenditures,
- replace existing synthetic organic chemical additives, or
- remove newly identified, potentially harmful materials.

Processes similar to those just described for publicly owned water treatment plants are also used in the treatment of industrial wastewater, particularly wastewater from the chemical, petroleum, food processing, and pulp and paper industries. For that reason, biotechnology-based improvements in bioprocessing or solids separation procedures that are applicable to public water treatment systems will very likely be applicable to the industrial sector.

IMPROVEMENT OF CONVENTIONAL WASTEWATER TREATMENT PROCESSES

Both physical and biological processes are utilized in the treatment of wastewater. Improvements in any of these operations would be reflected in reduced capital and operating costs for wastewater treatment. Some specific opportunities for biotechnology-based improvements in wastewater treatment are discussed below.

Solids Separation: Flocculation.—The major physical operation in wastewater treatment is that of solids separation. Suspended solids must be separated during both the primary and secondary treatment steps. Quite frequently, it is also desirable to "thicken" the sludges resulting from these settling operations. The present techniques for accomplishing these separation and thickening operations generally include the use of materials known as flocculants. Because of the increased use and reuse of water, the U.S. market for flocculants is expanding (8,10).

Examples of classical flocculants are iron or aluminum salts and activated silica. In recent years, synthetic polymers have been used as flocculants, and in some cases, they have produced very promising results (8,10). Unfortunately, most of these synthetic polymers are based on acrylamide, a toxic compound. Moreover, these synthetic polymers are usually subjected to postpolymerization chemical modification, which adds to their cost. For both safety and economic reasons, therefore, biologically derived flocculants could be very desirable.

A few microbially produced polyelectrolyte polysaccharides that may prove to be effective flocculants have been identified (15). Before these potential bioflocculants can be commercially applied, micro-organisms with the potential for high-level production of effective polysaccharides at low cost will have to be identified. The potential bioflocculants will also have to be tested for their flocculating ability in waste treatment situations. Because the potential bioflocculants are polysaccharides and not proteins, improving their production through recombinant DNA (rDNA) technology may be a complex task (see discussion of polysaccharide biopolymers in *Chapter 7: Specialty Chemicals and Food Additives*). It should be noted, however, that improvements in microbial polysaccharide production have already been achieved with classical chemical mutagenesis and selection (34).

Sludge Dewatering.—For ease of handling of solid residues from water treatment processes, the water content of such residues must be reduced to a minimum to reduce their total weight. It is particularly important to reduce the water content of these residues to the smallest practical value if the sludge is to be disposed of by incineration.

The sludge dewatering operations with current technology (filtration and centrifugation, for example) result in a solids content of 15 to 40 percent, leaving a water content of 60 to 85 percent.

A significant proportion of the water that is retained is "microscopic" in nature, i.e., it is associated with microbial cells and organic debris present in the sludge. If techniques for releasing this retained water could be developed, they would find a ready and profitable market in the field of residue disposal.

Because much of the water retained in sludge is probably held in polymeric matrixes composed of cellulosics, fats, polysaccharides, and proteins (38), partial degradation of these matrixes by using some combination of cellulases, proteases, amylases, and polysaccharide hydrolases should release it. Some enzymes potentially useful for sludge dewatering may already be available in sufficient quantities and at economically attractive costs. For other potentially useful enzymes, techniques for economic, high-yield production will have to be developed. In some instances, these developments will simply involve process development using known microbial strains. In other instances, it may be necessary to construct genetically strains of micro-organisms for high-level production of specific enzymes and perhaps specifically alter the characteristics of the enzymes through directed protein modification. It may also be desirable to identify new enzymes from nature that have superior characteristics for use in sludge dewatering.

Conventional Uses of Biological Processes.—Biological processes are used in two operations of wastewater treatment plants, the secondary treatment step involving an aerobic process and the sludge digestion operation involving an anaerobic process. The performance of these standard aerobic and anaerobic biological treatment processes could conceivably be improved by the addition of specific enzymes that could augment the ability of the natural micro-organisms to degrade, for example, protein, starch, polysaccharides, and cellulosics. Such enzymes could be applied selectively at specific wastewater treatment plants where their particular substrates are present in unusually high concentrations. Enzyme "augmentation" might also help accommodate fluctuating loads on a particular treatment plant. The R&D involved in providing enzymes for this purpose would be similar to that for providing enzymes for sludge dewatering.

One potential byproduct of anaerobic bioprocesses is gas. Solid wastes, when held in sanitary landfill, very often encourage the growth of micro-organisms that produce methane. The generation of methane has become a serious problem in many sanitary landfill sites around the country. Experiments concerning the possibility of tapping this methane as an energy resource are in progress (39). Preliminary results indicate that the costs of the required anaerobic equipment are so high as to make the methane gas thus generated uneconomic as an energy source (39). Research is continuing, however, and it is conceivable that at some point in the future, improved micro-organisms or added enzymes could improve to a limited extent the economics of methane production from solid waste.

CONTROL OF ORGANIC MICROPOLLUTANTS

In recent years, significant pollution problems have arisen with regard to drinking water (27). Analyses of surface waters in the United States and Europe have demonstrated the presence at low concentrations of certain naturally arising soluble organic compounds that, when chlorinated, lead to the formation of trihalomethanes (THMs) (23,24,25,28,35,36). Increasing attention is being focused on these precursors of THM, because THMs are classified as potential carcinogens (23,24,25,28,31,35,36). In addition, there has been a series of toxic compounds discovered in ground water called volatile organic compounds (VOCs). VOCs are apparently leached from a variety of sources in the ground. Both VOCs and the precursors of THMs are potentially amenable to biological treatment methods.

Biotechnology can potentially offer improved techniques for the removal of organic micropollutants (13). It is possible, for example, that their removal could be accomplished by the use of enzymes that are capable of polymerizing aromatic compounds (e.g., fulvic acids and phenolic compounds) that often contaminate drinking water. These low molecular weight aromatic compounds are not precipitated in the traditional flocculation procedures, and they do not adsorb readily to activated carbon (26). These compounds also contribute to the formation of THMs and chlorophenols during chlorination procedures (2,23,24,25, 28,35,36).

Enzymatic polymerization should result in the removal of most of these low molecular weight aromatic compounds during flocculation procedures. Horseradish peroxidase is one enzyme that can catalyze polymerization reactions of this type (1,19,20), but it is not clear that purified or even crude horseradish peroxidase could be employed in a cost-effective manner. Other potentially useful polymerizing enzymes are synthesized by micro-organisms, but the current production levels are much too low for these enzymes to be commercially viable (5,6,11,33). Development of enzymatic polymerization to remove low molecular weight aromatic compounds will therefore require one or more of the following biotechnological developments (13):

- microbial strain improvement and process development programs using known polymerizing enzyme-producing microbial strains;
- identification of micro-organisms that produce useful polymerizing enzymes in high yield; or
- the genetic manipulation of a micro-organism to produce high levels of a polymerizing enzyme.

Another potential approach for using biotechnology to remove organic micropollutants from water is to develop micro-organisms that will better degrade these contaminating compounds. Such micro-organisms could be introduced into the water treatment cycle by seeding them onto activated carbon. When activated carbon is employed in water treatment processes, it accumulates naturally occurring microbes from the water. The goal would be to expand the degradative capacity of that microbial population. Although certain micro-organisms of various genera (*Pseudomonas, Acinetobacter, Arthrobacter, Klebsiella*) will degrade a variety of organic compounds, it will probably be necessary to identify or develop novel micro-organisms for the degradation of specific classes of pollutants. One procedure for accomplishing this, plasmid-assisted molecular breeding, is discussed below in the section on toxic waste treatment. Because micro-organisms of the genera listed above are generally present in natural populations, it should be possible to transfer genes that encode degradative enzymes from strains developed in the laboratory to the naturally occurring micro-organisms to encourage their survival in the environment.

The comments above have been made with respect to the control of organic micropollutants in drinking water. Any technology developed to solve the problems associated with drinking water, however, would most likely be applicable to similar organic contamination problems in industrial wastewater.

CONTROL OF HEAVY METAL CONTAMINATION

Heavy metals in drinking water have long been of concern (3). The concern has focused on lead, zinc, copper, and cadmium, although iron, at relatively high concentrations, can also present health risks (38). In addition to contaminating drinking water supplies, heavy metals can have detrimental effects on the operation and performance of biological processes used in wastewater treatment (3). Moreover, heavy metal contaminants in effluents from wastewater treatment plants can have potentially deleterious effects on downstream flora and fauna (3).

Micro-organisms used in metal accumulation (see section on microbiological mining below) are not useful for concentrating the heavy metals discussed here (except copper), because most metals found in contaminated water are toxic to micro-organisms. One potential approach to solving the problems of heavy metal contamination involves the use of metallothioneins (see also section on microbiological mining). These proteins, found principally in higher organisms, have a high affinity for various heavy metals (21). The economics of this process would depend on efficient release of the bound metals and reuse of the metallothionein. In fact, the gene coding for mouse metallothionein has been cloned and expressed (22,46). It is possible, therefore, that this protein could be produced in large amounts by bacteria, immobilized on a solid support, and used to extract metals from any solution passed over the immobilized protein (41). This process would be highly controlled and could be used not only for decontamination of waste streams from any industrial process, but also for concentrating metals by the mining industry.

Toxic waste treatment

The chemical and petroleum industries produce a variety of highly toxic organic wastes that are not initially amenable to conventional microbial treatment. Such wastes can be either liquid or solid. For developing biologically based processes that will degrade or otherwise detoxify them, a variety of techniques can be envisioned. A specific micro-organism or enzyme will probably have to be developed for each toxic compound.

As the number of toxic compounds that are leached or dispersed into the environment increases, the development of technologies for the treatment of toxic wastes becomes more critical. Toxic wastes are often resistant to natural biological degradation and therefore persist in the environment. Because of their toxic character, developing biotechnological approaches for effective treatment of such wastes may be difficult.

Toxic wastes are generally present in the environment in one of two forms. In some cases, they are purposefully concentrated at specific disposal sites in the form of dumps or lagoons. In other instances, the toxic compounds have already been dispersed into the environment, and they are often present at very low concentrations in soil and water over a fairly large geographical area. In general, toxic wastes in dumps or lagoons are likely to be more amenable to biological treatment than those that have been more widely dispersed. Dumps and lagoons have the advantage of presenting a reasonably high concentration of a particular type of compound or family of compounds at a specific site. Thus, the feasibility of developing a very specific treatment process tailored to both the waste to be detoxified and the environment in which it is found is increased. For more widely distributed wastes, even if biological methods for detoxification are developed, it may be impossible to apply them effectively.

It has often been observed in traditional biological waste treatment systems that the microbial population will adjust to the presence of a toxic compound and eventually achieve some degree of efficiency in its decomposition. This phenomenon, traditionally termed acclimatization, probably represents the selection of mutant micro-organisms that are able to both tolerate and degrade the toxic compound. In the case of certain toxic wastes, it may be possible to accelerate this natural mutation and selection process in the laboratory by the use of a technique called chemostat selection.

In traditional chemostat selection, the natural microbial populations present in soil or water samples collected from or near the waste disposal sites are grown continuously over several months in the presence of steadily increasing concentrations of the relevant toxic compound. This process provides steadily increasing selective pressure for the growth of mutant micro-organisms able to tolerate and potentially degrade the toxic substrate. The mutation rate in the chemostat can often be increased by the use of chemical or physical agents.

In a more modern version of chemostat selection, plasmid-assisted molecular breeding, laboratory strains of *Pseudomonas* that contain plasmids encoding enzymes involved in the degradation of toxic compounds are added to the chemostat (16). This technique is based on the observation that in nature degradative plasmids often evolve by the recruitment of genes from other plasmids in other micro-organisms. Plasmid-assisted molecular breeding has resulted in the generation of both a mixed-culture and a pure *Pseudomonas* strain that degrade the normally recalcitrant molecule, 2,4,5-T, which is a component of herbicides and Agent Orange (16,17). It has also been possible to develop micro-organisms that degrade novel substrates by introducing into a single bacterial strain plasmids specifying the degradation of different, but analogous, compounds or different portions of a single degradative pathway (32). Because degradation of a toxic compound usually involves a complex and often uncharacterized series of reactions, it has generally been preferable to let nature select for the proper genetic combination rather than to attempt to construct it de novo in the laboratory.

More recently, however, in a joint research project between the University of Geneva (Switzerland) and the University of Göttingen (F.R.G.), researchers have cloned the gene for one of the key enzymes in the degradation of 2,4,5-T. Their hope is to understand better the degrada-

tion pathways that have been naturally selected and possibly use this knowledge to develop a more capable micro-organism (4).

One or more of the techniques described above could potentially lead to the isolation of either a mixed culture or a pure strain that degrades a particular toxic compound that might be able to be used at a disposal site or in a contaminated area. The *Pseudomonas* strain that degrades 2,4,5-T has been shown to function successfully both in laboratory tests using contaminated soil and in field tests (17). The micro-organisms being investigated now are aerobic. However, if the toxic waste is present in a dump, it may be necessary to develop anaerobic micro-organisms for detoxification.

The development of micro-organisms for the degradation of both organic micropollutants and toxic wastes will require screening of natural microbial populations or chemostat selection for the appropriate degradative abilities. Once micro-organisms with the ability to degrade the offending compound(s) are available, it may be desirable to transfer that ability to a different microbial host by using rDNA technology to increase the efficiency of degradation or to increase the ability of the micro-organisms to survive in the environment in which they are utilized.

For certain toxic wastes, an alternative approach to detoxification might involve the use of specific enzymes. Enzymatic processes would not totally degrade the toxic compound but simply would convert it to a nontoxic derivative that might then be degraded through natural biological processes. Development of such enzymatic processes would probably involve an extensive research effort, and only very hazardous toxic wastes would justify this degree of effort.

Slime control

Slime can be broadly defined as an aggregation of microbial cells held together by the extracellular polysaccharides produced by the micro-organisms. Wherever water moves in significant quantities, slimes proliferate. The proliferation merely requires the presence of a nutrient, even in minute quantities. In the manufacture of paper, slime control is of major concern because slimes have a very deleterious effect on product quality (7,9,29,30). This problem arises because of the high nutrient availability and favorable temperature and pH in the paper processing environment.

The slimicides currently in use are often heavy metal-based poisons that can result in significant pollution and waste treatment problems (7,9,29, 30). However, the potential for using enzymatic methods for slime control appears quite promising. The formation of slimes is principally due to the extracellular polysaccharides produced by micro-organisms, so it should be possible to use polysaccharide hydrolases to degrade the slimes rather than toxic agents to destroy the micro-organisms.

Grease decomposition

Facilities processing meats, poultry, and certain other foods have particularly difficult problems with grease. Grease problems also appear throughout the wastewater collection and treatment cycle. Both pipe collection branches and pump stations are susceptible to the problems of grease accumulation, which include plugging of lines, accumulation of debris in wet wells, slippery working surfaces, unsightly conditions, odor, and operational problems at the facility site. Scum layers on sedimentation tanks and scum mats in digesters cause additional problems. The two basic problems are the congealing (solidifying) of the grease and the difficulty, if not an impossibility, of decomposing the grease once it arrives at the wastewater treatment plant.

Techniques that result in the emulsification and decomposition of grease would significantly improve the operation of all waste treatment facilities. Bacterial formulations have been used in the past for grease decomposition (18). Improvement of these cultures might be possible. Additionally, an enzymatic approach, such as the use of lipases, could improve the operation of waste facilities.* However, because grease contamination generally is in the form of nonaqueous, congealed deposits, substrate availability may be a significant prob-

*See *Chapter 7: Specialty Chemicals and Food Additives.*

Photo credit: David W. Taylor, Naval Ship Research and Development Center

Grease buildup in a holding tank on a U.S. Navy ship after 5 months of normal operation

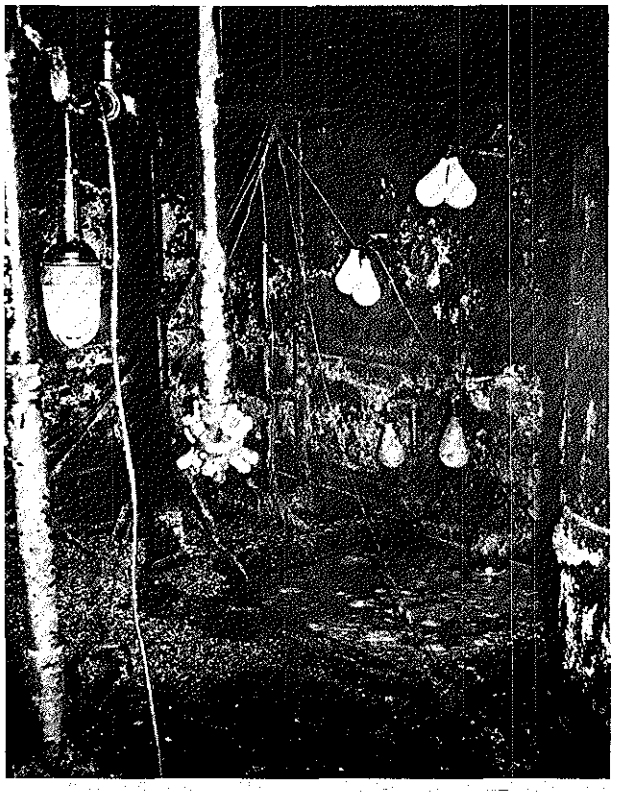


Photo credit: David W. Taylor, Naval Ship Research and Development Center

Grease buildup in the same tank after 4½ months of operation with daily addition of degreasing bacteria produced through classical genetic selection techniques

lem. A mechanism for delivering the enzyme to the substrate might solve the problem, but no approaches for accomplishing this have been postulated.

Commercial aspects of biotechnology in pollution control and toxic waste treatment

In contemporary times, basic developments and improvements in water treatment have originated primarily in Western Europe and spread through the Western Hemisphere. Higher population and industrial densities coupled with fewer water resources have forced Western European countries to advance the technology at a much faster pace than required in the United States. In a sense, Western Europe has been the proving ground for new technologies used for water and wastewater treatment. This historical pattern suggests that Western Europe has probably been making initial assessments of the impact of advanced biotechnology in this area. Japan is also conducting a small amount of R&D in this area.

In the United States, there probably is more activity oriented to biotechnology, much of it financed by the U.S. Government, in the municipal solid waste treatment sector than in either the air or liquid waste treatment sectors. Additionally, R&D efforts aimed at improving the technology of wastewater treatment are concentrated in a handful of small bioprocess-oriented companies and certain academic microbiology laboratories. Only recently did interactions begin between these research groups and the plant operators involved in purifying wastewater (14). In the past, industry has relied primarily on engineering consultants, not technology-based companies, to address pollution problems; these consultants have used the most basic existing technologies for treatment of organic wastes.

Two potential barriers to the commercial application of novel approaches to the problems of pollution control and waste treatment are the performance of the products that are developed and scientific uncertainty regarding their application. For example, although the technology for high-level production of enzymes and metallothioneins certainly exists or can be developed, the performance of these products in the desired application is as yet untested. If their performance turns out to be poor, then the R&D effort for commercialization would be much more extensive and might not be worth pursuing. Furthermore, although reasonable approaches can be designed to identify or develop micro-organisms for the degradation of organic micropollutants and toxic wastes, the success of these approaches is uncertain. It is also unclear whether genetically manipulated micro-organisms or micro-organisms that have been otherwise selected in the laboratory will be able to survive in a nonlaboratory environment. Their ability to survive and function in the field will probably be greatest if the desired degradative activities can be introduced through minimal alteration of a naturally occurring micro-organism.

If the technological barriers to commercial application can be surmounted, the other areas of importance will be markets, Government policy, and regulation. Biotechnological improvements in the area of conventional wastewater treatment processes and slime control would provide economic benefits. If the performance is satisfactory, markets for these products should develop. The primary limitation to commercialization will be the rate of acceptance by the treatment plant operators.

In the case of pollution control, whether it be control of organic micropollutants, heavy metals, or toxic wastes, the primary nontechnological barrier will be Federal Government policy. Biotechnological solutions to these problems are likely to be vigorously pursued only if the Government sets goals and criteria for reducing these contaminants that must be met by both the public and private sectors. The effort for developing these biotechnological solutions will probably initially require Federal funding. However, the requirements could eventually create a demand for a commercial product, and funding might then shift partially to the private sector. At the present time, most industries will not fund biotechnological research on waste treatment problems. They are only interested in licensing or purchasing such technology if it has already been developed.

Another potential barrier to commercialization of products for pollution control is Government regulation of the products themselves. In the case of enzymes and other proteins, few significant safety problems requiring regulation are anticipated, although care must be taken in handling these products. The application of micro-organisms, in contrast, could involve significant regulatory implications. Since the micro-organisms proposed here will have the potential for being released into the environment, it will probably be necessary to establish their safety or to develop methods for their containment at the site of treatment. U.S. policy with regard to the regulation of micro-organisms, particularly genetically manipulated ones, is dynamic. The regulatory constraints that will be placed on the use of micro-organisms in the future, therefore, cannot be accurately predicted. The benefits of using micro-organisms in the area of pollution control to protect human health will have to be carefully balanced against any perceived dangers associated with their use.

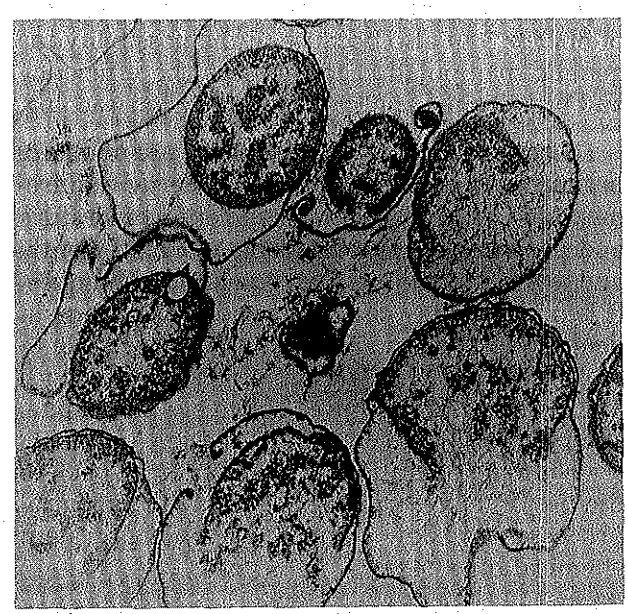


Photo credit: G. E. Pierce and M. K. Mulks

Pseudomonas putida, a bacterium capable of degrading hydrocarbons

Microbiological mining

Micro-organisms have been used to some extent in mineral leaching and metal concentration processes for many years. For the most part, these processes have been fortuitous, relying on micro-organisms found associated with mine dumps. With the recent advent of novel biological techniques, people in the mining industry and biologists have begun to think about ways to manipulate genetically some of the micro-organisms important in metal recovery processes to increase their efficiency and allow them to function on a larger variety of substrates.

Mineral leaching

More than 10 percent of the copper produced by the United States is leached from ores by micro-organisms (41,48). The micro-organisms used are found naturally associated with ores; the ores are not inoculated with selected strains. Until recently, the use of micro-organisms in the mining industry received little research attention because of the ease of mining high-grade ores and the relatively low energy cost for conventional mineral processing. The use of micro-organisms is gaining new attention, not only because of the depletion of high-grade ore and the soaring cost of energy, but also because of the possibility for genetic manipulation to increase the efficiency and broaden the application of microbial leaching.

There are many advantages to the use of micro-organisms. Besides having a low energy requirement due to their growth at ambient temperature and pressure, micro-organisms work efficiently and are less polluting than smelting techniques. It is possible they could be used for leaching in deep underground sites that are inaccessible to more traditional mining equipment. Mining with micro-organisms requires relatively low capital and operating costs, making it feasible for small-scale mining operations. The major drawback to the use of micro-organisms is that the biological processes are slow compared to the equivalent chemical ones (41).

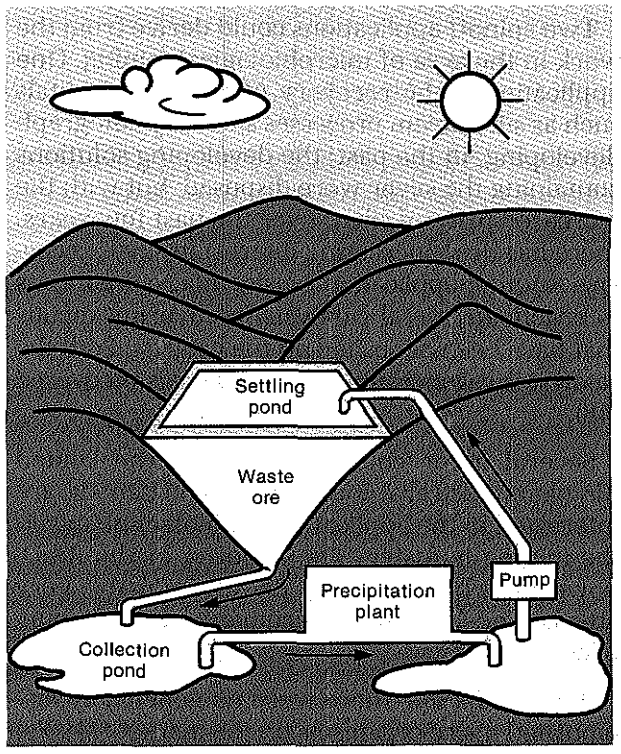
Micro-organisms have been used mostly to leach copper and uranium (40). The organism that is most often used in these operations, and consequently the best studied, is *Thiobacillus ferrooxidans*. *T. ferrooxidans* has also been shown to effect solubilization of cobalt, nickel, zinc, and lead (43). This organism, and most of the other bacteria found in mine dump sites, are autotrophic: they use carbon dioxide from the air for their carbon source, and they generate their energy from the oxidation of inorganic matter. In other words, they need no raw material input from miners who wish to exploit them.

The solubilization (leaching) of metals from ore by bacteria occurs in two ways: indirect and direct. The *indirect method* involves the transformation of ferrous iron to ferric iron by *T. ferrooxidans*. The ferric iron is a very powerful oxidizing agent that consequently converts metal sulfide minerals into acid soluble metal sulfate compounds. For example, ferric iron reacts with copper sulfide to form soluble copper sulfate. The *direct method* involves an enzymatic attack by the bacteria on sulfide minerals to give soluble sulfates and, in the process, also oxidizes the ferrous iron to ferric iron. The result is the same, i.e., the metal is soluble in an acid solution. The metal-laden solutions are collected and the metals are removed from solution by chemical and physical processes (see fig. 23). Additionally, since the use of coal as an energy source will increase, bacteria may be used to extract the sulfur from coal, making it less polluting.

Biotechnology could be used by the mining industry to create more efficient micro-organisms. Recombinant DNA technology could be used to effect the following improvements in selected bacteria:

- an enhancement in the rate at which the bacteria regenerate the ferric iron;
- greater tolerance to acidic conditions;
- greater tolerance to saline conditions;
- a decrease in the bacteria's sensitivity to some metals, especially thorium, silver, mercury, and cadmium; and
- an increase in the bacteria's ability to withstand high temperatures for deep mine operations.

Figure 23.—One Possible Configuration for a Leaching Process



SOURCE: Office of Technology Assessment.

It is likely that rDNA technology will be able to address some of these problems in the near future (41,43,47).

Micro-organisms used in a metal-leaching operation are subjected to very different stresses than those used in a laboratory setting. These differences must be kept in mind when considering the use of rDNA technology, especially since most of the experience with the new technology has focused on well-defined laboratory strains in controlled environments. The bacteria used in leaching endure variable weather conditions, some quite inhospitable for most organisms. When a micro-organism is placed in the environment, it will most likely have to interact with other organisms, and this fact has to be taken into account when researching organisms of interest. Additionally, the mineralogy at each mine site is unique, so micro-organisms either will have to be modified for each site or will have to be able to act on varied feedstocks. It is unlikely that feedstocks will be prepared to suit the micro-organism. It seems that the most likely application for genetically manipulated micro-organisms in mineral leaching will be in the same area in which micro-organisms are used now, for the treatment of large quantities of discarded waste rock that have small quantities of valuable metals (41,43).

Because the leaching process takes place in the environment, the biological process cannot be completely controlled. Nevertheless, there are ways to optimize the reaction conditions for the micro-organisms of interest. The particle size and particle-to-solution ratio of the mine dumps can be manipulated. It is also possible to some extent to control the pH, temperature, and oxygen and carbon dioxide levels. By optimizing these conditions, the leaching organisms can be given an advantage over naturally occurring organisms.

In recent years, the search for new micro-organisms in such primeval environments as hot acid springs, volcanic regions, and deep ocean thermal vents has revealed many micro-organisms capable of metal transformations under harsh conditions. Not only are these organisms likely to have application in commercial metal recovery, but they also represent an enormous gene pool for improving existing leaching bacteria through rDNA technology.

Concentration of metals

Another area where micro-organisms could be useful to the mining industry is the concentration of metals from aqueous solutions. The R&D of this kind of process is somewhat easier than R&D of leaching because it can occur in more controlled laboratory situations, making manipulation of the organism's environment possible. There are two biological methods for concentrating metals. In one case, the metals are nonspecifically adsorbed to the surface of the organism. In the other, the metals are specifically bound and taken up by the organism. In the latter mechanism, metals can be concentrated up to 10,000 times. There is a great diversity of organisms that have been shown to concentrate metals, including bacteria, fungi, and algae. The metals they concentrate are primarily copper, uranium, silver,

and the lanthanides. Recombinant DNA technology could be useful in developing organisms to expand the range of metals concentrated.

Another approach to concentrating metals involves the use of specific metal-binding proteins produced in higher organisms. One of the best studied metal-binding proteins is metallothionein, which binds cadmium, zinc, mercury, and copper. The use of these proteins is discussed earlier in the section on pollution control and toxic waste treatment.

Commercial aspects of biotechnology in microbiological mining

In the United States, there is no Federal R&D funding specifically earmarked for mining microbiology. The National Science Foundation and the U.S. Department of Energy (DOE) have funds under various programs that can be used for basic research studies on micro-organisms important in mining. In fiscal year 1984, neither agency anticipates funding at levels more than $300,000. The Bureau of Mines of the U.S. Department of the Interior did not fund any microbiology in fiscal years 1981 and 1982. In fiscal year 1983, it funded the Idaho National Engineering Laboratory at about $300,000 to study the leaching and concentrating of cobalt. The Bureau intends to continue the funding of this project at the same level in fiscal year 1984 (45).

Much of the R&D funding in this field comes from both large and small firms in the mining industry. Atlantic Richfield Co. is doing a substantial amount of research in this area. Other large companies investing in microbiological mining include General Electric, Koppers, Eastman Kodak, International Nickel Co., Chevron, W. R. Grace, and Standard Oil of California. Additionally, at least four small U.S. companies, Advanced Mineral Technologies, Inc. (Socorro, N. Mex.), Polybac (Allentown, Pa.), Genex, and Biogen S.A.* are researching mining and metal microbiology.

Two spinoff applications could derive from the work in the area of microbiological mining. One application is the recovery of expensive metals such as silver from processes such as photograph developing. In the past, the developing solutions containing the silver were disposed, but with the increased price of silver over the past few years, there has been increasing interest in silver recovery. Another application is using micro-organisms to reactivate metal catalysts, recovering metals that have been deposited on the catalyst. Both the catalyst is regenerated and the metal is recovered (48).

Several other countries, notably the United Kingdom, Australia, South Africa, and Canada, are interested in the applications of biotechnology in the mining industry. The majority of the R&D, however, is being done by private industry. Very little is funded by the Governments of these countries.

As of mid-1983, there were no genetically manipulated micro-organisms on the market (44). Yet it is possible that research efforts could yield useful, new bacteria for leaching and concentration of metals in a few years. If scale-ups and field trials (for leaching) were carried out expedientlly, marketable products for leaching and concentration could be available in less than 10 years (42). This research is proceeding slowly, however, because of the currently depressed state of the minerals market. Most industry experts hesitate to speculate when micro-organisms used for mining might reach the marketplace, because the worldwide availability and price of these metals will determine how fast the research will proceed. There will have to be a scarcity of the metal before much microbiological research will be done.

*Biogen is about 80-percent U.S. owned, but most of its work in microbiological mining is done by Biogen S.A. in Switzerland.

Microbial enhanced oil recovery

Conventional oil extraction technologies can recover only about 50 percent of the world's subterranean oil reserves. The balance either is trapped in rock or is too viscous to pump. The application of micro-organisms or their products possibly could be used to aid in the recovery of

trapped oil. The use of microbial processes for this purpose is called microbial enhanced oil recovery (MEOR).

The interest in MEOR has increased substantially since 1975. Several conferences on the subject have brought together petroleum engineers and microbiologists to begin to analyze the roles that micro-organisms could play in the recovery of trapped oil. To date, several field tests have been done, but none have yet revealed a micro-organism that is broadly applicable in MEOR (51).

There are three general experimental approaches to MEOR (51):

- the stimulation of endogeneous micro-organisms by injection of nutrients into the well,
- the injection of laboratory-selected micro-organisms into the well, and
- the production by micro-organisms of specific biological compounds and the subsequent use of these compounds in wells.

As discussed further below, new biotechnology offers possibilities in the latter two approaches.

Uses of micro-organisms in oil wells

Various micro-organisms are now being isolated and examined for properties useful for oil extraction. Micro-organisms evolve gases, notably carbon dioxide, that could aid in repressurizing an oil well. An ideal microbe would use the less valuable parts of oil as a carbon source to produce surfactants or emulsifiers to lower the viscosity of the oil allowing it to be pumped to the surface. Several problems complicate this senario. No micro-organism has yet been found that degrades only the less useful components of oil; micro-organisms usually also degrade the compounds important to the petroleum industry. Some micro-organisms will not degrade the oil at all, but these micro-organisms need to have a carbon source, usually molasses, pumped into the well, and this increases the cost of production.

Microbes currently being studied survive only under conditions of moderate heat, salinity, and pressure (55,56). Given the wide variability in geological deposits, these micro-organisms have limited usefulness. However, there is substantial evidence that the oil reservoir is not as an untenable, restrictive environment for micro-organisms as some laboratory studies would indicate. Micro-organisms can, in fact, be isolated from deep reservoirs, and they may have developed specialized mechanisms to cope with low amounts of oxygen. Other micro-organisms have been isolated that do not need oxygen for growth. Further study of these organisms may lead to the development of micro-organisms useful to the petroleum industry (52).

Use of microbially produced compounds in oil wells

Another approach to MEOR, the use of microbially produced compounds in oil wells, could be a relatively near-term application of biotechnology. Biological compounds that could be injected into wells include surfactants and viscosity enhancers and decreasers. The search has begun for these compounds, but it is becoming increasingly obvious that little is known about these compounds and the micro-organisms that produce them.

Even with the lack of knowledge, however, two promising compounds have been isolated and studied. One substance, characterized at the University of Georgia, is a glycolipid from a bacteria named H-13. This substance reduces the viscosity of various heavy crude oils (51). Another substance, originally isolated in Israel but now studied in the United States, is called emulsan and has the property of emulsifying oil, allowing better flow and dispersal (54).* Field trials have included the cleaning of an oil tanker hold and an aircraft carrier runway (57). Emulsan proved effective at these jobs and holds promise for use in oil wells. Emulsan is being developed by Petroferm, USA (Amelia Island, Florida), and produced and marketed by Pfizer (50).

*Emulsan is discussed further in *Chapter 7: Specialty Chemicals and Food Additives*.

Commercial aspects of biotechnology in microbial enhanced oil recovery

Many of the major oil companies are thought to be investing in MEOR (49). The U.S. leader in this field appears to be Phillips Petroleum. Small U.S. firms doing R&D in MEOR include Petroferm, Genetics International (Boston), and Worne Biotechnology (Medford, N.J.). Only one company, Shell Oil Co., has stated that MEOR is too speculative for its R&D laboratories (55). Additionally, the U.S. Government, through DOE, is investigating MEOR.

Foreign companies and countries are also investigating MEOR, notably the Swiss firm Petrogenetic AG, the British Government and British Petroleum, the U.S.S.R., and the Peoples Republic of China (49,53).

The status of potential markets for MEOR is very questionable because of the lack of knowledge about MEOR's real potential. However, MEOR could potentially increase the production of oil and decrease the costs of recovery significantly.

Priorities for future research

The applications of new biotechnology in the environment are at a rudimentary stage, primarily because of the lack of knowledge about the genetics and biochemistry of the potentially useful micro-organisms and the environment in which they operate. Currently, most basic research is done with pure cultures that do not represent the real world situation. There is certainly no guarantee that a species of bacterium will perform in an outdoor environment as it does in the laboratory. Additionally, scale-up problems will be great because of the large size of the operations. Studies in all of these research areas are interdisciplinary. Unless there is close collaboration between biologists and engineers, it is unlikely that the research will be very productive.

Specific challenges for pollution control and toxic waste treatment include:

- the isolation and characterization of enzymes to polymerize low molecular weight organic compounds,
- better characterization of metallothioneins from various species,
- the identification of polysaccharides to serve as bioflocculants,
- the development of enzymes for sludge dewatering,
- the development of microbial strains or enzymes that degrade toxic compounds, and
- the development of improved polysaccharide hydrolases to degrade slimes.

Specific challenges for microbiological mining include:

- the development of micro-organisms that could leach valuable metals such as thorium, silver, mercury, gold, platinum, and cadmium;
- a better understanding of the interactions between the micro-organisms and the mineral substances; and
- the development of DNA transfer technologies for use at low pHs.

Specific challenges for MEOR include:

- better biochemical and physiological understanding of micro-organisms already present in oil reservoirs,
- the development of a micro-organism that degrades only the less useful components of oil, and
- screening of micro-organisms for the production of surfactants and viscosity enhancers and decreasers.

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Chapter 9

Commodity Chemicals and Energy Production

Contents

Tables

Figures

Chapter 9

Commodity Chemicals and Energy Production

Introduction

In 1982, the U.S. chemical industry produced about 158 billion pounds (lb) of organic chemicals (36). About 30 commodity chemicals—defined in this report as chemicals that sell for less than $1 per lb*—constitute the majority of this market (see table 39).

*Chemicals with higher value such as vitamins, food additives, and amino acids, form the subject of *Chapter 7: Specialty Chemicals and Food Additives*. The difference between "commodity" and "specialty" chemicals is somewhat fluidly determined by price versus quantities produced. Some of the compounds described in chapter 7 are considered by some analysts to be commodity chemicals. These include vegetable oils and their derivatives, single cell protein, and fructose. Because of their predominant use as food additives, however, these compounds are considered in the earlier chapter.

Practically all commodity chemicals are currently made from petroleum and natural gas resources and are used as precursors for a variety of materials such as polymers and solvents. The United States, which now imports about 30 percent of its petroleum (34), uses about 7 to 8 percent of its total petroleum and natural gas supply for the production of commodity chemicals (10,18,22); the remainder of this supply is used as an energy source.

The chemical industry's reliance on petroleum feedstocks raises a number of problems. Two problems are the fluctuating cost and uncertain

Table 39.—Annual Production and Selling Price of the Major Organic Commodity Chemicals in the United States

Chemical	Production in 1982 (billion pounds)	Price in 1982 (¢/lb)	Major uses
Ethylene	24.7	25.5	Polyethylene derivatives
Toluene	15.3	26.7	Benzene, gas additive, solvents, polyfoams
Propylene	12.3	24.0	Polypropylene, isopropanol
Ethylene dichloride	10.0	13.7	Vinyl chloride
Benzene	7.9	21.1	Styrene, phenol, cyclohexane
Methanol	7.3	10.8	Formaldehyde
Ethylbenzene	6.6	30.0	Styrene
Vinyl chloride	6.5	22.0	Polyvinyl chloride, resins
Styrene	5.9	37.5	Polystyrenes
Xylene	5.3	18.9	p- and o-xylene, gas additive, solvent
Terephthalic acid	5.0	N.A.	Polyester fibers
Ethylene oxide	4.9	45.0	Ethylene glycol
Formaldehyde	4.7	24.4	Resins
Ethylene glycol	4.0	33.0	Antifreeze, polyesters
p-xylene	3.2	31.0	Synthetic fibers
Acetic acid	2.8	26.5	Vinyl and cellulosic acetate
Cumene	2.7	24.0	Phenol
Phenol	2.1	36.0	
Acrylonitrile	2.0	44.5	Polymers
Vinyl acetate	1.9	37.5	Polyvinyl acetates, alcohols
Butadiene	1.8	40.0	Rubber
Acetone	1.8	31.0	
Propylene oxide	1.5	40.5	Propylene glycol, urethanes
Isopropanol	1.3	32.9	Acetone, solvents
Cyclohexane	1.3	25.3	Nylon, caprolactum
Adipic acid	1.2	57.0	Nylon
Acetic anhydride	1.1	41.0	Cellulose esters
Ethanol	1.1	25.8	Detergent, solubilizer, cosmetics, solvent, fuel

SOURCE: Office of Technology Assessment, adapted from D. Webber, "Basic Chemical Output Fell Third Year in a Row," *Chem. Eng. News*, May 2, 1983, pp. 10-13; T. C. O'Brien, "Feedstock Trends for the Organic Chemical Industry," Planning Report 15, U.S. Department of Commerce, National Bureau of Standards, April 1983; and *Chemical Marketing Reporter*, "Weekly Price Report," May 31, 1982, pp. 35-39.

supplies of petroleum. Commodity chemical prices are especially sensitive to the cost of petroleum because feedstock costs typically represent 50 to 75 percent of commodity chemical manufacturing costs (6). Other problems of the commodity chemical industry include a current overcapacity of production by the capital-intensive petrochemical companies, the high costs of energy associated with "cracking" petroleum into chemical feedstocks, and environmental, safety, and ideological concerns surrounding the use of nonrenewable, fossil resources (6).

These well-publicized problems, which increase in urgency with the passing of time, have intensified the search for nonpetroleum feedstocks for chemical and energy production. The options being pursued at present include the liquification and gasification of coal, the development of synthetic fuel from natural gas, and the conversion of biomass** to fuels and a wide variety of organic chemicals.

The substitution of natural gas, coal, and other nonrenewable resources for petroleum are issues that have been discussed in several previous OTA reports (28,29,31). Despite the drawbacks outlined in those reports, coal is favored as an alternative resource by U.S. petroleum companies, which control 20 percent of U.S. coal production and 25 percent of U.S. coal reserves (3,27). Processed coal feedstocks fit readily into most petroleum feedstock schemes for the production of commodity chemicals and thus do not require large capital investments for new chemical plants. Nevertheless, at least one analyst thinks that petroleum will continue to be used as a feedstock for commodity chemicals for some time and that coal will not make a significant impact on the production of chemicals until the 21st century (22).

It appears that countries with substantial inexpensive supplies of petroleum, such as Mexico and Saudi Arabia, are turning to the production of commodity chemicals as a way of adding value to their resources. Thus, countries with petroleum may begin to control the price of these chemicals. Because such countries may be able to produce commodity chemicals at a lower price, companies in the United States, Europe, and Japan may have to develop new ways of using commodity chemicals to produce compounds of greater value or to move directly to the manufacture of higher value-added chemicals from biomass. In any case, a rapid or dramatic shift in feedstock use is unlikely; it is much more probable that there will be a slow transition to the use of biomass as a feedstock in particular instances.

Although nonrenewable resources such as coal will probably be adopted earlier, biomass—including crop and forest product wastes and municipal and agricultural wastes—may provide solutions to some of the long-term problems associated with chemical and energy production from petroleum. It is technologically possible to produce essentially all commodity chemicals from biomass feedstocks such as starch or cellulose, and most commodity chemicals can be synthesized biologically (10,24). A viable biomass feedstock for the production of commodity chemicals may be starch. Less than 1 percent of the U.S. corn crop would be required to obtain the cornstarch needed to produce a typical commodity chemical at the rate of 1 billion lb per year (18). Although a few high-volume chemicals that could be produced from biomass, such as ethanol, can be used for fuel, the volume of biomass needed to produce a nation's energy would be substantially greater than that needed to produce its commodity chemicals. Starch probably could not be used for energy production without putting a strain on food and feed uses. Thus, if biomass is to be used extensively for energy production, the biomass source will most likely be lignocellulose.

Biomass as an alternative to petroleum for U.S. energy production was described in OTA's July 1980 report *Energy From Biological Processes* (30). As emphasized in that report, substantial societal change, i.e., more public support and a higher priority for research on biomass use in the U.S. Departments of Agriculture and Energy programs, will be necessary if biomass is to become a viable alternative to petroleum as a source of energy in the near future. At present, the level of U.S. public support for biomass research is not high. Furthermore, Federal support of applied research and development (R&D) programs for al-

**Biomass is all organic matter that grows by the photosynthetic conversion of solar energy.

ternative fuel sources has been plummeting in the recent climate of intense fiscal scrutiny.

A shift from petrochemical processes to bioprocesses for the production of commodity chemicals will be difficult because of the existing infrastructure of chemical and energy production. This infrastructure allows a barrel of oil to be converted to products in a highly integrated system in which the byproduct of one reaction may form the substrate for another reaction. Most chemicals derived from biomass cannot yet compete economically with chemicals made from oil in this infrastructure.

As the costs of bioprocesses are reduced through R&D, however, a transition to biomass resources may become a more realistic proposition. This chapter examines ways in which biotechnology might improve the efficiency of biomass conversion, thus facilitating the transition to the use of biomass resources. The advances biotechnology could provide for the improved growth of plants used for biomass conversion are discussed in *Chapter 6: Agriculture.*

Since commodity chemicals represent only a small portion of today's U.S. petroleum consumption, a transition to biomass-based commodity chemical production without a concurrent transition to biomass-based energy production will not substantially reduce the country's dependence on petrochemical resources. For moving the United States toward the goal of reduced reliance on imported, nonrenewable resources, a unified approach to chemical and fuel production will be necessary.

Biomass resources

The United States has abundant biomass resources. The largest potential amount of cellulosic biomass is from cropland residues such as corn stover and cereal straw,* although the potential amount of cellulosic biomass from forest resources is also quite large. About 550 million dry tons of lignocellulose are easily collected and available for conversion to chemicals each year. In addition, some percentage of the 190 million dry tons of corn produced yearly could be converted to starch and used for chemical production (21).

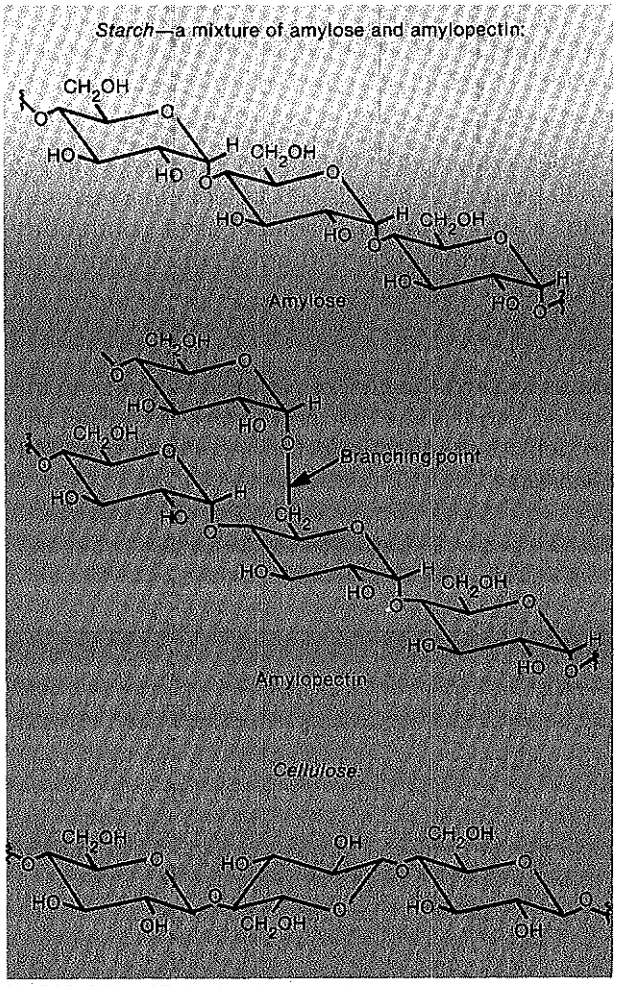
Parameters used to determine the optimal kind of biomass used in microbial systems include availability of the biomass, its energy content per dry weight, the amount of energy that must be expended to achieve the desired products, the environmental impact of the process, and the amenability of the material to conversion by existing microbial systems. Ultimately, biomass resources that minimize usurpation of food sources are sought (e.g., nonfeed crops grown on extant arable land).

This chapter emphasizes the use of the two most abundant feedstocks from biomass: starch and cellulose. Starch and cellulose are both polymers of glucose units (6-carbon simple sugars) which, when hydrolyzed, yield glucose molecules (see fig. 24). These glucose sugars provide the starting point for biological chemical production, for example, the transformation of glucose to ethanol. Other derivatives of biomass, such as vegetable oils, are used in bioprocesses, and those resources are considered in *Chapter 7: Specialty Chemicals and Food Additives.*

One drawback to the use of biomass as a feedstock for commodity chemical and energy production is its relatively low energy content per unit dry weight. Dry cellulose biomass, for example, yields roughly 16 million Btu per ton and cornstarch yields 15 million Btu per ton, whereas petroleum yields 40 to 50 million Btu per ton. Thus, the energy yield per unit of weight is lower for biomass than for petroleum. Furthermore, the costs of transporting biomass to a factory may be an important economic consideration. Raw material and transportation costs are particularly important in the production of commodity chemicals, because of the low value added to the feedstock in the synthesis of final products.

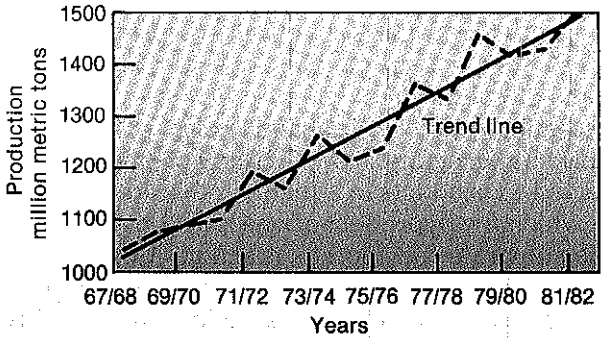
*Agricultural residues left on the soil aid in the sustainability of soil. The environmental impact of the removal of these residues must be studied more thoroughly in order to determine whether agricultural wastes are, in fact, true wastes.

Figure 24.—Polysaccharides of Biomass: Starch and Cellulose



SOURCE: Office of Technology Assessment.

Figure 25.—Trends in World Grains Production (million metric tons)



SOURCE: Office of Technology Assessment, adapted from CPC, Int., 1983.

Starch

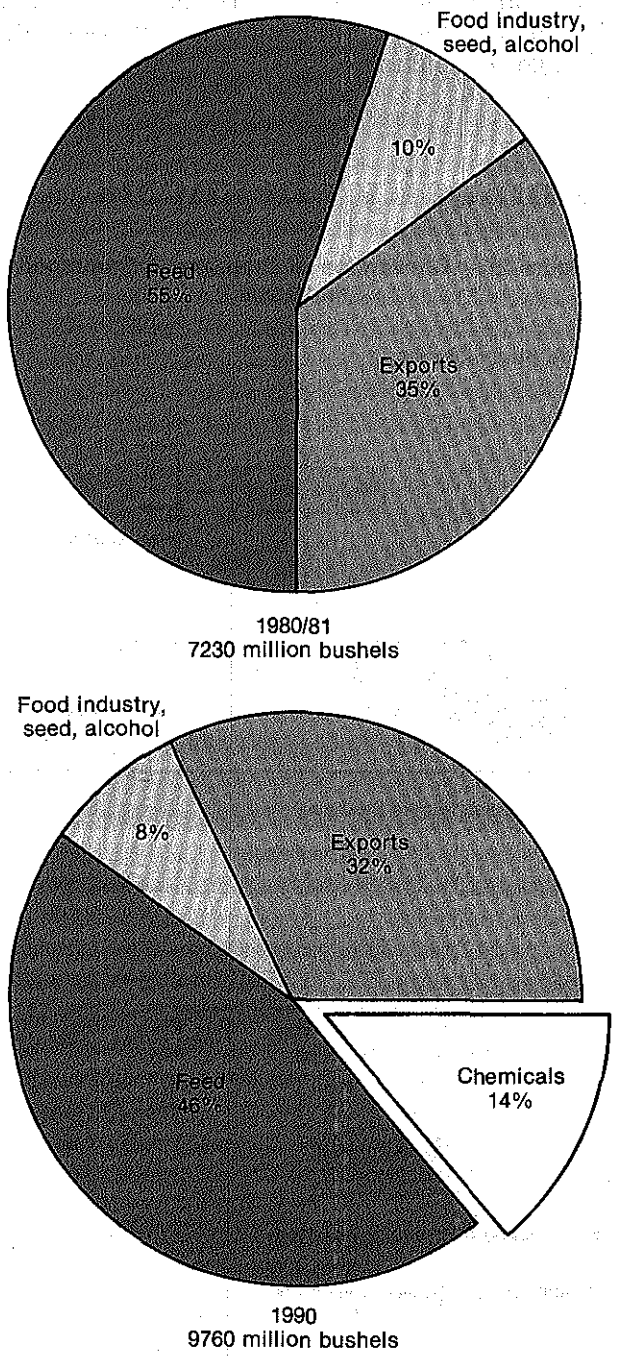
Starch, a molecule composed of many hundreds of glucose units bound together in branched or unbranched chains, is the principal carbohydrate storage product of higher plants and is readily available from such crops as corn and potatoes. In 1979, the United States produced about 666 billion lb of grain from six major cereal crops, and this grain contained 470 billion lb of starch. The major grain produced, corn, contained 316 billion lb of starch (10), which could provide 285 billion lb of glucose.

As shown in figure 25, world grain production has increased steadily over the past several years, and this trend is expected to continue through the end of the century as the result of yield improvement and an expansion of acreage planted (19). Furthermore, the price of corn has remained relatively constant over the past decade, especially when compared to the nearly tenfold increase in the price of oil over the same period of time.

The utilization of U.S. corn has changed over the past 10 years. A decrease in U.S. meat consumption caused a concurrent decrease in the amount of corn used for animal feed, while at the same time, technological advances increased corn yields. Consequently, the export market for U.S. corn has risen from 15 percent of the crop to 35 percent. Since U.S. corn production is expected to increase and meat consumption is expected to decrease, U.S. farmers will need new markets for their corn. Commodity chemical production from a starch feedstock could provide a market for U.S. corn. The potential for industrial use of starch from corn alone is large, and an increase in the industrial use of corn would probably aid in supporting farm prices. Currently, only about 7 percent of the corn produced in the United States is processed into cornstarch (7,19). Figure 26 suggests that 14 percent of the 1990 corn crop could go to chemical production, and enough corn would still be available for other uses.

Because of its high solubility in water and ease of hydrolysis into individual glucose units, starch is highly amenable to bioprocessing and may be an ideal feedstock for chemical production. The use of starch for both chemical and fuel production, however, might be at the expense of its use

Figure 26.—Trends in U.S. Corn Utilization



in food production. Starch may not be produced in large enough quantities to be used both as a source of food and a source of energy.*

Lignocellulose

Lignocellulose is composed of cellulose, an unbranched chain of glucose units, lignin, a linked mixture of aromatic molecules, and hemicellulose, a polymer composed mainly of 5-carbon sugars. This structure provides the rigidity necessary for cellulose's primary function, the support of plants. Because of its wide availability, lignocellulose has the potential to be the most important of all the raw materials for use in bioprocessing. Currently, however, several problems impede the use of lignocellulose on a large scale. Lignocellulose is highly insoluble in water and its rigid structure makes cellulose much more difficult than starch to hydrolyze to individual sugars. Furthermore, most micro-organisms cannot utilize lignocellulose directly without its having been pretreated either chemically or physically. Despite the considerable advances made in both chemical and enzymatic hydrolysis techniques, the cost of glucose derived from cellulose is still much higher than that derived from starch.

The inherently diffuse nature of lignocellulose resources means that very high collection costs, especially in energy and manpower, will be encountered in any attempt at large-scale utilization. These considerations have given rise to the concept that the utilization of lignocellulose for energy will be feasible only through a widespread network of smaller manufacturing facilities that draw on local resources and supply local needs. Indeed, this pattern has already been established for farm-scale alcohol production from corn. An alternative to multiple small-scale production units

*As detailed in OTA's July 1980 report *Energy From Biological Processes* (30), starch could be used to produce approximately 1 billion to 2 billion gal of ethanol in the United States each year (about 1 to 2 percent of U.S. gasoline consumption) before food prices might begin to rise.

is the concept of centralized, intensive lignocellulose production on so-called "energy plantations." The potential ecological problems and highly questionable economics have detracted from prospects for success, but the development with biotechnology of more effective biological agents for lignocellulose utilization could radically change this picture.

Conversion of biomass to commodity chemicals

As noted above, there are numerous types of biomass resources, including lignocellulosic products and feed crops such as corn. Because of the varying compositions of these raw materials, different methods are used in rendering them into useful chemicals. Nevertheless, all microbial conversion of biomass to marketable chemicals is a multistep process that includes:

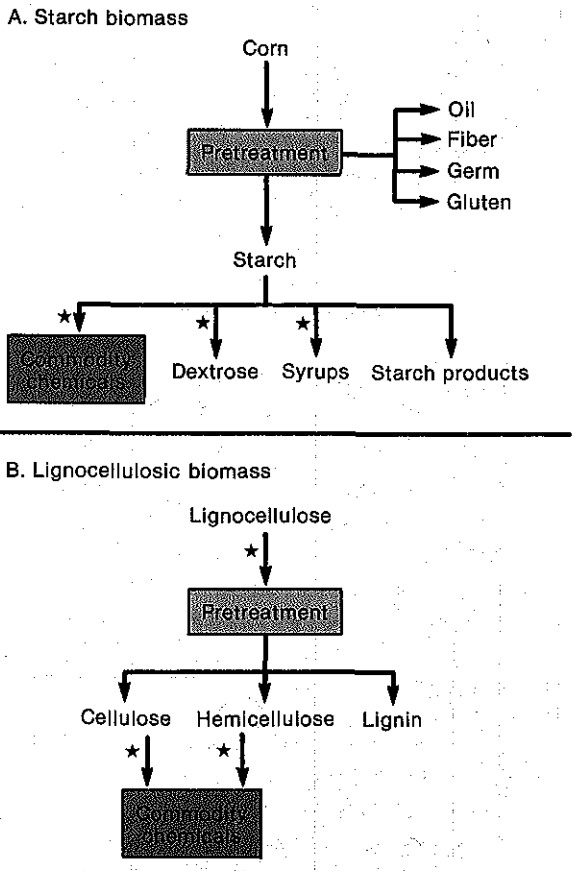
- pretreatment (particularly with lignocellulosic biomass),
- hydrolysis (saccharification) to produce hexose (6-carbon) and pentose (5-carbon) sugars,
- bioprocessing of these sugars by specific micro-organisms to give commodity chemicals,
- subsequent bioprocessing or chemical reactions to produce secondary commodity chemicals, and
- separation and purification of end products.

Figure 27 is a schematic summary of the multistep processes for the conversion of starch and lignocellulosic biomass to commodity chemicals. Although figure 27 emphasizes the microbial steps that could be used for these processes and applications of biotechnology to them, it should be noted that a variety of chemical syntheses can also be used to convert the components of biomass into useful chemicals (9,10,17,18).

Pretreatment

Before either starch or lignocellulosic biomass can be used as feedstocks for bioprocesses, they must be pretreated in preparation for hydrolysis. Starch from corn requires little pretreatment. Lignocellulosic materials such as wood, however, demand extensive pretreatment to make cellulose and hemicellulose available for hydrolysis.

Figure 27.—Conversion of Biomass to Commodity Chemicals



SOURCE: Office of Technology Assessment.

STARCH

The United States relies primarily on corn for starch feedstocks. About 500 million bushels are processed by corn refiners yearly to produce

cornstarch products. In the production of cornstarch, refiners employ a process known as "corn wet milling" in which corn kernels are cleaned, soaked in warm, dilute acid, and ground to yield a slurry composed of starch, protein, and oil. Much of the starch is further converted to sweeteners, such as glucose and high fructose corn syrup (7). Cornstarch is the milling product that could be used to make commodity chemicals.

The pretreatment of starch requires minimum inputs of acid and heat. Energy requirements are low compared with the potential energy gained, and almost all byproducts are marketable. Combined with starch thinning and saccharification costs (see below), corn wet milling is estimated to yield monomeric sugar at a cost of 12¢/lb (at $3.40/bushel of corn) (21).

LIGNOCELLULOSE

Methods used to pretreat lignocellulosic biomass include chemical pretreatment in acids and bases, steam explosion, and mechanical grinding. These methods, described in OTA's July 1980 biomass report (30), add substantially to the costs involved in using lignocellulosic biomass as a chemical resource.

In the future, biodelignification (the biological degradation of lignin) by micro-organisms may prove useful in the pretreatment of lignocellulosic biomass (8,24). Biodelignification results in removal of lignin, exposing the crystalline cellulose and lowering the costs of mechanical pretreatment. At present, however, biodelignification is an inadequate, expensive means of pretreatment, and it is not used in the pilot projects for use of lignocellulose currently underway. As yet, there are no valuable uses for lignin. Uses must be found for lignin derivatives before these processes will be commercially viable (2).

Several groups are working toward obtaining faster biodelignification using mixed cultures of micro-organisms, but microbial reaction rates at present do not approach those needed for economic feasibility. With use of the best candidate, the degradative mold *Chrysosporium pruinosum*, 40 percent of lignin remains intact after 30 days of treatment (1). At least 20 strains of bacteria that have lignodegradative abilities have been identified, but efforts to use micro-organisms for delignification are hampered by the fact that lignin metabolites are toxic to these micro-organisms. Thus, more work remains to be done before biodelignification and other methods of biological pretreatment are competitive with the currently used chemical or mechanical pretreatment methods. Were more information available on these micro-organisms, biotechnology could be used to improve their efficiency.

Hydrolysis

STARCH

Enzymes from microbial systems are widely used industrially to catalyze hydrolysis of starch into sugars.* Batch bioprocesses are used for hydrolysis. Three enzymes, alpha-amylase, beta-amylase, and glucoamylase, are used to hydrolyze the starch chains to yield complete hydrolysis and the formation of glucose (15). The largest industrial use of enzymes is in the corn wet milling industry.

The major U.S. corn refiners have ongoing active research programs for the improvement of enzymatic degradative processes, and these manufacturers have made major advances in the areas of bioprocessing and enzyme immobilization. These manufacturers have continued their efforts toward improvement of enzymes by using new biotechnology (32).

CELLULOSE

The well-ordered crystalline structure of cellulose necessitates harsher treatments than those used for starch. Whereas hemicellulose is readily hydrolyzed into its 5-carbon sugars under mild conditions, the hydrolysis of cellulose requires strong acids, heat, and pressure. These conditions lead to the formation of byproducts which must be separated and utilized to minimize the overall costs of lignocellulose use. In addition, the acid used for the hydrolysis of cellulose must be neutralized before the mixture is used for bioprocessing, a requirement that raises the cost of hydrolysis.

*For further discussion of these enzymes, see *Chapter 7: Specialty Chemicals and Food Additives.*

The use of enzymes known as cellulases (and micro-organisms that produce cellulases) to hydrolyze cellulose, either alone or in conjunction with chemical treatment, offers an increasingly popular alternative to chemical methods of hydrolysis. Cellulose is the most abundant biological compound on earth, and a myriad of micro-organisms employ cellulases to obtain energy for growth from the resulting glucose molecules. Research efforts to improve cellulase activity by mutagenesis and selection of cellulolytic (cellulose-degrading) micro-organisms have yielded mutant strains of micro-organisms (particularly fungi) that produce cellulases with higher tolerance to glucose (the product of hydrolysis that inhibits cellulase activity), increased efficiency and reaction rate, and better functioning at the elevated temperatures and high acidities used in industrial bioprocesses (1).

The enzymatic activity of cellulases has been improving over the past several years, and in some cases, the time needed for saccharification and subsequent bioprocessing to produce ethanol from cellulose has been reduced several fold (11). Despite these improvements, however, the activity of cellulases does not begin to compare with the activities of amylases, which are about 1,000 times more catalytically efficient (5).

Although research into the molecular biology of cellulases is in its early stages, biotechnology is being used to improve the cellulase-catalyzed hydrolysis of cellulosic biomass in several ways. Two challenges for biotechnological approaches to cellulase production are increasing the low activity of the cellulase and making sure the entire cellulase gene complex is expressed. Processes that optimize cellulase activity and efficiency are prerequisite to the use of lignocellulosic biomass resources.

Researchers at the National Research Council of Ottawa, Canada, the University of British Columbia, the University of North Carolina, and Cornell are using recombinant DNA (rDNA) techniques to clone cellulase genes from several micro-organisms into bacteria that may be induced to produce cellulase in large quantities (20). Similarly, researchers at the U.S. Department of Agriculture are cloning cellulase genes from the fungus *Penicillium funiculosum* (12).

Another possibility for a biotechnological improvement is to transfer the ability to utilize the 5-carbon sugars from hemicellulose into cellulose-utilizing micro-organisms. A third possibility is improving the specificity of organisms that can utilize lignocellulose directly, e.g., *Clostridium thermocellum.* The "wild types" of these micro-organisms produce a range of products, typically ethanol and several organic acids. This varied synthesis results in low yields for each product and great difficulties in subsequent recovery and purification. Genetic mechanisms could be used to select for high production of any one of the products.

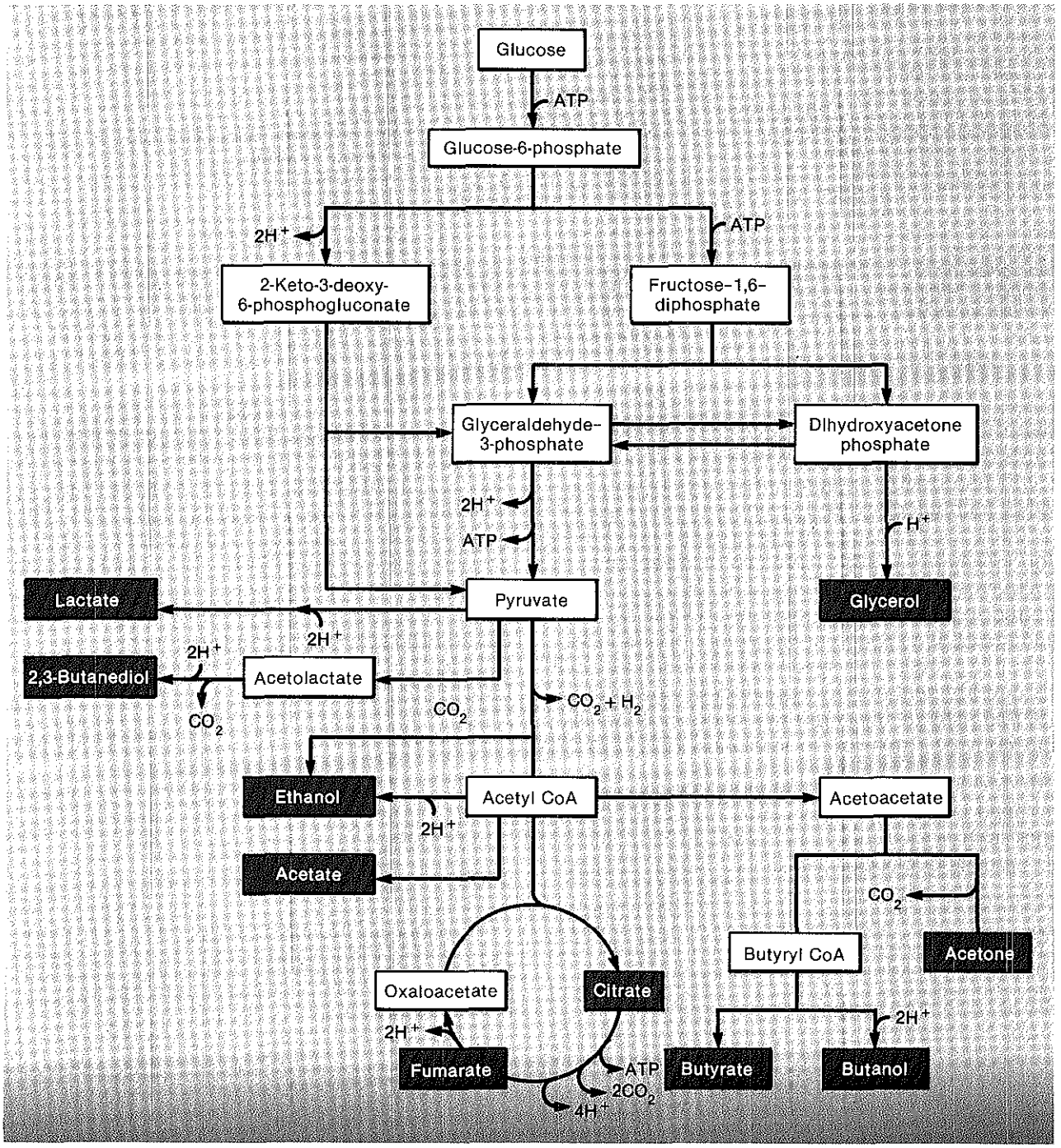
Microbial production of commodity chemicals

Some commodity chemicals, including ethanol and acetic acid, are now produced in the United States with microbial bioprocesses (9), while other chemicals, such as ethylene and propylene, will probably continue to be made from petroleum feedstocks because of lower production costs. The commodity chemicals that are attractive targets for production from biomass include ethanol, acetone, isopropanol, acetic acid, citric acid, propanoic acid, fumaric acid, butanol, 2,3-butanediol, methyl ethyl ketone, glycerin, tetrahydrofuran, and adipic acid (9,18). Additionally, some chemicals, such as lactic and levulinic acids, could be used as intermediates in the synthesis of polymers that might replace petrochemically derived polymers (18).

Because the chemical composition of biomass differs from that of petroleum and because micro-organisms are capable of a wide range of activities, it may be that the most important commodity chemicals produced from biomass will be, not chemicals that directly substitute for petrochemicals, but other chemicals that together define a new structure for the chemical industry. Micro-organisms used to produce organic chemicals could be used with micro-organisms that fix nitrogen to produce nitrogeneous chemicals, either higher value-added compounds or ammonia, a high volume commodity chemical. Other micro-organisms, such as the methanogens or the micro-organisms that metabolize hydrogen sulfide, may be used to produce sulfur-containing chemicals (14).

The aerobic and anaerobic microbial pathways leading to a number of important compounds are shown in figure 28. Some of the micro-organisms responsible for these reactions are listed in table 40. Knowledge of biochemical pathways for the synthesis of particular chemicals will lead to the

Figure 28.—Metabolic Pathways for Formation of Various Chemicals



SOURCE: T. K. Ng, R. M. Busche, C. C. McDonald, et al., "Production of Feedstock Chemicals," *Science* 219:733-740, 1983.

Table 40.—Potentially Important Bioprocessing Systems for the Production of Commodity Chemicals

Micro-organism	Carbon source(s)	Major fermentation product(s)
Saccharomyces cerevisiae	Glucose	Ethanol
Saccharomyces cerevisiae	Glucose	Glycerol
Zymomonas mobilis	Glucose	Ethanol
Clostridium thermocellum	Glucose, lactic acid	Ethanol, acetic acid
Clostridium thermosaccharolyticum	Lactic acid	Glucose, xylose, ethanol, acetic acid
Clostridium thermohydrosulfuricum	Glucose, xylose	Ethanol, acetic acid, lactic acid
Schizosaccharomyces pombe	Xylulose	Ethanol
Kluyveromyces lactis	Xylulose	Ethanol
Pachysolen tannophilus	Glucose, xylose	Ethanol
Thermobacteroides saccharolyticum	Xylose, glucose	Ethanol
Thermoanaerobacter ethanolicus	Glucose, xylose	Ethanol, acetic acid, lactic acid
Clostridium acetobutylicum	Glucose, xylose, arabinose	Acetone, butanol
Clostridium aurianticum	Glucose	Isopropanol
Clostridium thermoaceticum	Glucose, fructose, xylose	Acetic acid
Clostridium propionicum	Alanine	Propionic acid, acetic acid, acrylic acid
Aeromonas hydrophilia	Xylose	Ethanol, 2,3-butanediol
Dunaliella sp.	Carbon dioxide	Glycerol
Aspergillus niger	Glucose	Citric acid
Aerobacter aerogenes	Glucose	2,3-butanediol
Bacillus polymyxa	Glucose	2,3-butanediol

SOURCE: Office of Technology Assessment, from T. K. Ng, R. M. Busche, C. C. McDonald, et al., "Production of Feedstock Chemicals," *Science* 219:733-740, 1983; J. C. Linden and A. Moreira, "Anaerobic Production of Chemicals," *Basic Biology of New Developments in Biotechnology* (New York: Plenum Press, 1983); and D. I. C. Wang, Massachusetts Institute of Technology, personal communication, 1982.

identification of the genes that control the synthesis of these chemicals. With such knowledge, it will be possible in some instances to employ rDNA technology or cell fusion methodology to yield micro-organisms with improved bioconversion efficiencies. Improvements of these micro-organisms by genetic manipulation at present are limited to a few cases. Examples include the development of a *Pseudomonas putida* plasmid that codes for proteins that hydroxylate chemicals and the development of rDNA plasmids in *Escherichia coli* that provide the genes that code for enzymes that convert fumarate to succinate (21).

In developing commercial bioprocesses, a major need is for micro-organisms with characteristics such as tolerance to increased levels of products during bioprocess reactions;* better efficiency of sugar utilization; faster rates of production; tolerance to higher temperatures, so that separation and purification methods (which often require elevated temperatures) can be coupled with bioprocesses;** selected drug tolerance, so that growth of contaminant bacteria can be inhibited by drug treatment; and better growth on a variety of biomass sources (26). Another major need is the identification of plasmids that can be used as vectors for the transmission of useful genetic information.

*The most commonly used micro-organism for ethanol fermentation is yeast, which tolerates ethanol concentrations up to about 12 percent. Since the purification of ethanol from such dilute solutions is costly, a desirable goal is to develop organisms (and thus enzymes) whose tolerance to end products is higher. Such organisms could be used as hosts for cloned bioconversion genes.

**A combination of bioprocessing and purification could be implemented whereby products are continuously removed and collected. In this case, the high temperatures would minimize contamination by other organisms and avoid product concentrations high enough to kill the micro-organisms (13,37).

International research activities

Biomass-related research in the United States is conducted by the Department of Energy (DOE), the National Science Foundation, and private companies. Programs within DOE include the Biomass Energy Technology program, which examines the technical feasibility of innovative biomass feedstock production and conversion technology; the Alcohol Fuels program; and the Biological Energy Research program (within DOE's Office of Basic Energy Science), which funds research on genetic manipulation of plants for increased biomass production and of micro-organisms for improved bioprocessing. DOE's Energy Conversion and Utilization Technologies (ECUT) group recently started a program in biocatalysis specifically in response to the potential use of rDNA organisms in chemical production processes. The goal of this generic applied research program is to build "biocatalysis technology to enable industry to displace a significant level of nonrenewable resource requirements by [the year] 2000" (33). The ECUT program focuses on research on scale-up of bioprocesses, monitoring continuous bioprocesses, bioreactor design, and downstream product separation.

The Reagan administration's proposed fiscal year 1984 budget is not generous to biomass conversion for energy programs. The budget requests $17.3 million to support "fundamental R&D" in this area, a small increase of $1.3 million (8.1 percent) from fiscal year 1983. Alcohol fuels R&D, formerly budgeted separately, would be combined with biomass energy programs (25). Since some of this R&D relates to studies of microbial chemical production, any change in Federal support for R&D of biomass energy will effectively alter R&D for biological commodity chemical production. The only DOE program specifically directed toward the use of new biotechnology, the ECUT program, received no funding for fiscal year 1984.

Differing emphasis is placed on the biological production of chemicals and fuels by the governments of foreign countries. The United Kingdom funds biotechnological applications to chemical production processes through several governmental departments. The Canadian Development Corporation is pursuing technology development for producing ethanol from aspen wood ($21 million over 5 years), and several other Canadian Government agencies are addressing chemical and energy production from biomass. Japan, France, and Sweden also have Government-funded programs pursuing the use of biomass as a feedstock for chemicals and energy (33).

Profiles of recent U.S. patent activity indicate widespread attention by private inventors and companies in the United States and other countries to biomass conversion, particularly in areas related to hydrolysis of starch to sugar, the production of higher value-added chemicals such as amino acids from microbial systems, and improvements in bioprocess systems such as enzyme immobilization (32). Organizations with the most U.S. patents in starch hydrolysis and related bioprocesses include CPC International Inc. (U.S.), with 21; A. E. Staley Manufacturing Co. (U.S.), with 18; A. J. Reynolds Tobacco Co. (U.S.), with 8; France's National Agency for the Funding of Research (L'Agence Nationale de Valorisation de la Recherche); Anheuser-Busch, Inc. (U.S.), and Hayashibara Biochemical Laboratories, Inc. (Japan), with 7 each; and Novo Industri A/S (Denmark) and Miles Laboratories Inc. (U.S.), with 5 each (32). Even though patents in starch hydrolysis do not give a conclusive view of future biotechnological applications to the commodity chemical industry, they do indicate that U.S. companies are the predominant developers of the bioprocess technology underlying the utilization of starch biomass.

Conclusion

The production of low-value-added, high-volume commodity chemicals demands the use of the most economic production schemes available. The most economic schemes for chemical and energy production at present favor the use of petrochemical feedstocks. In the future, however, decreasing petroleum supplies, increasing oil prices, and technological advances in biomass utilization may foster a transition to the use of feedstocks derived from biomass. Such a transition is not expected to occur on an industrywide scale in the near future, but bioprocesses are being used to produce significant amounts of fuel-grade ethanol from corn and other crops economically.

Because of the potential for disruption of the existing industrial structure, the complex interrelationships that characterize the production of commodity chemicals will affect the success of the introduction of particular compounds produced by microbial bioprocesses. Projected bioprocessing costs of commodity chemicals and the structure of the chemical industry have been investigated by B. O. Palsson, et al. (23). These investigators concluded that the potential exists for a smooth introduction of four microbial products (ethanol, isopropanol, n-butanol, and 2,3-butanol) into the U.S. chemical industry, and that these products may foster other bioprocess development. In order for this transition to take place, however, either the costs of producing these products must be reduced (about 20 to 40 percent of their existing costs) or the price of petroleum must rise. Reducing the costs of production of chemicals from biomass is a prerequisite to commercial success in all case studies thus far.

U.S. Government support for applications of biotechnology to the conversion of biomass is decreasing, while high levels of government support are provided in several competitor countries, particularly Japan and the United Kingdom. U.S. companies appear to be active in developing certain biotechnological applications, but most of this activity as reflected in patents is concentrated in applications to starch conversion, with primary emphasis on higher value chemicals which are expected to be produced before biomass-based commodity chemicals are made. Some companies in the United States and other countries are active in bioprocess development, but given the current slow pace of R&D in microbial systems that perform the chemical conversions, these processes will not be applicable in the chemical industry for some years.

Priorities for future research*

Biotechnology will be a key factor in developing economic processes for the conversion of biomass to commodity chemicals. A number of priorities for research that will improve the efficiency of the conversion of biomass to useful chemicals can be identified:

- bioprocess improvements, including the use of immobilized cell and enzyme systems and improved separation and recovery methods,** an area especially important to the production of commodity chemicals because incremental improvements in bioprocess technology will be readily reflected in the price of these chemicals.
- screening programs to identify micro-organisms (and their biochemical pathways) useful to processes such as commodity chemical synthesis, cellulose hydrolysis, lignin degradation, and catalysis of reactions that utilize by-products that are currently unmarketable;
- developing host/vector systems that facilitate increased production of commodity chemicals by gene amplification and increased gene expression of desired products and that allow

*Many of these suggestions are from Rabson and Rogers (24).
**See *Chapter 3: The Technologies* for a more extensive discussion.

the transfer of genes into industrially important micro-organisms;
- understanding the structure and function of the cellulase and ligninolytic activities of micro-organisms;
- understanding the mechanism of survival of micro-organisms in extreme environments, such as high temperature, high pressure, acid, or salt;
- understanding the mechanism of cell tolerance to alcohols, organic acids, and other organic chemicals;
- understanding the genetics and biosynthetic pathways for the production of commodity chemicals, especially for the strict anaerobic bacteria such as the methanogens and the clostridia;
- understanding microbial interactions in mixed cultures; and
- developing an efficient pretreatment system for lignocellulose.

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Chapter 10

Bioelectronics

Contents

Figure

Chapter 10

Bioelectronics

Introduction

The potential for the use of proteins in electronic devices has received attention recently with the advent of recombinant DNA (rDNA) technology and the potential for computer-aided design of proteins (1,2,3,5,6,7,11,13,14,15,19,21). Work is focused in two areas: biosensors and biochips. Biosensors (biologically based sensors) have been used for several years, but design problems have limited their acceptance. Biotechnology is expected to increase the variety, stability, and sensitivity of these devices. Biochips (biologically based microchips) capable of logic and memory are still only speculative, and their development is many years away.

Biosensors

A potential application of biotechnology is in the development of improved sensing devices. Because of their high specificity for given substances, enzymes and monoclonal antibodies (MAbs) are particularly suited for use as sensors. Sensors using these biological molecules have the potential to be smaller and more sensitive than traditional sensors.

Biosensors using enzymes have been used to detect the presence of various organic compounds for many years (12). Most of them have used a free or immobilized enzyme and an ion-sensitive electrode that measures indirectly (e.g., by temperature or color changes produced during an enzymatic reaction) the presence of a product the formation of which is catalyzed by the enzyme. Because of the proximity of the enzyme and electrode, these biosensors are rapid and sensitive. They have not had wide application, however, because of the high cost of many enzymes, lack of particular enzymes, and temperature instability.

The use of rDNA and MAb technology and computer-aided design of enzymes and other proteins may allow the problems associated with existing biosensors to be overcome. The cloning in bacteria of genes coding for useful enzymes, for example, could allow the enzymes to be made in large amounts cost effectively. The use of MAbs, which can be made for virtually any molecule, not only could obviate the need for enzymes but also could substantially broaden the applications of biosensors. A longer term solution to the lack of particular enzymes might be to have computers design enzymes with particular catalytic functions. Finally, features of proteins that determine temperature stability could be incorporated into the genes that code for important sensing enzymes.

A new approach to fabrication is yielding biosensors with greater speed, sensitivity, and ease of operation (4). The new biosensors use a field-effect transistor that translates a chemical reaction, such as that catalyzed by an enzyme, into an electronic signal. Because the electronic response is a direct measure of the chemical reaction, the sensitivity and speed of the device is increased. (It is postulated that these sensors could use MAbs as specific detection agents.) The British Government has one of these new biosensors on the market; it detects a particular nerve gas (4).

There are many potential applications for improved biosensors in the medical, industrial, environmental, and defense fields (2,12). These are discussed in turn.

In medical diagnostics, many substances need to be measured accurately and rapidly, but the sensors now available are often expensive, slow, and insensitive. Improved biosensors could poten-

tially solve many or all of these problems. Such biosensors could detect, for example:

- antigens associated with infectious disease,
- hormonal levels to examine endocrine function, and
- serum protein levels indicative of disease.

One particularly important medical application of improved biosensors could be in the treatment of diabetic patients for whom proper levels of insulin and glucose must be maintained. Small, implantable devices that sample blood for glucose and regulate the delivery of insulin could be developed.

As mentioned in *Chapter 3: The Technologies,* one of the hindrances to effective bioprocess monitoring and control is the need for a wide range of sterilizable sensors. Biosensors could be developed to measure levels of key reaction substances, such as reactants, intermediates, nutrients, and products. Continuous monitoring of several substances with biosensors interfaced to a computer would allow better control over the reaction process and thus increase productivity. The use of thermotolerant enzymes could potentially allow these sensors to be sterilized in place.

A potential environmental application of improved biosensors would be to monitor water and air quality. However, cost considerations limit the use of the extremely sensitive sensors now available. Additionally, very few measuring systems are portable enough for monitoring in the field. Better biosensors might circumvent these problems. Other environmental biosensors could be developed to detect exposure of workers to hazardous substances and to monitor indoor air pollution in the office or at home.

The U.S. Department of Defense (DOD), in the near future, will be the major supporter of biosensing research in the United States ($8 million over the next 4 years). DOD's aim is to develop biosensors for the detection of chemical and biological warfare agents that are small, have high sensitivity, quick response times, and no false alarms (18). If such devices were developed, they would have broad civilian applications such as those just mentioned. Companies funding research on biosensors for a number of uses include IBM, IT&T, and Johnson & Johnson in the United States and Cambridge Life Sciences in the United Kingdom (4,9,16).

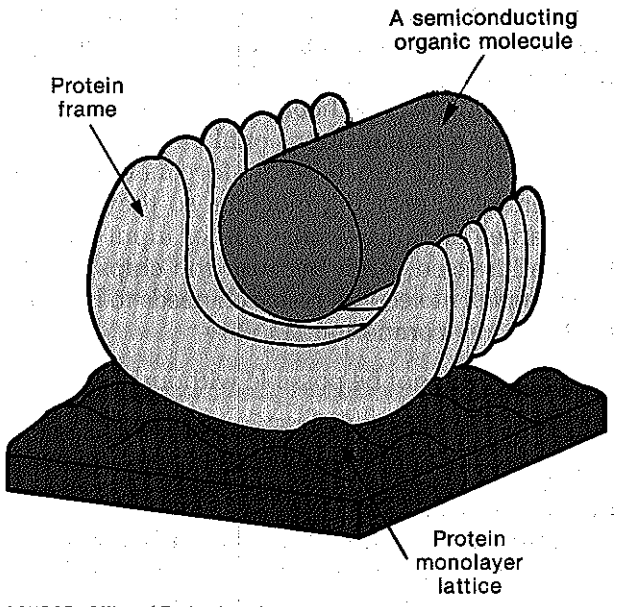
Many technical barriers to developing highly reliable biosensors remain (8,17). Operating limitations (e.g., a narrow temperature range) and fabrication problems have yet to be overcome. Research is needed to identify which proteins are most appropriate for this technology. Moreover, sensors implanted in animals or used to monitor bioprocesses must be sterilized prior to implantation or use, and research is needed to develop biosensors that are not destroyed by sterilization methods. Over the next 5 to 10 years, many of these generic problems inherent in the development of biosensors will probably be solved (2,18).

Biochips

Probably the most novel potential application of biotechnology is in the production of a biomolecular electronic device. Such a device would contain a specially designed organic molecule that would act as a semiconductor surrounded and stabilized by specially designed proteins, as shown in figure 29. Researchers have studied the use of proteins as a matrix for semiconductors since the early 1970's, but the possibility of designing proteins aided by computers and producing the proteins with rDNA technology has sparked more intense interest.

Two small entrepreneurial firms in the United States are doing research on biological microchips, or biochips: Gentronix (Rockville, Md.) and Ean-Tech (San Francisco, Calif.). Furthermore, DOD will be funding biochip research beginning in fiscal year 1984 at $3 million to $4 million for 5 years. A few large electronics companies in the United States (Westinghouse, General Electric, and IBM) have small inhouse programs in this area. Japan, France, the United Kingdom, and the U.S.S.R. have indicated interest in biomolecular computers (10,20).

Figure 29.—The Use of Proteins in Constructing a Circuit



SOURCE: Office of Technology Assessment.

Bioelectronics research is in its infancy. Although most potential applications of proteins in this field are only speculative, the successful development of these applications could have a substantial effect on the electronics industry. Computers using protein-based biochips, for example, would be smaller, faster, more energy efficient, and possibly more reliable than computers using silicon chips.* The impact of such biochips would be as broad as that of present computers, from hand-held calculators to robotics.

The biological nature of biochips also raises the possibility of some exciting medical applications—they could be implanted in the body to interface with the living system. Some possibilities include:

- brain implants to circumvent damage that has caused blindness and deafness,
- cardiac implants to regulate heart beat,
- blood implants to regulate drug delivery (e.g., insulin for diabetics), and
- implants to control artificial limbs.

DOD considers biochip technology potentially very useful. Because the circuits would be the width of molecules, the resulting devices would be very small and should find use in areas where small size is essential (e.g., in missile guidance). Furthermore, because of the nonmetallic nature of biochips, it is thought that they would be immune to "electromagnetic pulse," the extraordinary electrical charge that results from a nuclear explosion and renders useless all metallic devices in a large area. In spite of the potential uses, however, it is likely to be many years before any complex biochip will be developed.

A conventional silicon chip contains a set of optically imprinted circuits on a wafer of silicon. Four factors limit the number of circuits contained on a chip. First, the lower limit of the width of a circuit is determined by the wavelength of light used for imprinting. The current limit is 1 to 10 microns; it has been postulated that by 1990 the width could be 100 times narrower (2). Second, the distance between circuits is limited by the nature of the silicon circuit construction itself. When circuits are too close together, electrons can "tunnel" between circuits. This tunneling decreases the reliability of the electronic device. The lower limit for the distance between circuits is rapidly being approached for silicon chips. The third limiting factor for conventional chips is heat dissipation. As circuits are packed more closely together, the chip becomes too hot to function effectively. Lastly, as the amount of information processing ability per chip increases, the problems with fabrication and quality control increase.

Biological and chemically synthesized molecules conceivably could solve these problems associated with conventional silicon chips as well as provide additional advantages in design. Because the molecules themselves would be the conductors, the lower limit of the circuit width would be the width of molecules, which is several orders of magnitude narrower than silicon circuits used (or even postulated) at present. Molecular circuits could be placed very close to one another without tunneling effects, because the proposed molecules conduct current without losing electrons. Furthermore, since almost no energy is required for molecules to conduct current, very little heat would be generated even when the circuits were close together. The specificity of complex interactions among proteins and the self-assembling

*Mutations that occur at a certain low level during growth of micro-organisms could affect the reliability of the final product.

processes characteristic of biological systems would facilitate the fabrication of very reliable biochips.

The fabrication of complex three-dimensional biochips with the fabrication technology now used in the electronics industry is probably impossible. An essential feature of the use of a protein matrix is that the proteins direct their own assembly and the appropriate positioning of the semiconductor molecules. There are numerous examples of self-assembling protein structures, including virus particles, and these are being studied intensely for potential applications to biochip technology.

Several proteins, including MAbs, have been suggested for constructing a biochip in three dimensions. The movement of microelectronics from two- to three-dimensional structures would allow not only for increased complexity but also for greatly reduced size. The use of a three-dimensional protein matrix necessitates the design of proteins that will interact with other proteins at correct and unique angles. The construction of these proteins will rely on computer-aided design and rDNA technology.

There are many problems to be solved before a three-dimensional biochip will become available. Biological equivalents of capacitors, transistors, and resistors are yet to be developed. Switching devices, necessary for use with the computer binary system, are only theorized. No one has determined how a three-dimensional biological structure will do logic functions or store memory. The problem of interfacing biochips so they can be programed or can assimilate other input has not been addressed. And, because the chips would use complex molecules, research needs to be done on their environmental stability.

Biochips will not be possible without computer-designed proteins and rDNA technology. Yet it will probably be several years before rDNA technology will be able to contribute substantially to biochip research, because it is first necessary to understand more about the relationship between protein structure and function, the biological self-assembly processes, and the mechanisms by which molecules could do logic functions and store memory.

Priorities for future research

Increased funding for research in the following areas could speed the development of bioelectronics:

- computer-aided design of proteins,
- temperature stability of proteins,
- field-effect transistors,
- miniaturization of sensors,
- biological self-assembly processes, and
- molecular-switching mechanisms for electronic signal propagation.

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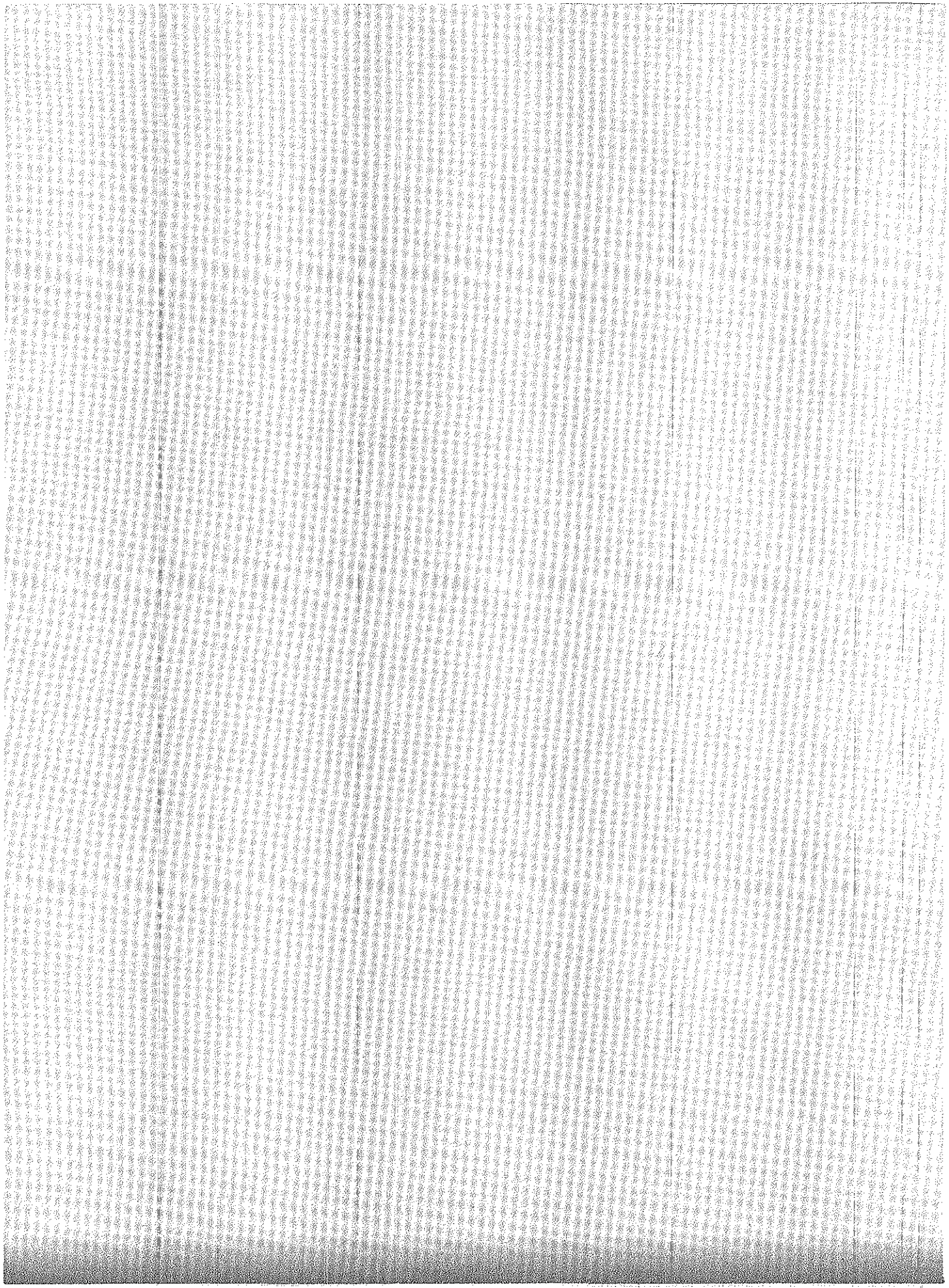
PART IV
Analysis of U.S. Competitiveness in Biotechnology



Chapter 11

Framework for Analysis

Contents

Chapter 11

Framework for Analysis

With the increasing importance of high-technology industries in the United States and the decreasing competitiveness of U.S. goods in world markets, U.S. policymakers need to be able to assess the country's future with respect to the commercialization of emerging technologies. If the country's potential competitive position can be defined, policy analysis can suggest possible governmental steps to improve that position.

Factors influencing competitiveness in biotechnology

To analyze the future competitive position of the United States in biotechnology, OTA identified 10 factors believed to have potential influence on the international competitiveness of products resulting from an emerging technology.* Many of these factors relate to the legal system and various governmental policies, although societal and private sector factors were also identified. The 10 factors are:

- financing and tax incentives for firms;
- government funding for basic and applied research;
- personnel availability and training;
- health, safety, and environmental regulation;
- intellectual property law;
- university/industry relationships;
- antitrust law;
- international technology transfer, investment, and trade;
- targeting policies in biotechnology; and
- public perception.

These 10 factors are described in the chapters that follow. The chapters are presented, more or less, in the order of the factors' importance to competitiveness in biotechnology. Each of these factors was analyzed for the United States and five countries identified as the major potential competitors of the United States in biotechnology: Japan, the Federal Republic of Germany, the United Kingdom, Switzerland, and France.

The three factors that OTA believes to be most important to a country's success in commercializing an emerging technology such as biotechnology are financing and tax incentives for firms, government funding of basic and applied research, and the availability of trained personnel.

The first of these factors encompasses the availability of capital both for starting new firms and for financing the growth of existing firms. It also includes tax policies that affect the formation and availability of capital as well as the strategic decisionmaking in firms.

Funding of basic, generic applied,* and applied research is necessary both to maintain a science base and to ensure the availability of the technical means to apply scientific knowledge industrially. The distinction between basic, generic applied, and applied science research is an important one, because, in establishing a competitive position, a comparative advantage in applied science may be more important than an advantage in basic research. Optimally, an analysis of funding for basic, generic applied, and applied research would include funding from both government and industry. Industry figures are usually proprietary, however, so the analysis in this report necessarily concentrates on government funding.

The third factor, availability of personnel trained in essential disciplines in a new tech-

*OTA's model for determining the future competitive position of different countries with respect to the commercialization of biotechnology could very well be useful in determining international competitiveness with respect to the commercialization of other emerging technologies. For emerging technologies other than biotechnology, however, the relative importance of specific factors would not necessarily be the same.

*Generic applied research is research whose objective is to gain the understanding necessary to solve a problem common to a particular industry. Such research falls between basic research, the objective of which is to gain understanding of the basic aspects of phenomena without goals toward the development of specific processes or products; and applied research, the objective of which is to gain understanding necessary to meet a recognized and specific need, process, or product.

nology, is important to firms considering the commercialization of that technology. Furthermore, the quality of science and engineering education is a major factor in determining the future availability of personnel.

Three factors were identified as having moderate importance in the commercialization of biotechnology: health, safety, and environmental regulation, intellectual property law, and university/industry relationships.

To determine the importance of health, safety, and environmental regulation, several issues had to be weighed. On the one hand, the more stringent the regulations protecting against potential risks of the technology, the more positive the public's reaction to the development of the technology is likely to be. On the other hand, stringent regulations may discourage commercialization. Most companies will seek to enter domestic markets first, and for these companies, the domestic regulations will be of primary importance. Companies interested in developing international markets, however, must also consider the regulations of other countries. Some countries' regulations are effective nontariff trade barriers that discourage entry by foreign firms into domestic markets.

The intellectual property laws of a country partially affect whether a company will pursue a line of inquiry. If one is unlikely to reap the benefits of the discovery of an invention, then one is less likely to work on such an invention. Furthermore, if a country's patent laws are not sufficiently protective, then a company may choose to keep its inventions as trade secrets. Protection through trade secrets usually discourages technology transfer.

Active interaction between industry and academia is a factor that could promote the competitiveness of a country in an emerging technology. Usually when a technology is in the early experimental phase, most of the important research is carried out in universities. Ongoing dynamic university/industry relationships are an effective means of domestic technology transfer. Generally, therefore, such interactions promote a country's competitiveness.

Three factors were determined not to be very important to the development of biotechnology now, although these factors could increase in importance as biotechnology becomes a more mature technology. They are antitrust law; international technology transfer, investment, and trade policies; and government targeting policies in biotechnology.

U.S. and foreign antitrust laws were originally intended to stimulate competitiveness among domestic industries by prohibiting restraints of trade and monopolization. As countries have sought international markets, however, questions have been raised about whether antitrust restrictions accomplish their intended purpose. Governments of some countries have taken a relaxed attitude toward the interpretation of these laws with respect to research joint ventures and technology licensing, while the governments of some countries continue to have strict interpretations. It is possible that the strict interpretation of antitrust law with respect to joint ventures and technology licensing could decrease a country's international competitive position.

Trade policies and laws that guide the transfer of products and technology internationally could influence a country's competitive position if the laws and policies are not reciprocal among countries. Technology transfer laws are generally concerned with national security issues and transnational joint ventures. Investment control and exchange laws when applied to technology licensing or technical assistance agreements or foreign investment, can restrict the importation of foreign technology or capital into particular countries and thereby restrict foreign access to that local market. Trade policies important to biotechnology include tariffs and nontariff barriers, such as packaging requirements and nonacceptance of foreign clinical data.

Some governments target selected emerging technologies to promote rapid commercialization. In consultation with experts from academia and industry, they formulate the direction, backed by funds, that technologies should take to ensure rapid commercialization. Countries with targeting policies may have a competitive advantage in commercializing an emerging technology.

The last factor analyzed is how the public perceives the benefits and risks of the technology.

In democratic countries in particular, public perception can promote or undermine the commercialization of an emerging technology. Depending on the nature and intensity of the public's response to an emerging technology, which cannot be readily predicted, public perception could be an overriding factor in the commercialization of a new technology. In the case of biotechnology, the public's perception of an accident or perceived risk could significantly influence the development of the technology.

Firms commercializing biotechnology

In addition to analyzing the factors just discussed, it is also necessary for this competitive assessment to analyze the aggregate level of industrial activity. OTA's industrial analysis, presented in *Chapter 4: Firms Commercializing Biotechnology,* was approached from the following perspectives:

- the number and kinds of companies commercializing biotechnology,
- the commercial areas toward which industrial biotechnology R&D is being directed,
- the interrelationship among the companies applying biotechnology, and
- the overall organization of the commercial effort.

The analysis focused on the United States and then made comparisons with other countries.

U.S. efforts to commercialize biotechnology are currently the strongest in the world. The U.S. strength is in part derived from the unique complementarity that exists between small entrepreneurial firms founded specifically to develop new biotechnology and established companies in a variety of industrial sectors. While the entrepreneurial new biotechnology firms (NBFs) specializing in research-oriented phases of development have been the major force behind the commercialization of biotechnology in the United States to date, the role of established companies is expanding. Established companies have assumed a major share of the responsibility for production and marketing of, and, when necessary, obtaining regulatory approval for, some of the earliest products developed by NBFs. Through equity investments and licensing and contract agreements, these companies have also provided many of the NBFs with the necessary financial and marketing resources to remain solvent. Furthermore, many established companies are now beginning to make substantial contributions to the commercialization of biotechnology in the United States through their increasing investments in their own research and production facilities.

In European countries such as the Federal Republic of Germany, Switzerland, France, and the United Kingdom, biotechnology is being commercialized almost exclusively by large pharmaceutical and chemical companies, many of which already have significant strength in biologically produced product markets. Large established companies are critical to the development of biotechnology in Europe, and they also establish the rate at which biotechnological development takes place. Although such companies have been slow to invest in biotechnology R&D, their inherent financial, production, and marketing strengths will be important factors as the technology continues to emerge internationally.

In Japan, dozens of strong "old biotechnology" companies from several industrial sectors have extensive experience in bioprocess technology, and these large companies are using new biotechnology as a lever to enter profitable and expanding pharmaceutical markets. Japanese companies dominate biologically produced amino acid markets and are also major competitors in new antibiotic markets. They could dominate new specialty chemical markets as well.

Pharmaceutical markets will be the first proving ground for U.S. competitive strength in biotechnology. International competition will be intense. American pharmaceutical and chemical companies will be competing not only against Japanese

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companies, but also against the pharmaceutical and chemical companies of Western Europe, all of whom expect to recover their biotechnology investments through extensive international market penetration.

Results of the analysis

The results of the analysis of the relative importance of the factors affecting the competitive position of the United States and other countries in biotechnology both now and in the future is presented in *Chapter 1: Summary*. Also discussed is the current U.S. competitive position with respect to the other countries analyzed.

Congressional issues and options for improving the competitive position of the United States in biotechnology are discussed at the end of the following chapters. To improve the competitive position of the United States, legislation could be directed toward any of the factors discussed, although coordinated legislation directed toward all the factors might be more effective in promoting U.S. biotechnology.

The chapters that follow discuss only those congressional options that are specific to the development of biotechnology or were pointed out to OTA by U.S. firms commercializing biotechnology. Policy options in some areas are not specific to biotechnology, but to high technology or industry in general. These options are:

- to improve U.S. science and engineering education and the retraining of industrial personnel,
- to ease U.S. antitrust law to promote more research joint ventures among domestic firms,
- to regulate U.S. imports to protect domestic industries,
- to regulate the transfer of technology from the United States to other countries, and
- to target specific industries or technologies for Federal assistance.

There are many arguments for and against these options that are beyond the scope of this report. Because of their broad applicability to industry in general, these options are not discussed in the chapters that follow. It is important to note, however, that legislation in any one of these areas could affect the development of biotechnology.

Chapter 12

Financing and Tax Incentives for Firms

Contents

Tables

Figure

Chapter 12

Financing and Tax Incentives for Firms

Introduction

Two of the most important factors in the development of biotechnology in the United States have been the supply of venture capital to finance the startup and growth of new biotechnology firms (NBFs)* and the tax incentives provided by the U.S. Government to encourage capital formation and stimulate research and development (R&D) in the private sector. As noted in *Chapter 4: Firms Commercializing Biotechnology,* the types of companies commercializing biotechnology in the United States include a large number of NBFs and a smaller yet growing number of established companies from a variety of industrial sectors. In Japan and the European countries, by contrast, it is predominantly established companies that are commercializing biotechnology. A variety of reasons might explain the different nature of foreign commercialization efforts, but certainly of major importance is the fact that venture capital to fund the startup of new companies is not generally available outside the United States.

The first section of this chapter examines financial needs of firms commercializing biotechnology, emphasizing the needs of NBFs in the United States. It also evaluates the sources and availability of capital for firms in the United States and other countries. The second section examines tax incentives for firms. Tax incentives are an indirect source of government funding.** Such incentives can expand or contract the supply of funds available to companies engaged in biotechnology and can thereby affect the overall rate at which biotechnology develops. They also can affect the financial decisionmaking and thus the methods of financing used by companies applying biotechnology.

*NBFs, as defined in *Chapter 4: Firms Commercializing Biotechnology,* are firms established around 1976 or later specifically to pursue applications of biotechnology.

**Direct government funding of basic and applied research is treated in *Chapter 13: Government Funding of Basic and Applied Research.* Direct government funding in the United States is provided exclusively for research. In some countries, notably Japan, the Government provides direct funding to industry. Such funding is discussed in this chapter.

Financing in firms commercializing biotechnology

Starting a new company, expanding the product line of an existing company, and manufacturing an existing product in a new way all require some form of financing. The discussion below outlines the financial needs of U.S. companies applying biotechnology. It also examines the sources and availability of private sector funds to meet these needs. Brief comparisons are made with the five countries likely to be the major competitors of the United States in the commercialization of biotechnology—Japan, the Federal Republic of Germany, the United Kingdom, Switzerland, and France.

Financial needs of firms commercializing biotechnology

As discussed in chapter 4, a distinction can be made in the United States between two types of firms that are active in the commercialization of biotechnology: NBFs and established companies. NBFs, as defined in this report, are firms established around 1976 or later specifically to pursue applications of biotechnology.* Established

*Cetus (U.S.) and Agrigenetics (U.S.), though established before 1976, are included in the NBF category. Cetus was founded to capitalize on classical genetic techniques for product development.

(footnote continued on next page)

companies have considerably longer corporate histories than NBFs and are generally much larger. In Japan, the Federal Republic of Germany, the United Kingdom, Switzerland, and France, efforts to commercialize biotechnology are led by established companies, although the United Kingdom and France do have a few NBFs. Because of their large financial assets, established companies generally do not need external sources of funds for R&D in new areas such as biotechnology. Furthermore, if they do need such funds, established companies are generally able to obtain debt financing. Debt financing, a traditional means to fund corporate growth, is not available to NBFs, because they lack both collateral to secure a loan and sufficient means to repay the lender (27). The discussion in this section, therefore, focuses on the financial needs of NBFs.

(continued)
It showed early interest in biotechnology and began aggressively pursuing product development with the new techniques. Agrigenetics was formed in 1975 to link new genetic research with the seed business. Thus, the behavior and research focus of both Cetus and Agrigenetics places them in the new firm category despite their early founding dates.

Even the most mature NBFs at present have only a few products to generate revenues that can be used to cover operating expenses and provide capital for future growth. In order to generate revenue, as described in chapter 4, NBFs in the United States are currently relying heavily on research contracts. The reliance of entrepreneurial firms on research contracts to generate revenue is almost without parallel, except perhaps for the small firms that do defense contracts.

Table 41 shows profit/loss figures for 18 NBFs in the United States, all of which are publicly held. Of these firms, only three, Cetus, Genentech, and International Genetic Engineering (INGENE), have shown earnings in the most recent fiscal year for which data are available. The favorable financial position of Cetus and Genentech is mostly due to earned interest income from funds obtained in public offerings. However, revenues from sales (including contract research) fall far short of expenses for all three of these companies, and all three are losing money on an operating basis.

As shown in table 42, NBFs' investment in R&D is currently very large in comparison to their op-

Table 41.—Breakdown of Revenues and Net Income/Losses for 18 New Biotechnology Firms in the United States, Fiscal Year 1982 (millions of dollars)

	Operating revenues						
New biotechnology firm	Revenues from research	Contract revenue as a percent of total revenues	Revenues from product sales or royalties	Total	Interest income	Total revenues	Net income/loss[a]
Amgen[b]	$ 0.13	9.4 %		$ 0.13	$ 1.38	$ 1.5	($7.0)
Biogen	12.1	58.8		12.1	8.5	20.6	(3.9)
Biotechnica International	0.031	34		0.031	0.059	0.09	(1.6)
Bio-Technology General	0.15	93		0.15	0.16	0.011	(2.3)
Centocor	2.4	84.2		2.4	0.45	2.85	(2.76)
Cetus	15.2	46.5	$0.79	15.99	16.7	32.7	4.5
Chiron[b]	1.58	92		1.58	0.14	1.72	(2.2)
Damon Biotech	0.81	48		0.81		1.7	(1.38)
Enzo Biochem[c]	0.10	11.2	0.17	0.27	0.62	0.89	(1.25)
Genentech[c]	28.8	88.3		28.8	3.76	32.6	0.625
Genetic Systems	2.2	71.66		2.2	0.87	3.70	(1.0)
Genex	5.2	85.3		5.2	0.67	6.1	(5.6)
Hybridoma Sciences[d]	0.07	73		0.07	0.024	0.095	(0.186)
Hybritech	1.3	27.4	1.8	3.1	1.6	4.75	(7.26)
Integrated Genetics	0.6	60		0.6	0.46	1.0	(1.76)
International Genetic Engineering (Ingene)	1.78	90		1.78	0.211	1.98	0.13
Molecular Genetics	0.66	61		0.66	0.42	1.08	(3.75)
Monoclonal Antibodies[b]	0.10	1.5	0.16	0.26	0.39	6.5	(2.7)

[a] Losses are shown in parentheses.
[b] Fiscal year 1983.
[c] Stock split.
[d] Units offered (one unit=three shares of common stock and three Class A Warrants).

SOURCE: Office of Technology Assessment, based on information from E.F. Hutton & Co., company annual reports, and company prospectuses.

Table 42.—Capital Expenditures, R&D Budgets, and Operating Revenues of Nine New Biotechnology Firms in the United States, Fiscal Year 1982 (millions of dollars)

New biotechnology firm	Capital expenditures	R&D budget	Operating revenues	R&D as a percent of operating revenues
Biogen	$ 8.7	$ 8.7	$12.1	72%
Cetus	22.9	25.9	16.0	143
Enzo Biochem	0.09	1.2	0.3	400
Genentech	31.8	31.9	28.8	111
Genetic Systems	0.46	3.9	2.2	177
Genex	1.8	8.3	5.2	160
Hybritech	1.44	5.0	3.1	161
Molecular Genetics	1.4	2.8	0.66	424
Monoclonal Antibodies	0.57	1.1	0.26	423

SOURCE: Office of Technology Assessment based on information from company annual reports.

erating revenues. Furthermore, NBFs that are incurring large R&D costs to develop products are sustaining large losses relative to their earnings (see table 41).* These losses, which will likely continue for several years, are eroding the capital bases of many NBFs and increasing their need for additional sources of funds. NBFs such as Biogen N.V.** do not expect operating revenues to meet R&D expenses, and consequently do not expect to operate at a profit for at least several years (2). For the next several years, expenditures by NBFs for R&D will probably equal 20 percent or more of sales (27).

*The cumulative losses shown in table 41 understate the level of funding required to sustain these companies because they do not fully reflect capital outlays. Only the depreciated portion of capital outlays shows up in a profit and loss statement and, hence, in cumulative loss (27).

**Biogen N.V., the parent company of the Biogen group, is registered in the Netherlands Antilles but is about 80-percent U.S. owned. Biogen's principal executive offices are located in Switzerland. Biogen N.V. has four principal operating subsidiaries. Biogen Research Corp. (a Massachusetts corporation) and Biogen S.A. (a Swiss corporation) conduct research and development under contract with Biogen N.V. Biogen B.V. (a Dutch corporation) and Biogen Inc. (a Delaware corporation) conduct marketing and licensing operations. Available figures pertaining to Biogen refer to Biogen N.V. and its subsidiaries.

Because of the emphasis on R&D in biotechnology, skilled labor for firms applying biotechnology is relatively more important than labor for firms in other areas. Such labor is also quite expensive. The average Ph. D., supported by two technicians, costs on the order of $150,000 to $175,000 per year with overhead (27). As a result, labor may initially constitute a large percentage of a new firm's operating expenses.

The most revealing indicator of the NBFs' potential need for cash is the *rate* at which such firms are consuming funds. Table 43 shows decreases in working capital for six NBFs. Except for Cetus, which raised an exceptional amount of money in its initial public offering, the drop in working capital for these firms is large compared to their equity capital. In 1981, Genentech used up 21 percent of its ending equity capital, while Molecular Genetics used up 10 percent, and Cetus 12 percent (27). Hybritech increased its working capital by 72 percent of beginning equity in 1981 by means of a public stock offering; by October 1982, however, Hybritech had returned to the public markets to raise additional equity because its

Table 43.—Cash Drain Relative to Equity for Six New Biotechnology Firms in the United States, Fiscal Year 1982 (millions of dollars)

New biotechnology firm	Equity capital	Cash flow[a]	Yearly change in working capital	Cumulative deficit
Biogen	$ 61.9	($3.0)	($12.1)	$10.0
Cetus	128.3	5.7	(15.7)	(0.3)
Genex	13.3	0.6	(9.4)	(2.3)
Genentech	53.1	1.0	(11.4)	(0.03)
Hybritech	17.6	(4.3)	6.3	(12.8)
Molecular Genetics	1.5	(3.6)	(1.6)	(4.0)

[a] Cash flow is sum of net income or loss plus noncash expenses such as depreciation.

SOURCE: Office of Technology Assessment, based on information from company annual reports.

working capital had dropped to 43 percent of stockholder's equity by the end of 1981 (27). Other NBFs, including Monoclonal Antibodies, Genex, and Molecular Genetics, have also had to return to the public market not long after their initial or second public offerings.

The financial needs of NBFs are largely dependent on which market they are trying to enter. To enter each of the markets described below, increasing amounts of funds are necessary.

Contract Research and Development Market. The funding needed to support entry into the contract R&D market is generally less than that required for entering product markets, because research that a firm does for another company, university, or government agency is funded by that organization, often through progress* or advance payments. Most NBFs perform contract R&D to generate revenues to fund their own proprietary research, although the costs of proprietary research generally exceeds their contract research fees (27).

*In Vitro Monoclonal Antibody Diagnostic Products Market.*** The funding needed to support entry into the market for in vitro (used outside the body) monoclonal antibody (MAb) products is more than funding needed to support entry into the contract research market. Because of the small amount of plant and equipment required to develop such products and because of the comparatively low cost of complying with the Food and Drug Administration's (FDA's) testing requirements for in vitro diagnostic products for humans, the financial requirements are relatively low.*** A number of NBFs, including Hybritech, Monoclonal Antibodies, Molecular Genetics, Centocor, and Genetic Systems, have developed in vitro MAb diagnostic products for humans that are "substantially equivalent" to products that FDA has already approved and thus do not require rigorous testing. Other MAb products being developed by these firms are intended for research or production (e.g., separation and purification) purposes and thus do not require FDA approval. Several of these NBFs are within a few quarters of achieving operational profitability for these product lines (27).

*Specialty Chemicals Market.** Specialty chemicals are defined in this report as chemicals whose price exceeds $1 per pound (50¢ per kilogram). These include substances such as enzymes, amino acids, vitamins, fatty acids, and steroids. Most specialty chemicals do not need regulatory approval. For specialty chemicals considered foods or food additives, however, FDA approval is required, and significant funds may be expended to meet FDA requirements. Thus, the amount needed to enter the specialty chemicals market varies depending on the product. In general, though, the amount of funds needed to enter the specialty chemicals market is more than the amount required to enter the contract research market but less than that needed to enter the commodity chemicals market.

*Agricultural Products Market.*** For the animal agricultural market, the R&D cost are very similar to those for pharmaceuticals (in vitro and in vivo products), because many of the products, such as diagnostics, vaccines, and hormones, are essentially the same. However, the regulatory requirements promulgated by the U.S. Department of Agriculture (USDA) and FDA for animal health products are much less stingent than the requirements for pharmaceuticals. Some animal agriculture products (e.g., vaccine for colibacillosis) have received approval and are already reaching the market.

The R&D costs for applications of biotechnology to plant agriculture vary over a broad range. The genetic manipulation of micro-organisms important to plant agriculture, for the most part, is less costly than the genetic manipulation of the plants themselves. Furthermore, the various traits being investigated are at different stages of research. For instance, plants with traits conferring resistance to drought or saline stress are more near term than those with improved photosynthesis or nitrogen fixation. The financial requirements for developing the latter plants are much greater

*Progress payments are received when the contracting company reaches certain milestones in the research project.

**In vitro MAb products are discussed in *Chapter 5: Pharmaceuticals*.

***For a discussion of FDA's regulatory processes, see *Chapter 15: Health, Safety, and Environmental Regulation*.

*Applications of biotechnology to specialty chemicals are discussed in *Chapter 7: Specialty Chemicals and Food Additives*.

**Applications of biotechnology to animal and plant agriculture are discussed in *Chapter 6: Agriculture*.

than those for developing simpler genetic applications. Firms doing research in the more complex agricultural applications of rDNA technology are unlikely to have commercial products available until the late 1980's or 1990's. Some companies, such as Plant Genetics (U.S.), hope to finance themselves through the research period by developing commercial products using conventional plant genetics (27).

*In Vivo Diagnostic and Therapeutic Products Market.** The financial requirements for entering the market for in vivo (inside the body) diagnostic and therapeutic products for human use are very large, in part because such products require extensive clinical testing to meet FDA regulatory requirements. Taking a pharmaceutical product from research to market in the United States generally requires 7 to 10 years and costs $70 million or more (14). To date, no NBFs attempting to enter this field are operationally profitable, nor are they likely to be in the near future (27). Hybritech, for example, does not anticipate profitability for its therapeutic line until about 1988 (26).

*Commodity Chemicals Market.*** For several reasons, the financial requirements for entering the commodity chemicals market are the largest. Currently, practically all commodity chemicals, defined in this report as chemicals that sell for less than $1 per pound, are made from petroleum feedstocks. Although it is theoretically possible to produce essentially all commodity chemicals from biomass feedstocks such as starch or cellulose, and most commodity chemicals can be synthesized biologically, most commodity chemicals derived from biomass cannot yet compete economically with chemicals made from petroleum in the highly integrated production infrastructure that now exists. Furthermore, profitability in commodity chemicals requires the achievement of economies of scale in production plants costing hundreds of millions of dollars (27).

*Applications of biotechnology to in vivo diagnostic and therapeutic products intended for human use are discussed in *Chapter 5: Pharmaceuticals*.

**Applications of biotechnology to commodity chemical production are discussed in *Chapter 9: Commodity Chemicals and Energy Production*.

With the exception of firms developing in vitro MAb assays and diagnostic products, it will be some time before NBFs, most of which are U.S. companies, can be self-financing; some estimate that NBFs cannot be self-financing before the late 1980's (27). The new firms must finance not only losses due to operating expenses but also expenditures needed for capital assets. For some NBFs, meeting FDA regulatory requirements will also require substantial funds. Because, as noted earlier, debt financing may not be available to many NBFs, the financial needs of these firms must for the most part be met by additions to equity capital (27). Thus, in many cases, the receptivity of the public market to NBF stock issues and the use of R&D limited partnerships is a matter of great importance.

Sources and availability of financing for U.S. firms

The sources and availability of financing for the two types of firms that are important to the development of biotechnology in the United States—i.e., NBFs and established companies—are quite different. The discussion below, therefore, treats each type of firm separately.

NEW BIOTECHNOLOGY FIRMS

The main sources of financing for NBFs, the small, new firms specializing in biotechnology, are the following:

- revenues from contract research and interest on cash previously obtained from public or private offerings;
- various sources of venture capital; and
- public stock offerings.

Revenues From Contract Research, Product Sales or Royalties, and Interest.—Research and product development agreements between NBFs and established companies are generally cost reimbursement contracts with additional fees and incentives for reaching agreed on milestones. The NBF generally retains the patent rights to any technology involved and grants the contracting company an exclusive license to that

technology. Thus, such agreements usually provide for royalty payments to the NBF by the established company on the future sales of the product that results from the R&D work; these royalties may range from 2 to 10 percent of total sales, depending on the size of the product market.

Table 41 breaks down total fiscal year 1982 revenues for 18 NBFs into operating revenues received from contract research or product sales or royalties and interest income. In most NBFs, no income or very limited income was obtained from the sale or licensing of products. Most revenue, even for the larger NBFs such as Genentech, Cetus, and Biogen, was contract revenue and interest on cash raised through public offerings and private investment. Genentech reports, for example, that 88 percent of its total $32.6 million revenue in 1982 was derived from contracts and the balance derived from interest income. Cetus reports that, in fiscal year 1982 (which ended in June 1982), income from contracts accounted for almost 47 percent of its total revenues and interest income for most of the remainder. Similarly, Biogen reports that 59 percent of its revenue comes from contract sales with the balance being interest income.

Biogen and Genentech are concentrating on product development using rDNA technology. Some NBFs, including Genetic Systems, Monoclonal Antibodies, Centocor, and Hybritech, are developing MAbs for in vitro assays, diagnostics, and research products. These firms will probably achieve an income stream from product sales more quickly. In fiscal year 1982, however, these firms also show primarily interest income. Currently, Hybritech has the greatest percentage of total revenue coming from product sales, 38 percent. In the near future, product sales should contribute more substantially to revenues for Hybritech as well as other diagnostic product companies.

Venture Capital.—In the United States, there are several sources of venture capital. These are:

- corporate venture capital,
- R&D limited partnerships,
- venture capital funds, and
- Small Business Investment Corporations (SBICs).

Each of these is discussed further below.

From 1969 to 1977, the total venture capital pool in the United States remained relatively unchanged, at the level of about $2.5 billion to $3 billion each year (27). Since then, however, the venture capital pool has increased sharply, reaching between $3.5 billion and $4 billion in 1979 (45), $5.8 billion in 1981 (46), and an estimated $7.5 billion as of the end of 1982 (48).

Variability in the amount of venture capital in the United States is influenced by many factors. These include general macroeconomic variables (e.g., interest rates and inflation), changes in capital gains tax laws, and changes in pension fund investment rules. In 1969, the U.S. capital gains tax was increased from 29 to 49 percent. In addition, the U.S. inflation rate increased sharply in 1972, causing investors to seek a much higher rate of return on their investments. In 1973-74, the price index of the National Association of Security Dealers Quotation of over-the-counter securities, which represents smaller companies, declined more than did the Dow-Jones industrial price index, which represents larger companies (27), indicating a decline in investor interest in newer, smaller firms relative to larger, more established companies.

Recent changes in U.S. laws and regulations affecting the formation of venture capital have led to a resurgence in the supply of venture capital in this country. In 1979, Employee Retirement Income Security Act pension fund regulations were interpreted to allow some pension fund money to flow into venture capital investments. Around the same time, the Securities and Exchange Commission adopted Rule 144 allowing founders of companies to liquidate their "restricted" stock holdings sooner than previously allowed. The opportunity to liquidate sooner provides investors with a stronger incentive to invest. Especially important to the supply of venture capital in the United States have been decreases in the rate at which long-term capital gains are taxed. The current long-term capital gains tax rate for individuals, established under the Economic Recovery Act of 1981, is 20 percent (28 percent for corporations), making venture investments even more attractive than they were under the pre-1969 rate of 29 percent.

Table 44 shows the distribution of venture capital disbursements in the United States by industry for 1980 and 1981. In 1980, investments in "genetic engineering"* accounted for 4.2 percent of the total number of investments but 7.6 percent of the dollars invested. In 1981, "genetic engineering" accounted for 6.2 percent of the number of investments but absorbed 11.2 percent of venture dollars. The disproportionately large average size of "genetic engineering" investments reflects the fact that a large amount of funds must be dedicated to R&D before a concept is proven. In other high-technology industries, "seed money" is usually sought to prove a concept and averages around $1 million per project. But in biotechnology, seed money and startup financing from venture capitalists is generally combined to obtain enough money for product development and initial marketing. Financing for biotechnology projects averaged about $2.2 million per project in 1982 (27). As shown in table 45, seed money is a very small percentage of total venture capital disbursements in the United States. In biotechnology, venture investments have tended to combine both seed and startup financing, making the average disbursement disproportionately high.

The peak period for raising venture capital in biotechnology in the United States occurred in 1980. That year, the valuations of NBFs ranged from $5 million to $25 million for 25 percent of the company (41). The stock market decline of 1981-82 was accompanied by changes in the venture capital market with respect to biotechnology ventures. Valuations of NBFs ranging from $2 mil-

*A definition of "genetic engineering" was not given by the *Venture Capital Journal*.

Table 44.—Distribution of Venture Capital Disbursements in the United States by Industry, 1980 and 1981

	Percent of total number of investments		Percent of dollar amount invested	
	1980	1981	1980	1981
Communications	11.5%	11.4%	10.9%	11.2%
Computer related	27.4	30.0	25.7	34.3
Other electronics related	9.6	14.5	9.6	13.1
Genetic engineering	4.2	6.2	7.6	11.2
Medical/Health related	10.5	7.0	9.3	5.8
Energy	8.3	4.9	19.9	5.8
Consumer related	7.5	4.9	3.7	1.9
Industrial automation	4.5	6.2	2.7	5.3
Industrial products	3.6	4.4	2.0	3.4
Other	12.9	10.5	8.6	8.0
Total	100.0%	100.0%	100.0%	100.0%

SOURCE: *Venture Capital Journal* 22(6):8, June 1982.

Table 45.—Distribution of Venture Capital Disbursements in the United States by Stage of Investment, 1981

	Percent of number of investments		Percent of dollar amount of investments		Average size of venture financing
State of investment	Venture development	Total activity	Venture development	Total activity	($000)
Seed	4%		2%		$1,000
Startup	26		31		2,200
Other early stage	19		19		2,000
Total early stage	49%	39%	52%	46%	$2,000
Expansion	51	40	48	41	$1,750
Total	100%	79%	100%	87%	$1,900
Other		10%		8%	1,850
Stage unrecorded		11		5	900
Total		100%		100%	

SOURCE: *Venture Capital Journal* 22(6):9, June 1982.

lion to $4 million for 40 to 50 percent of the company became more common. The following two factors may have accounted for the decrease in the valuation of NBFs in 1981 and 1982:

- increased investor knowledge of the time that would be required for commercializing applications of biotechnology, and
- decreased investor interest in biotechnology because most venture capitalists who desired to invest in an NBF had already done so.

At least one venture capitalist stated that the number of new proposals based on biotechnology decreased substantially from 1981 to 1982 (27). Possible reasons for the decrease in proposals include the following:

- the existence of many competing companies in each of the major application areas discouraged additional entrants, and
- the fact that many of the scientist/entrepreneurs who wanted to form a new firm had already done so.

Table 46 shows the cost of venture capital for selected NBFs in the United States, although it should be noted that few general rules can be determined from this table. Genentech and Hybritech, which the venture capital firm Kleiner, Perkins, Caulfield, and Byer partly organized as well as financed, turned out to be particularly good investments. For Hybritech, a $300,000 investment initially purchased 72 percent of the company at a price of $0.20 per share. At the time of the public offering at $26.75 per share, Kleiner, Perkins, Caulfield, and Byer held 29.3 percent of Hybritech worth $1.7 million. For Genentech, a $200,000 investment eventually equated to 14.3 percent of the common stock ($0.21 share cost) worth around $33 million at the time of the public offering. Wilmington Securities, a later investor in Genentech, purchased 6.2 percent of the company for $500,000 or $2 per share of a stock that went public at $35. Lubrizol, a still later investor in Genentech, paid $10 million for 24 percent of the company or $6.43 per share.

Table 47 contrasts the private valuations and public (market) valuations of some recently offered NBF issues. Hybridoma Sciences exhibits the greatest increase in valuation (and thus the highest rate of return to original investors) in the shortest period of time—over 1,100 percent in just over 2 years.

The four sources of venture capital in the United States, which were mentioned at the beginning of this section, are discussed further below. Independent private venture capital funds have accounted for an increasing share of total venture capital relative to that provided by corporate investors and SBICs, as shown in table 48.

Corporate venture capital. A number of major corporations provide revenue to NBFs through R&D contracts as well as equity investments and joint ventures. Contractual relationships provide benefits to the corporate investors as well as the NBF. *Chapter 4: Firms Commercializing Biotech-*

Table 46.—Cost of Venture Capital for Selected New Biotechnology Firms in the United States

	Private venture capital			
New biotechnolcgy firm	Venture capital invested	Percent of company purchased	Price per share	Price per share in public offering
Cetus:				$23.00
1st stage	$ 1,999,600	16.5%	$ 0.91	
SOCal—2d round	5,000,000	10.4	3.60	
Genentech:				35.00
Wilmington Securities, early stage	500,000	6.2	2.00	
Lubrizol	10,000,000	24.0	6.43	
Genetic Systems	200,000	9.7	0.51	6.00
Hybritech	300,000	72.0	0.20	26.75
Molecular Genetics:				9.00
Founders	40,560	59.9	0.02	
Sale of 632,366 shares to American Cyanamid	2,750,000	18.7	4.35	
Monoclonal Antibodies	825,116	29.2	0.52	10.00

SOURCE: Office of Technology Assessment, based on information from company prospectuses.

Table 47.—Comparison of Private and Public (Market) Valuations of Eight New Biotechnology Firms With Initial Public Offering in 1983 (millions of dollars except offering price per share)

New biotechnology firm	Date company founded	Private valuation[a]	Date of initial public offering	Public valuation		Ratio of private valuation to public valuation
				Offering price and millions of shares offered	Total market valuation and millions of shares outstanding	
Amgen	1980	$54—Feb. 1981	6/17/83	$18 2.35	$187 10.4	1:3.5
Advanced Genetic Sciences	3/79	$48—April 1981	7/83	$20[b] 2.0	$242[b] 12.2	1:5
Biogen	1978	$100—April 1981	3/83	$23 2.5	$425 18.5	1:4.25
Cambridge Bioscience	3/81	$8.3—July 1982	3/31/83	$ 5 1.0	$ 20.3 4.08	1:2.4
Chiron	5/81	$29—April 1983	8/83	$12 1.5	$ 87.6 7.3	1:3
Hybridoma Sciences	4/81	$2.2—Feb. 1983	8/83[b]	$ 6[c] 0.70	$ 25.7 4.29	1:11.7
Immunex	7/81	$10.5—July 1982	7/1/83	$11 1.65	$ 64.3 5.85	1:6.1
Integrated Genetics	1981	$33.3—Dec. 1982	7/19/83	$13 1.6	$107.9 8.3	1:3.2

[a]Based on most recent transaction.
[b]Estimated
[c]One unit. One unit = three shares common stock and three Class A Warrants.

SOURCE: Office Technology Assessment, adapted from E. F. Hutton, prepared July 18, 1983.

Table 48.—U.S. Venture Capital Pool, 1977 and 1982 (millions of dollars)

	1977	Percent of total	1982	Percent of total
Independent private funds and venture capital partnerships	$ 887	35%	$4,400	58%
SBICs (exclusive of nonventure capital related SBICs)	612	24	1,300	17
Corporate (financial and industrial subsidiaries and non-SBIC public funds)	1,022	41	1,900	25
Total pool	$2,521	100%	$7,600	100%

SOURCE: *Venture Capital Journal* 22(10):7, October 1982.

nology provides a discussion of these joint ventures and the costs and benefits accruing to both parties. Table 13 in chapter 4, entitled "Equity Investments in New Biotechnology Firms by U.S. Established Companies, 1977-1983," summarizes established U.S. firm equity investments in and joint equity ventures with NBFs.

R&D limited partnerships. R&D limited partnerships, consisting of at least one general and one limited partner, are a financing mechanism that allows businesses to engage in research activities without paying for the activities out of retained earnings or borrowed capital.* Most of the 300 to 400 R&D limited partnerships that exist in the United States have been formed since 1980 (29).

From August 1982 to May 1983, over $200 million was raised through R&D limited partnerships by NBFs alone (4). One analyst estimates that R&D limited partnerships will raise a total of $500 million in 1983 (3). In R&D limited partnerships in biotechnology, the NBF typically serves as the general partner and assumes liability. The limited partners are the investors whose money buys a share of the partnership's future profits or losses. The liability of the limited partners is limited to the loss of their investment. More than 10 R&D limited partnerships in biotechnology have been formed since 1980, and 10 to 20 more are now being formed (40).

Such partnerships have enabled NBFs to reduce their reliance for financing on established companies and venture capital firms and to reduce their costs of capital. They have also provided many NBFs with a stable source of financing for the next 4 to 5 years—the time frame written into most of the partnerships. In other words, R&D limited partnerships are providing NBFs with the financial ability to undertake their own proprietary research and early product development and in some cases clinical testing without relying on established companies and venture capital firms.

As shown in table 49, the total amount raised by 12 NBFs for R&D limited partnerships in biotechnology exceeds $400 million. The amount raised for each partnership ranged from just under $1 million (Neogen) to $80 million (Cetus). The first NBF to raise a fairly large amount of money ($55 million) through an R&D limited partnership was Agrigenetics. Genentech, which is using an R&D limited partnership as a novel approach to financing clinical trials of human growth hormone and gamma interferon, raised

Table 49.—R&D Limited Partnerships Used by 12 New Biotechnology Firms in the United States

New biotechnology firm	Partnership formation date	Amount (millions of dollars)
Agrigenetics	1981	$ 55.0
Genetic Systems	1982	3.4
Cetus	1982	80.0
California Biotechnology	1982	27.5
Genentech	1982	55.0
Molecular Genetics	1982	11.1
Neogen	1982	0.96
Hybritech	1982	7.5
Cetus	1983	78.0
Genentech	1983	34.0
Genetics Institute	1983[a]	25.0
Serono Labs	1983	29.0
Total		$405.46

[a] As of 8/83 not yet closed.

SOURCE: Office of Technology Assessment, based on information from the trade press and company reports.

*The U.S. Supreme Court decision in the 1974 precendent-setting *Snow* v. *Commissioner* (416 U.S. 500) held that limited partners could offset their other income with partnership research or other experimental expenditures. It also extended the reach of section 174 (Title 26 U.S.C. IRS §174) to include businesses that had not yet offered any products for sale.

$34 million (27). R&D limited partnerships can provide more financing than the average amount raised by NBFs in the most recent initial public stock offerings (see below).

One advantage to the general partner in an R&D limited partnership is the fact that partnership funds appear on the corporate balance sheet as contract revenue rather than as debt or equity, thus enhancing future investment prospects. Another advantage for the general partner is that the limited partners do not participate in the management of the partnership; in this respect, an R&D limited partnership is unlike other forms of equity financing where investors may sit on the board of directors and shareholders vote on major management decisions.

The limited partner (investor) in an R&D limited partnership is generally interested in investing in such a partnership because R&D limited partnerships, unlike corporations, are treated under the U.S. Internal Revenue Service (IRS) Code as nontaxable entities, meaning that partnership profits and losses are "passed through" to the individual partners who then combine them with their other items of income and expense.* Since an R&D project typically generates tax losses in its initial years (because of large R&D expenditures), limited partners can use those losses immediately to offset other income which might be taxable at rates as high as 70 percent. Furthermore, partners can deduct as much as 85 to 95 percent of their initial investment, immediately decreasing their after-tax cost (and risk) and more than doubling the potential rate of return.

Venture capital funds. Venture capital funds are professionally managed funds dedicated to investment in one or more industries. Sources of capital for these funds include pension funds (e.g., John Deere, General Electric, and Ohio Public Employees Retirement Fund), insurance companies (e.g., Wausau Insurance, Prudential Life, and Metropolitan Life), trust departments of commercial banks such as Morgan Stanley or City Bank, and corporate investors interested in potential profit from discoveries arising from the fund's support.

Of interest is the fact that a few independent private venture capital funds have been formed to invest a significant percentage of their funds in biotechnology. One example is Plant Resources Venture Fund, a $15 million to $20 million fund that invests in companies doing plant-related R&D. In the first 18 months of its operation, this fund invested in three companies, taking all the outside equity in each. Two of the companies are engaged in tissue culture research and the other is a plant genetics company. The strategy of the Plant Resources Venture Fund is to invest $500,000 to $1.75 million in each company in several stages. In first-stage financing, the fund expects to assume the major share of investment. In subsequent financings, the fund will take progressively smaller amounts as other investors are brought in. Plant Resources Venture Fund anticipates financing another seven to nine companies by 1984 (10).

Small Business Investment Corporations. In 1982, approximately 17 percent of the venture capital funds in the United States were raised by SBICs. SBICs are private companies licensed by the Small Business Administration (SBA) that must invest their funds in U.S. small businesses. There are three major groups of SBICs: 1) bank affiliates, 2) subsidiaries of venture capital and other financial companies, and 3) independent SBICs and units of nonfinancial companies. Each SBIC must have paid-in equity capital contributed by shareholders of at least $500,000. After the paid-in capital requirement is met, SBA will loan up to three times the paid-in amount of capital, thus extending the resources of the SBIC. In effect, SBICs leverage their paid-in capital by four times with SBA's assistance. SBICs obtain funds from SBA at very favorable interest rates, several points below the prime rate. They then lend the money to small businesses at a rate that is higher than the rate at which they have obtained it but still less than the prevailing rate.

An SBIC provides at least three kinds of tax advantages for shareholders (34). First, a loss on the sale or exchange of the stock can be treated by stockholders as an ordinary loss, i.e., such loss does not have to be offset against gains from sales of stock, and it can be regarded as a business loss for net operating loss deduction purposes. Second, a loss on the sale or exchange of convertible debentures purchased from small businesses (or stock obtained through conversion) can be

*Corporate profits, by contrast, are taxed both at the corporate and the shareholder level, and deductions for losses incurred by the corporation are not available to the individual shareholders.

treated by the company as an ordinary loss. Third, rather than the normal 85-percent deduction for dividends received from domestic corporations, the company gets a 100-percent dividends received deduction.*

For NBFs that might want to use funds from SBICs, there are two problems. First, because SBICs obtain much of their money as loans from SBA and must repay the SBA in a prescribed period of time, SBICs lend their money rather than use it to buy stock in small businesses. However, an increasing number of equity investments are being made by SBIC bank affiliates such as First Capital Corp. of Chicago. Most NBFs do not seek money from SBICs, because such firms need to retain dollars internally rather than use them to pay interest on debt to an SBIC. Second, SBICs do not generally commit public funds guaranteed by public institutions to high-risk ventures, which is exactly what NBFs are. However, in spite of the interest risks associated with investments in new high-technology firms, some SBICs have invested in NBFs. SBICs raised $4,108,197 in capital for NBFs in 1981 and $3,383,333 in 1982 (50).* They invested in 15 NBFs in 1981 and 9 NBFs in 1982. Thus, although the total amount of capital invested by SBICs decreased from 1981 to 1982, the average amount of capital invested per company increased.

Public Stock Offerings.—Public offerings can be divided into initial public offerings, the first time a firm attempts to raise money by offering shares in itself to the public, and subsequent public offerings, when the firm returns to the market to raise additional funds. As a way to obtain funds, the initial public offering differs in an important way from the other methods for raising funds that have already been discussed. The initial public offering is the first time that the firm must publicly disclose its financial and product development status. Going public also requires registration with an oversight organization, the Securities and Exchange Commission, and commits the firm to continued public scrutiny through publicly available reports to shareholders and annual statements to the Securities and Exchange Commission (Form 10-K). Meeting the requirements for public accountability is expensive, both in time and money, and meeting the earnings expectations of the investors can inhibit long-term R&D. In confirmation, Gabriel Schmergel of Genetics Institute in Boston says "reasons why companies haven't gone public is because sometimes they are under great pressure to produce earnings" (18). Thus, although a great deal of money can be raised in a public offering, its costs, both fiscal and otherwise, must also be considered.

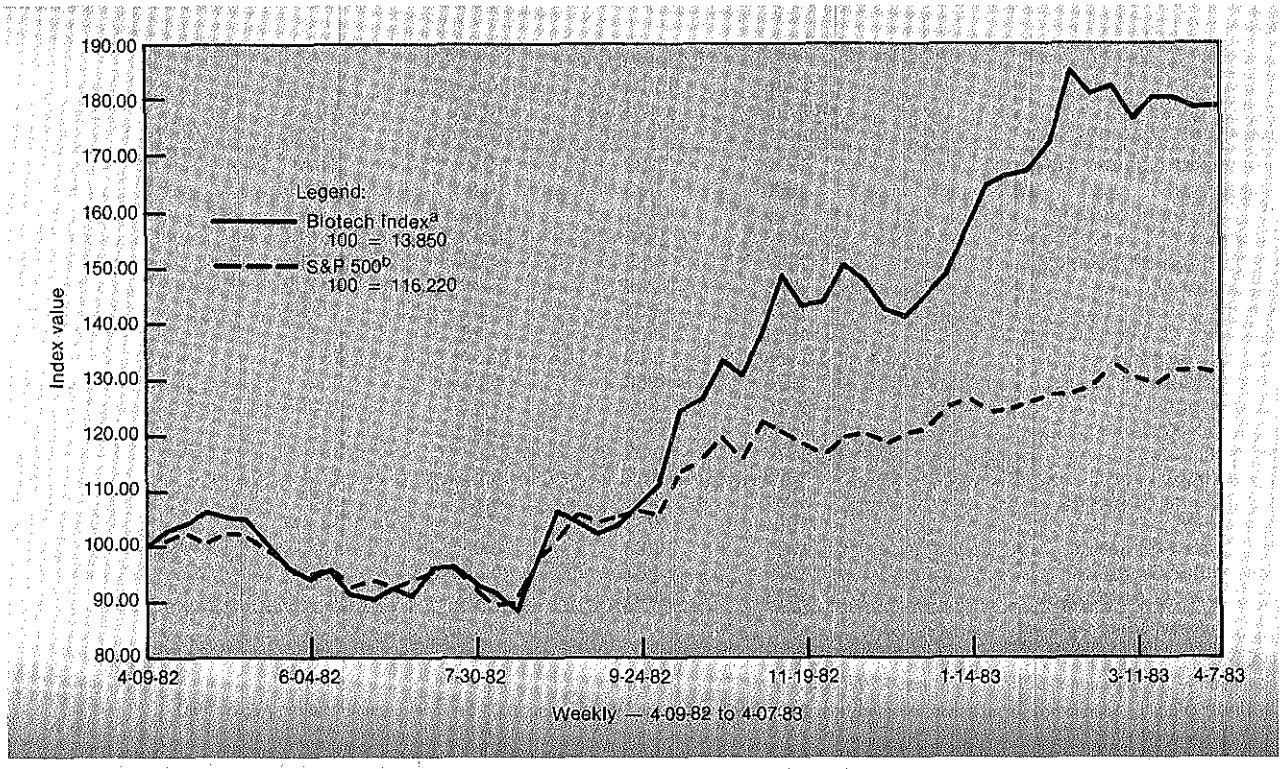
The amount that a firm can raise through a public offering depends not only on the performance of the firm itself but also on the stock market and the receptiveness of investors. In times of recession, institutional investors tend to undervalue high-technology stocks because they are interested in short-term gains (16). Yet, during the early 1980's, despite the recession, high-technology issues were fairly successful, with the peak years for biotechnology stocks being 1980 and 1981. In 1982, some NBFs that made public offerings were not able to raise as much as they had expected. Until September of 1982, the performance of biotechnology stocks paraleled that of Standard and Poor stocks. After September, however, the biotechnology stocks outperformed the Standard and Poor stocks. Thus far, the 1983 bull market has been accompanied by a boom in new issues, greater in magnitude and scale than ever before. For biotechnology issues, 1983 is a banner year. Between March and July of 1983, 23 NBFs raised about $450 million (18). Figure 30 provides a comparative market performance of some MAb, rDNA, and biotechnology support companies with the Standard and Poor 500 for the period April 1982 through April 1983..

During the 1970's, venture capitalists were accustomed to waiting 5 to 7 years before seeing their investments achieve liquidity in the public markets. With the advent of the microprocessor, a number of electronic companies developed applications that became profitable quickly. In some cases, these companies were able to achieve profitability in 18 months and a public offering within 2 to 3 years from founding, in part because of better capital markets after 1978 (8). As a result,

*A corporation pays tax on dividends distributed. The dividend is also taxed as part of income of the distributee. To partially compensate for this double taxation, if the distributee is a corporation, 85 percent of dividends received is excluded from this second taxation. However, if the corporation is an SBIC, 100 percent of dividends received is excluded.

*The 1982 figures available from the SBA did not include November and December figures.

Figure 30.—Comparative Market Performance: Companies Using Biotechnology vs. Standard and Poor's 500 Companies, April 1982 through April 1983



[a]Biotech index includes A. B. Fortia, Bioresponse, Cetus, Damon, Enzo-Biochem, Flow-General, Genentech, Genetic Systems, Hybritech, Monoclonal Antibodies, Novo Industri A/S. OTA did not include A. B. Fortia or Flow General as companies using biotechnology.
[b]Standard and Poor's 500 is an index of a broad cross section of companies traded on American stock exchanges.

SOURCE: Office of Technology Assessment, adapted from E. F. Hutton.

some venture capitalists may have shortened their investment time horizons (41), a development that now might be affecting the time taken to bring NBFs to the public market. Table 50 shows the elapsed time between company founding date and initial public offering for 19 NBFs.

The number of, and the amount of money raised in, initial public offerings in all industrial sectors in the United States over the past 10 years is shown in table 51. As can be seen, both the number of offerings and the amount raised first decreased and then increased dramatically. The years 1981 and 1982 were record years for new stock offerings, both in the number of offerings and in the amount raised (though the total amount raised in 1982 was 25 percent less than the amount raised in 1981). Not since the boom of the late 1960's, however, has the new issues market been as active as in 1983.

The initial public offering history and market valuations as of July 1983 for 19 NBFs is shown in table 50. No NBFs made offerings prior to 1980. Two firms went public in 1980, five in 1981, and three in 1982; as of August 1, nine had gone public in 1983. The drop in the number of biotechnology public offerings between 1981 and 1982 parallels the drop in initial public offerings in all sectors during the same period (table 51).

The first recognized "biotechnology firm" to go public, in October 1979, was BioResponse,* with an offering of 1,320,000 units** at $2.50 per share. Thus, the total raised was $3.3 million. It is interesting to note that at the time of the initial public offering, BioResponse had no revenues and a negative net worth of more than $600,000.

*BioResponse was founded in 1972 and is not included here as an NBF.

**One unit = one share of common stock plus one warrant.

Table 50.—Initial Public Offering History and Market Valuations as of July 1983 for 19 New Biotechnology Firms in the United States

New biotechnology firm	Date company founded	Date of initial public offering	Market valuation as of July 1983: Millions of shares outstanding	Price per share as of 7/15/83	Market value (millions of dollars)
Advanced Genetic Sciences	1979	7/83	12.2	N/A[a]	N/A
Amgen	1980	7/83	10.0	$13 3/8	133.75
BioCell Technology	1980	8/81	N/A	1/2	N/A
Biogen	1978	3/83	18.5	15 3/4	291.375
Cambridge Bioscience	1981	4/83	4.08	11 3/4	48.175
Centocor	1979	12/82	5.3	17 1/2	92.75
Cetus	1971	3/81	22.0	17 1/4	379.5
Chiron[a]	1981	8/83	7.28	12[b]	87.4
Damon Biotech	1983	6/83	19.5	16	312
Enzo Biochem[c]	1976	6/80	5.8	30	174
Genentech[c]	1976	10/80	1.4	46 3/4	65.45
Genetic Systems	1980	6/81	1.8	14	25.2
Genex	1977	9/82	12.6	19	239.4
Hybritech	1978	10/81	10.3	27 1/4	280.67
Hybridoma Sciences	1981	8/83	4.29	6[b,d]	25.7
Immunex	1981	7/83	5.7	13 1/4	7.5
Integrated Genetics	1981	6/83	8.3	13	107.9
Molecular Genetics	1979	4/82	6.13	18 3/4	114.94
Monoclonal Antibodies	1979	8/81	2.4	18 3/4	45

[a]N/A—Information not available.
[b]After public offering August 1983.
[c]Stock split.
[d]One unit = 3 shares common stock + 3 Class A Warrants.

SOURCE: Office of Technology Assessment, adapted from E.F. Hutton & Co., Inc., Washington, D.C., personal communication, August 1983.

Table 51.—Number of Initial Public Offerings and Amount Raised in All Industrial Sectors in the United States, 1972-83

Year	Number of initial public offerings	Amount raised[a] (millions of dollars)
1972	568	$2,700
1973	100	330
1974	15	51
1975	15	265
1976	34	234
1977	40	153
1978	45	249
1979	81	506
1980	237	1,400
1981	448	3,200
1982[b]	222	1,470
1983[a,b]	516	7,900

[a]Through August 1983.
[b]Howard & Co., Philadelphia, personal communication 1983.

SOURCE: Office of Technology Assessment, adapted from K. Farrell, "Going Public 1982," *Venture*, April 1982, p. 30.

No revenues had been recorded by September 1982 (27), yet stock in BioResponse is trading in 1983 at about $13 per share. The successful experience of BioResponse established a precedent for bringing NBFs with similar financial characteristics to the market.

The history of the initial public offering of BioResponse illustrates the extraordinary investor interest in firms commercializing biotechnology. Indeed, biotechnology has produced two "firsts" on Wall Street. In 1980, Genentech set a new record with a price rise from $35 to $89 per share in the first 20 minutes of trading in its initial public offering. In 1981, Cetus set a new high for an initial public offering—$120 million (net amount was $107 million). Even in 1983, the best year ever for raising money for biotechnology, few products had been introduced.

Public offerings in 1982 were less successful than had been hoped for, probably because of an increasing realization by the public that the fruits of biotechnology R&D might be more distant than was first anticipated and also because the stock market was depressed in 1982. Thus, Collaborative Research in February of 1982 raised less than half of the $28.5 million it had hoped to raise in its initial public offering, while Molecular Genetics obtained only $3.3 million, less than one-third of its goal. Genex, in a 2.5 million share initial offering, sought to raise about $30 million to sup-

port scale-up of its research products, but first day over-the-counter sales totaled only about 1 million shares, and the closing price was $9 rather than the $10 to $12 initially predicted.

The boom in the 1983 public offerings market has provided many new firms including NBFs, with capital. Venture capital for NBFs increasingly difficult to obtain, the result being that public offerings in 1983 are supplying second- and third-round financing. NBFs that are either seeking or already have raised second- and third-round financing in 1983 include Cambridge BioScience, Damon Biotech, Molecular Genetics, Biotechnica, Genetics Institute, Biogen, Integrated Genetics, Applied BioSystems, California Biotechnology/ Synergen, DNA Plant Technology, Amgen, Hybridoma Sciences, INGENE, Advanced Genetic Sciences, Biotechnology General, Immunex, and Chiron. Table 52 lists some recent initial public offerings by NBFs and the amounts raised.

The price/earnings ratios for NBFs appear high in 1983, given their negative or low earnings records. Continued reliance on the public market for funds will place increased pressure on public NBFs to earn a profitable income stream quickly. If products are not manufactured and income generated within the time frame demanded by investors in the stock market, NBFs will face additional financial constraints. If they have to rely on the stock market and R&D limited partnerships for funds, NBFs might face problems in financing the long-term risky research in scale-up processes that is needed to commercialize biotechnology products.

ESTABLISHED COMPANIES

Established U.S. companies like Eli Lilly, DuPont, and Monsanto can finance their entry into biotechnology using internal funds generated from a variety of sources, (e.g., the sale of products, interest income on capital, and other sources). Such companies also have ready access to debt financing (e.g., loans) or through debt offerings and the sale of bonds. The cost of borrowing is less for established companies than for new companies, because financing is available to established companies at or near the prime rate. Those NBFs that are able to qualify for loans may pay 2 or 3 percentage points over the prime rate (27). In sum, for established U.S. companies considering commercial applications of biotechnology, the question is not whether financing is available, but whether or not to spend their sizable resources (or those that they borrow) on the new commercial pursuits of biotechnology.

To illustrate the magnitude of established company resources to enter biotechnology, a few examples can be noted. In 1981, DuPont budgeted $120 million for biotechnology R&D out of a total R&D budget of $570 million (19). In 1982, DuPont began construction of a new $85 million life sciences center, and it acquired New England Nuclear (U.S.) for $340 million, in part to expand its capability in the life sciences. As another example, in 1984, Eli Lilly expects to complete a $60 million research center that will emphasize rDNA and immunological applications of biotechnology (13). The annual R&D budgets of established U.S. companies such as DuPont and Eli Lilly dwarf the

Table 52.—Amounts Raised in Recent Initial Public Offerings by Six New Biotechnology Firms

New biotechnology firm	Date of initial public offering	Shares offered (in millions)	Offering price per share	Amount raised (millions of dollars)
Amgen	6/83	2.35	$ 18	$ 42.3
Biogen	3/83	2.5	23	57.5
Cambridge Biosciences	3/83	1.0	5	5.00
Chiron	8/83	1.5	12	18.0
Immunex	7/83	1.65	11	18.15
Integrated Genetics	7/83	1.6	13	20.8

SOURCE: Office of Technology Assessment, adapted from E.F. Hutton & Co., Inc., Washington, D.C., personal communication, July 18, 1983.

amounts that have been raised by NBFs in the United States in even the most successful public stock offerings. In 1981, for example, the NBF Cetus raised a record breaking $120 million in its initial public offering—a little more than 20 percent of DuPont's annual R&D budget.

Sources and availability of financing for firms in other countries

The sources and availability of financing for companies commercializing biotechnology in Japan, the Federal Republic of Germany, the United Kingdom, Switzerland, and France—the five countries considered the major competitors of the United States in the area of biotechnology—are outlined in the discussion below.

JAPAN

As noted in *Chapter 4: Firms Commercializing Biotechnology,* predominantly large established companies are developing biotechnology in Japan. Established companies in Japan, like those in the United States, are able to rely on debt financing or revenues generated from the sale of products and other internal sources of funds to finance their entry in the field of biotechnology.

The industrial and financial structures of Japan are very different from those of the United States and most European countries. In Japan, equity markets are relatively unimportant for allocating capital. Instead of raising capital by sharing equity, Japanese companies continue to favor debt financing.* The emphasis on personal savings by Japanese families has produced a large pool of funds in banks and postal savings accounts, and these funds are lent to Japanese corporations. Thus, private sector financing of biotechnology in Japan is usually mediated through the banking system.

NBFs, especially prevalent in the United States, and to a lesser extent in the United Kingdom and France, are not found in Japan because of the low level of equity funds there (39).* Public offerings, venture capital, and other equity instruments are of relatively minor importance there. The low level of equity funding available in Japan is illustrated by comparing the over-the-counter securities markets in Japan with those in the United States. About 111 companies are traded on the Japanese market, compared to 13,000 in the United States. Differences in venture capital investments are also indicative of the relative importance of venture capital in the two countries. In 1982, venture capital investments in Japan amounted to about $84 million, whereas those in the United States amounted to $5.8 billion (6). The low level of interest by Japanese investors in venture capital is further shown by the fact that a venture capital firm established in July 1982 by the Daiwa Securities and Long Term Credit Bank was the first venture capital company to be started in 8 years (6).

The Japanese Government has made two efforts to encourage the development of a venture capital industry in Japan. One effort was made by the Ministry of International Trade and Industry (MITI) in the early 1970's but yielded little in the way of results (22). In a resurgence of interest in this area, in 1982, MITI set up an Office of Venture Enterprise Promotion in parallel with the creation of the Office of Biotechnology Promotion (32).

Japan's private sector has recently taken some initiative in developing a source of "venture capital" by pooling corporate resources. The Japan Associated Finance Corporation (JAFCO) is a private venture capital fund that was organized by Nomura Securities Company. One French, three Hong Kong, and 10 Japanese firms are involved in JAFCO, which plans to offer financial help to new businesses until they qualify for listing as a joint stock company. When the firm reaches this stage of maturity, its income gains will be distributed among the partners of the fund accord-

*A majority of Japanese companies commercializing in biotechnology have debt to equity ratios that exceed 3 (39), as compared to U.S. ratios that are generally closer to 1. Although the Japanese figures are biased upwards because of differences in land values and because off-sheet financing is used more frequently in the United States than in Japan, the differences in debt to equity ratios are significant.

*Other reasons for the scarcity of NBFs in Japan are cultural attitudes that discourage entrepreneurism, the rigid separation in Japan between university basic research departments and industry, and Japan's weak basic science base in molecular biology (39). Some of these subjects are addressed in *Chapter 17: University/Industry Relationships*.

ing to the ratio of the capital contribution of the fund (22).

These new sources of venture capital may or may not succeed in increasing the supply of venture capital in Japan. In any case, the amount of venture capital these sources currently provide is very small when compared to the amount available in the United States.

The one source of "venture capital" that has been very important to the development of biotechnology in Japan is personal loans of sizable amounts by wealthy individuals who are the managers of progressive Japanese companies such as Hayashibara, Suntory, and Green Cross. As entrepreneurial managers, these individuals are very unusual in Japanese history. A venture by Hayashibara for producing interferon with hamsters was possible only because the owner, who owns or controls 12 institutions (hotels, gas stations, and candy manufacturing firms) and does about $150 million worth of business a year, put his capital behind it (51). The diversification by Suntory (a whiskey company) into rDNA research to produce pharmaceuticals was similarly supported. Significantly, Japan's giant pharmaceutical companies were far slower and more bureaucratic in their response to the potential of biotechnology than these newer Japanese more progressive firms.

In fiscal year 1981, a Government-related organization called the Center for Promoting R&D Type Corporations guaranteed approximately $3.7 million (¥ 750 million) in loans (a total of 24 loans). Beginning in 1982, the center was to begin making loans as well as guaranteeing other lender's loans. Up until now, however, the Japanese Government has not been a major source of financing for Japanese companies developing biotechnology.

There is no indication that significant funds are being channeled into biotechnology by financial institutions connected with the Japanese Government to make up for the shortage of venture capital. In the past, Government-funded banks like the Japan Development Bank (JDB) lent only to projects that fit into articulated Government policy and were located in Japan. In the past decade, however, private bank loans have expanded to such an extent that they are competitive commercially with the Government financial institutions (39). Certain funds within the JDB loan portfolio are targeted for technology promotion. For the past 4 years, this fund has remained fairly constant at the level of $500 million (¥ 100 billion), approximately 10 percent of the total loan portfolio. Loans from the JDB are made at interest rates between 7.5 and 8.4 percent. There is no indication that any of these funds are being channeled into biotechnology.

FEDERAL REPUBLIC OF GERMANY

In the Federal Republic of Germany, nearly all private sector investment in biotechnology has been made by the established pharmaceutical and chemical companies. There is no parallel in the Federal Republic of Germany to the U.S. venture capital industry. Commercial banks provide most of the funds used for industrial expansion, and it is common for such banks in Germany, unlike those in the United States, to have equity participation in companies in which they invest. The West German commercial banking sector is dominated by three banks, and the linkages between the banking and corporate structures are so close that the Monopoly Commission concluded in 1976 that the banks effectively utilize management functions to the detriment of competition (23).

In 1975, a consortium of 28 banks recognized that the German banking system is not conducive to high-risk, innovative, startup firms and formed a venture capital concern called Risk Financing Society (WFG, Deutsche Wagnisfinanzierungs-Gesellschaft) (7). The principal objective of this organization is to aid small and medium-sized firms in commercializing their products. So far, the electronics industry has been the major recipient of WGF funds; biotechnology firms have not yet been of great interest to WFG. Since 1980, WFG has been looking for innovations that could achieve commercial success within 24 months. If this continues to be the criterion for any firm receiving funds from WFG, then it would be surprising if many startup firms in biotechnology were established in the Federal Republic of Germany with WFG funds (23).

UNITED KINGDOM

The present Government of the United Kingdom believes that the successful industrial development of biotechnology depends on private industry. The main source of funds will be the retained earnings of established companies and the capital provided by private financial institutions. The United Kingdom does not have a well-developed venture capital market, and the tax structure in the United Kingdom is not conducive to the formation of risk capital (the capital gains tax rate there is higher than in the United States, as are the marginal income tax rates for higher incomes).

Despite the little direct availability of venture capital, the United Kingdom is providing public and institutional support to encourage the formation of small firms. The Unlisted Securities Market (USM), for example, was formed in 1980 primarily to raise capital for small companies. At the time of its opening, USM had 6 firms; 2 years later, it had a membership of 115 firms and was capitalized at a total of $2 billion. Most of the trading volume in this market is accounted for by small investors. The value of the shares of USM's 20 largest companies has increased 45 percent over the past 2 years, excluding dividends (43). Before USM was established, companies could be listed only on the London Stock Exchange, and listing there required profits of at least $1 million. In addition, until 1977, the London Stock Exchange required a company to sell off at least 35 percent of its equity for listing (the requirement has since been scaled down to 25 percent).

The British Government has introduced two new measures to encourage the formation of small firms. The first measure is designed to encourage the private sector to make equity investments in startup firms by offering tax relief at the top marginal rate to investors in new (up to 5 years old) qualifying businesses. As a result of this measure, a number of professionally managed funds have been established wherein individuals have pooled their money allowing the professional managers of the fund to make their investments. Cambridge Life Sciences, the first British biotechnology firm to go public, used this measure in April 1982 (43). The second Government measure is to guarantee loans made by banks and other financial institutions for qualifying projects that are considered to be viable (in the institution's judgment) but are not backed by personal securities. This measure means that individuals need not have substantial income in order to form a company.

Views on whether there is a shortage of funds available for biotechnology firms in the United Kingdom vary depending on the source of information. Financial institutions say funds are not in short supply; rather, the shortage is in well-presented ideas with commercial value that are capable of earning the relatively high rates of return desired by investors with risk capital. Entrepreneurs say that there is a shortage of funds because institutions demand more evidence than they can supply to prove that their products are capable of earning high profits.

Several institutions in the United Kingdom are supplying funds for the development of biotechnology, including Biotechnology Investments Ltd., Prutec, Advent Eurofund, Cogent, and Technical Development Capital (43). Biotechnology Investments Ltd., a branch of N.M. Rothschild Asset Management, is the largest, with an initial capital pool of $55 million (17). Although Rothschild has invested mostly in U.S. NBFs and other foreign companies, it recently purchased equity in Celltech (U.K.) and is considering several proposals from other British firms. Another fund, Technical Development Capital (TDC), provides equity financing in addition to loans and has a policy of becoming actively involved in management teams. TDC has an annual budget of $5.7 million (£10 million) of which $1.4 million (£2.5 million) is devoted to biosciences, one of three priority areas. The time scale of investments required depends on the industrial sector (e.g., in the medical field, the time horizon is 5 to 7 years; in agriculture, it is 15 to 20 years). TDC has investments in Celltech, Imperial Biotechnology, and three other NBFs in the United Kingdom. Prutec, a wholly owned subsidiary of the Prudential Assurance Co., Ltd., was established in 1980 and makes investments in technology-based firms. Prutec has identified biotechnology as one of 10 strategic areas for investment.

A public institution, the British Technology Group (BTG), is sponsored by the Department of Industry and is the major public source of venture capital in the United Kingdom. BTG invests a certain percentage of its funds in high-risk, long-term investments. The aim of BTG's investment group is to invest on commercial terms in minority partnership with private industry. The best known example of this policy is BTG's investment in Celltech.

Although the number of NBFs forming in the United Kingdom is increasing, the established firm sector is largely responsible for the development of biotechnology there.

SWITZERLAND

Funding for new, high-risk enterprises in Switzerland is not readily available. Analysts attribute this situation to many factors. The Swiss banking industry is oriented to large-scale international financial transactions in areas such as securities, foreign exchange, and precious metals. The banking expertise to evaluate and finance new technologies is lacking. Some argue that the structure of the savings system is changing, with private savings declining and pension funds, traditionally more conservative in investment policies, increasing. Added to these factors is the national reluctance to take risks. The NBF Biogen S.A., for example, has relied heavily on U.S. venture capital and the U.S. stock market to obtain needed capital to finance operations (24).

All of the established Swiss chemical and pharmaceutical companies have substantial capital investments in the United States. Because of the small size of Switzerland's domestic market, most Swiss companies are multinational. The Swiss companies spend a substantial fraction of their R&D costs abroad (this fraction varies among companies). Ciba-Geigy, for example, traditionally spends about 60 percent of its research expenditures in Switzerland and 40 percent in other countries; in 1981, Ciba-Geigy's expenditures on R&D in the United States rose to 23 percent of its total research expenditures, and expenditures on R&D in Europe and in Asia accounted for 20 percent (24).

FRANCE

The number of companies involved in commercializing biotechnology in France is fairly small, and the Government expects this situation to continue. The French Government, which generally believes that only large companies have the necessary resources to undertake biotechnology, has identified three centers of development in the private sector: Rhone Poulenc, Elf Aquitaine, and Roussel Uclaf. Rhone Poulenc and Elf Aquitaine are now nationalized, and Roussel Uclaf is 40-percent Government owned (44).

The venture capital market is poorly developed in France. Banks are the major source of financing. Banks in France, like their counterparts in the United Kingdom but unlike those in West Germany, have always hesitated to take equity positions in industry. The Government of France would like to change this attitude (28). A mutual guarantee company, INODEV, was established by the French Government to guarantee bank credit for the purpose of innovation (33). Since French banks do provide long-term financing, French firms do not have to worry as much about second- and third-round financing as do firms in the United States (44).

Tax incentives relevant to firms commercializing biotechnology

The various tax provisions in the United States, Japan, and Western Europe that are potentially important to companies commercializing biotechnology* are those pertaining to R&D expenditures, capital formation, corporate taxation, and tax treatment of small businesses.** A summary of the tax provisions described for the United States, Japan, the Federal Republic of Germany, the United Kingdom, and France is presented in table 53. Switzerland is excluded from the table, because Swiss tax rates vary among cantons, and the Federal tax system is less important.***

U.S. tax provisions affect NBFs and established companies differentially. In order for corporate tax rates to make a difference in the decisionmaking process of firms, taxable income, the base on which taxes are figured, must be present. Since the NBFs are not experiencing substantial profits, and because there are loss carry-forward provisions in the tax code (for the United States, the period that a company can carry forward losses is 7 years), most NBFs are not now focusing a lot of attention on tax incentives.* Established companies earning taxable income from a number of product lines, by contrast, are interested in current tax benefits.

In a recent study of California biotechnology companies, few participants in the survey stated that tax abatement programs would be useful to their companies (16). Tax abatement programs were rated on a scale of possible utility to the company; evaluations of these programs by the executives responding to the survey ranged from "possible" (at best) to "unlikely." This pattern may reflect the essentially entrepreneurial nature of the NBFs included in the survey. The more established firms with a diversity of product lines would be more interested in tax incentives not primarily focused towards capital formation. It may happen that as established companies become more important in the field, tax incentive programs will be viewed with more interest.

It is important to note that some countries rely more on tax provisions to stimulate capital formation or industrial development than others that use grants or subsidies to assist specific industrial projects. The United States, Switzerland, and to a lesser extent the United Kingdom, for example, tend to rely more on tax incentives to encourage overall capital formation than, for example, the Federal Republic of Germany or France, which use grants or subsidies for specific projects. Other countries (e.g., the United Kingdom, France, and Japan) use tax incentives to encourage investment in R&D or plant and equipment required for scale-up or scientific research. Furthermore, some countries (e.g., the United States and Japan) favor formation of small businesses by tax provisions that are specifically aimed at smaller establishments. Japan targets particular industries and uses both tax incentives and grants.

Some analysts state that the tax incentives in the United States, when compared to those in Western Europe, are not a major factor in decisions about the location of foreign subsidiaries of biotechnology companies (26). However, others argue that sharp differences in the corporate tax rate between countries such as the Netherlands Antilles (whose nominal corporate tax rate is 3 percent) and the United States (whose nominal corporate tax rate is 46 percent) have led some

*The tax codes of various countries change frequently. The discussion here is based on the latest information available in existing sources. The intent of this section is to sketch the major provisions, not to detail specifics of each tax code.

**Local or regional taxes are not included, except in the case of Switzerland, which taxes primarily on a cantonal level. Value-added taxes are also not included, since not all countries have this tax.

***In Switzerland, taxes are governed by Federal law and the tax laws of 26 cantons. While the Federal Government collects practically all indirect taxes, it receives only a small portion of direct taxes levied. The 26 Swiss cantons have a number of obligations, which in other countries would be the responsibility of the Central Government, such as education, road construction, health, police, and justice expenses. To be able to meet these obligations, tax revenue is collected from taxes on income and net assets of individuals and business entities by each canton.

*For this analysis, OTA solicited the views of the following companies engaged in biotechnology: Biogen, Cetus, Genex, Genentech, DuPont, Hybritech, and Monoclonal Antibodies. Industrial Biotechnology Asssociation and the U.S. Department of Commerce were also contacted. Most stated that tax incentives are of secondary importance to other tax provisions (e.g., loss carry forward provisions, R&D limited partnership, and capital gains treatment) given the stage of the company's development.

Table 53.—Tax Treatment of Innovation Activities in the United States and Other Countries

Capital expenditures for R&D	Current expenditures for R&D	Venture capital investments in new technology-based firms	Small business tax treatment	R&D tax credits/ investment grants[a]
United States:				
Treated in same manner as other depreciable assets	Immediately expensed	R&D limited tax partnerships allow investors to write off current expenses as losses and treat future gains as capital gains Investors can pool funds in a regulated investment company of which venture capital corporations are a member, and the company can avoid taxes if the company distributes all its income	SBIC treatment: 1) dividends-received deduction of 10% is allowed to SBICs for dividends received from taxable domestic corporations; 2) loss on stock is treated as an ordinary loss and does not have to be offset against gains from sales of stocks; 3) gains are treated as capital gains Subchapter S corporations: A sub S company gives owners of closely held corporations the advantage of limited liability for depts while taxing the corporation's income at shareholder's income rates. Number of shareholders permitted is 35	Can deduct 25% of the difference between the current year's R&D expenditures and the moving average of a 3-year period.
Japan:				
Firms that are members of Research Association can take 100% depreciation allowance on all fixed assets used in connection with Research Association activities	Immediately expensed	No special provisions	The corporate tax rate for small-and medium-sized corporations on the first ¥ 7 million ($28,107) is 22% (as opposed to regular rate of 30%). A small business can add each year to the ordinary depreciation allowance up to 14% of the original value of new equipment and machinery acquired between Apr. 1, 1972 and Mar. 31, 1983 Additional depreciation allowances are allowed for small businesses that are entering new industries.	Can deduct each year from its income tax 20% of the difference between the current year's R&D expenditures and the highest R&D expenditures in a year before the current year if the difference is positive
Federal Republic of Germany:				
Depreciated in same way as other assets. For expenditures of plant and equipment embodying new technology, the depreciation allowance includes reasonable allowance for obsolescence	Immediately expensed	No special corporate tax treatment for venture capital investments	There is no special corporate tax treatment apart from a provision applicable to foundations and associations. For these organizations, there is a deductible tax free amount of DM5,000 (U.S. $2,060). If corporate income exceeds DM10,000 ($4,120), the tax-free amount is reduced by half the excess	Investment grant of 20% of cost can be claimed for the first DM500,000 (U.S. $206,049) of the costs of assets used in R&D. The excess of cost DM500,000 qualifies for an investment grant of 7.5%
United Kingdom:				
For scientific research assets, a 100% tax allowance (or deduction) is given. Allowances are given for capital expenditures (e.g., labs) and current expenditures (e.g., research workers' salaries)	Immediately expensed.	No special tax provisions for venture capital investments	A closely held company's investment income is apportioned, provided it is surplus to the requirements of the business. Corporation tax rate is 40% if profits do not exceed £ 70,000 (U.S. $122,527)	—

Table 53.—Tax Treatment of Innovation Activities in the United States and Other Countries (Continued)

Capital expenditures for R&D	Current expenditures for R&D	Venture capital investments in new technology-based firms	Small business tax treatment	R&D tax credits/ investment grants[a]
France:				
Can depreciate 50% of the cost in first year with the balance depreciable over useful life	Current expenditures are immediately expensed—carry-backs are not allowed	Businesses which purchase shares in Qualified Research Companies and shares in Innovation Finance Companies may deduct 50% of the cost of the shares in the year of acquisition. If shares are sold, the additional gain attributable to this 50% deduction is eligible for capital gains tax treatment. If shares are held for 3 years or more, no capital gains tax is assessed	Small and medium-sized businesses (fewer than 2,000 employees, not legally dependent on a larger business and having less than 50% of their shares held by quoted companies) are entitled to an exceptional deduction of 50% of the cost of equipment and tools used for R&D Tax allowance amounting to one-third of the firm's taxable profits in the fiscal years of its establishment and in the 3 subsequent tax years	—

[a] Information on the tax rules of foreign countries obtained from tax services and other secondary sources, not from the foreign statutes themselves. While efforts were made to obtain accurate and up-to-date information, it should be noted that reliance on secondary sources does increase the potential for error.

SOURCE: Office of Technology Assessment, based on information from National Science Foundation, *Corporation Income Tax Treatment of Investment and Innovation Activities in Six Countries*, Washington, D.C., 1981; Price Waterhouse & Co., *Price Waterhouse Information Guide: Doing Business in Germany*, September 1978; Price Waterhouse & Co., *Price Waterhouse Information Guide: Doing Business in France*, 1979; Price Waterhouse & Co., *Price Waterhouse Information Guide: Doing Business in the United Kingdom*, 1980; and Price Waterhouse & Co., *Price Waterhouse Information Guide: Doing Business in Switzerland*, 1982.

biotechnology companies to incorporate in the Netherlands Antilles and then form a subsidiary in the United States (20). Generally, tax incentives aimed at capital formation, such as the R&D limited tax partnership or capital gains tax rate, are viewed with much more interest in the short term by U.S. NBFs than tax incentives because NBFs need taxable income to use them.

Tax incentives relevant to new biotechnology firms in the United States and other countries

Tax incentives beneficial to NBFs include R&D tax incentives, capital formation tax incentives, and tax treatment of small businesses.

R&D TAX INCENTIVES

The U.S. tax code offers no special incentives for R&D beyond those available for investment generally and for investment in depreciable structures or equipment used for research and experimental design. The buildings used for R&D are not given preferential tax treatment in the United States as they are in Western European nations. Thus, the United States has no special tax incentive for construction of plant or equipment used in biotechnology. Such an incentive may be, depending on the importance of the costs of depreciable assets in the total production costs, an important factor in determining cost competitiveness in biotechnology products. As products move from research to scale-up stages of production, these costs become more important.

Companies in the United Kingdom are entitled to a 100-percent first year writeoff on capital expenditures for scientific research, the most rapid allowance offered by any country (1). Tax provisions allowing the immediate deduction of capital expenditures for assets used in R&D provide a current tax benefit* rather than a deferred tax benefit, because the capital expenditures for R&D may be offset against income earned in the year of the capital asset's acquisition rather than offset against income earned over the useful life of the asset. Accelerated depreciation provides a tax benefit in that it permits a much faster recovery of the cost of an R&D asset; however, the immediate deduction of the total cost of the asset provides an even faster recovery of costs. The Federal Republic of Germany allows accelerated depreciation for R&D assets in the form of additional depreciation taken in the first few years the assets are used. For investments of less than $234,750 (DM570,000), there is an investment grant of 20 percent of the cost of the assets used in R&D (9,30). France allows 50 percent of the cost of buildings used for scientific or technical research to be written off in the first year.

The United States, Japan, the Federal Republic of Germany, the United Kingdom, and France allow deductibility of current R&D expenditures, but only the United States and Japan give a tax credit for incremental R&D. The Japanese tax credit allows a company to deduct each year from its income tax 20 percent of the difference between the current year's R&D expenditures and the highest R&D expenditures in a base year before the current year. The U.S. tax credit allows a company to deduct 25 percent of the difference between the current year's R&D expenditures and the moving average of a 3-year period's R&D expenditures. In order to qualify for the credit, a company must be carrying on a trade or business. The U.S. Treasury was given leeway in defining the trade or business, and it was widely hoped that the newest proposed regulations would give small firms, primarily engaging in research but not yet selling products, an advantage. Some have stated that Treasury's position is inflexible towards the small firms not yet able to produce products (5).

Some analysts argue that the U.S. tax credit for incremental R&D encourages more R&D than Japan's tax credit, because the base used in the United States (the moving 3-year average) may be lower than the base used in Japan (the highest R&D expenditure in a previous year); the lower base in the United States may allow a higher tax credit given the same rate of increase in R&D expenditures. The U.S. tax credit is currently scheduled to expire in 1985, and many are urging an automatic extension of the credit, especially since the planning and implementation of R&D is a long-term process. Legislation introduced in

*This current benefit is of immediate benefit only to firms with sufficient current taxable income to use the tax benefit.

the 98th Congress, H.R. 3031, sponsored by Representative Fortney Stark, and S. 738, sponsored by Senator John Danforth, would amend the IRS Code by making the R&D credit permanent in the United States. France is considering a 25-percent tax credit for R&D expenditures, thus encouraging through the tax system an increase in R&D expenditures (49). Whether the implementation of additional tax credits will affect the amount of money devoted to R&D expenditures will depend in part upon the permanency of the tax provision in each country.

The treatment of income derived from the sale or license of technology differs among countries. In the United States, proceeds from the sale of patents are treated as long-term capital gains (taxed at the long-term corporate capital gains tax rate of 28 percent). Royalties are taxed as ordinary income (30). In Japan, both proceeds and royalties are treated as ordinary income. Sales of patent rights, technical and manufacturing processes, and know-how are taxable in France at the reduced 15 percent long-term capital gains tax rate (1). Royalties are taxed at the standard 50-percent corporation tax rate unless industrial property rights have the characteristics of fixed assets or the license is granted for 8 years and for exclusive use within a geographical area. In the latter instances, royalties are taxed as long-term capital gains. In the United Kingdom, any capital sum received on the sale of a patent by a U.K. resident is charged as if it were a corporation (at a tax rate of 52 percent); the sum is generally spread over 6 years, so that one-sixth of the sum is liable to tax in each year. Royalties received are treated as ordinary income (30). Overall, the United Kingdom has the most adverse tax treatment of income resulting from the sale of technology (whether involving the sale of patents or licensing).

CAPITAL FORMATION TAX INCENTIVES

Tax incentives designed to stimulate capital formation are of special importance to the formation and growth of NBFs, because few NBFs have enough income derived from product sales or contract revenue to sustain high costs for both R&D and scale-up production. In affecting the amount of capital available to smaller firms, the tax treatment of individual capital gains and R&D limited partnerships are important.

Tax Treatment of Individual Capital Gains.—The long-term capital gains tax rate for individuals in the United States is 20 percent, down from 49 percent in 1976. Industry analysts suggest that this decrease in the individual capital gains tax rate is the primary reason for the substantial increase in venture capital available in the United States (27).

In Japan, capital gains on the sale of securities are exempt from tax, unless the sales are habitual or in the course of business. For nonexempt gains, the first $2,232 (¥ 500,000) is exempt, and the remainder of gain is either taxed as short-term capital gains (treated as ordinary income) or long-term gains (50 percent taxed at ordinary income tax rates) (42).

In the Federal Republic of Germany, no capital gains tax is payable by individuals on assets held longer than 6 months. If an asset is held less than 6 months, the capital gains income is taxed as ordinary income. Capital gains arising from the sale of business assets by an individual are liable to tax at normal rates where the assets form part of the business property. Extraordinary income arising as a result of a gain from the sale of an entire unincorporated business or from the sale of shares by a substantial shareholder are taxed at half the individual's marginal tax rate, i.e., at a maximum of 28 percent (35).

In the United Kingdom, capital gains income is subject to a tax rate of 30 percent (42). The tax treatment of capital gains in France depends on the length of time the asset is held. Short-term capital gains (on assets held for less than 2 years) are included in operating profit and are taxable at a 50-percent tax rate (37). The taxpayer may elect to spread the capital gains tax over 3 years. Long-term capital gains (on assets held for 2 years or more) are taxable at a 15-percent tax rate. Long-term capital gains and losses of the same fiscal year are offset against each other.

Tax Treatment of R&D Limited Partnerships.—As discussed in the section of this chapter on "Financing in Firms Commercializing Biotechnology," an important tax tool used for risk

capital formation in the smaller companies engaged in biotechnology in the United States is the R&D limited partnership. Some NBFs using R&D limited partnerships as a method of raising capital have stated that they prefer the partnerships as a method of financing, because the revenues from a partnership are treated as revenues and allow a company to show a profit even if it has few or no products to sell (27). By using R&D limited partnerships, NBFs have postponed issuing stock, selling equity to established firms, or searching for venture capital, thereby keeping more control over their company. Neither Japan nor West European countries use a similar type of tax treatment.

An R&D limited partnership is formed to support R&D that will result in something that is marketable and patentable. As discussed below, financial advantages accrue to the limited partners (investors) at both the R&D phase and the marketing phase, provided certain conditions are met.

Turning attention first to advantages at the R&D phase, the applicable part of the Internal Revenue Service (IRS) Code is section 174 (Title 26 U.S.C. IRS §174). Section 174 allows each limited partner to deduct all expenses for research (generally, the amount the limited partner invested in the partnership) from income in the year the expenses were incurred, provided the limited partners were at risk.* If the limited partners are *not* at risk, such deduction is not allowed. The challenge, therefore, is to write the agreement establishing the partnership so that the limited partner is at risk. This is generally done by structuring the agreement so that the general partner does not *automatically* buy the results of the research from the limited partners. An automatic purchase provision in the agreement would presume the research would be successful and imply that there was no risk. Similarly, agreements usually base any financial return to the limited partners that may arise from the partnership on sales rather than profits, because the term "profits" in the agreement implies success and hence a no-risk situation.

Upon successful completion of an R&D project supported by an R&D limited partnership, the limited partners may realize economic returns either through royalties or license fees derived from the sale or transfer of a patent or by sale of the product back to the general partner or to a third party. Both of these may qualify for favorable tax treatment. If the research results in a patent, the patent may be sold or transferred by the limited partners to the general partner, generally in return for royalties or license fees. Under section 1235 of the IRS Code (Title 26 U.S.C. IRS §1235), any royalties received as a result of transfer of a patent qualify as long-term capital gain rather than ordinary income. The current tax rate on long-term capital gains for individuals is 20 percent, whereas the tax rate on ordinary income can be as much as 50 percent. The usual 1-year period necessary for the sale of a capital asset to qualify for capital gains treatment does not apply.

Generally, section 1235 treatment applies to a transfer of property consisting of all substantial rights to a patent by any holder. A holder is defined as any individual whose efforts created the patentable property or any other individual who has acquired interest in the patentable property in exchange for money paid to the creator prior to the actual reduction to practice of the invention.* This definition of holder makes it difficult for R&D limited partnerships to acquire rights to a patent when a university has the rights to the patent through employment agreements with its university scientists. Universities that have obtained patent rights through employment agreements with university scientists are excluded from the present definition of holder. As a result, relatively few universities have formed R&D limited partnerships as a means for helping to commercialize their research results.

If the research results in nonpatentable know-how or technology, the sale of the property must meet the requirements of sections 1221-1223 or section 1231 of the same IRS code for the proceeds to be taxed to the limited partners as capital gains rather than ordinary income. Under this

*To ascertain whether the partners bear the required risk, one asks, "Who loses if the research effort is a complete failure?"

*Reduction to practice is a term used in patent law referring to when the invention has been tested under operating conditions.

section, capital assets must be held for at least 1 year before they are sold to qualify for long-term capital gains treatment. Another challenge then is to write R&D limited partnerships so that they result in a patent.

Two recent changes in the U.S. tax code have increased investor interest in economic return from tax shelters, rather than just a tax deduction. First, the maximum tax rate on unearned income has been reduced from 70 percent to 50 percent. This reduction in the maximum tax rate makes unearned income for individuals in high tax brackets more valuable than it used to be and also reduces their need to shelter it. Second, investors may no longer deduct more than the amount they are actually at risk; thus, they can no longer recoup more than their full cash investment in tax savings.

There are two potential disadvantages of R&D limited partnerships for the limited partner. The first is low liquidity: the only way for a limited partner to get out of the agreement is to convince the general partner to buy his or her interest in the partnership. The second is that patents are the only assets that qualify for tax treatment under section 1235. Other types of intellectual property, such as plant variety protection certificates and trade secrets, do not qualify.*

R&D limited partnerships permit the partners to deduct partnership expenses for R&D activities from their individual incomes and then allow any income from the sale of the successfully developed invention to be treated as capital gains income, which is taxed at lower individual tax rates.

Because the financial markets are so dissimilar amoung countries, it is difficult to compare the effect on investments of different capital gains tax treatment. However, the United States has a more developed capital market than its competitors in biotechnology and also has more options for financing smaller firms. If the NBFs continue to serve as an important source of innovation, the expanded financing options for these firms will help the competitive position of the United States. The ability of firms to commercialize innovations will serve as a better indicator of a country's competitiveness than the ability of firms to serve as a source of innovation.

*Patent law and plant breeders' rights statutes are discussed in *Chapter 16: Intellectual Property Law*.

TAX TREATMENT OF SMALL BUSINESSES

Some countries have special tax incentives to promote the growth of small businesses. Studies suggest that small businesses serve as an important source of innovation as well as of the diffusion of technology.

The most favorable tax treatment for smaller businesses is provided by the United States. Subchapter S corporations* give the owners the advantage of limited liability for debts, while the corporation's income is taxed at the shareholder's tax rate rather than at the corporation's tax rate. A key advantage of subchapter S is that if a company generates operating losses, these can be "passed through" to the individual shareholders. The shareholders can use the losses to offset other taxable income. If the owners of a small company have incorporated as a "Sub-S" and they are in the 50-percent tax bracket, then the effect is that the U.S. Treasury is financing 50 percent of the new company expansion. Most NBFs are experiencing losses, so this form of corporation is attractive.

Japan also has special tax treatment for small businesses. A small business can add each year to the ordinary depreciation allowance up to 14 percent of the original value of new machines and equipment. In addition, there is a special depreciation allowance for encouraging small businesses to enter new industrial sectors. A small business that plans to change its business can treat its old machines and equipment as ones newly acquired when it calculates depreciation allowance. Special first-year depreciation credits are now allowed on this machinery (39).

A recent study by the Organisation for Economic Co-Operation and Development (OECD) outlined member government policy towards small businesses and concluded that European countries had fewer policies aimed at small firms than did either the United States or Japan (33).

*Any corporation satisfying requirements described in the Subchapter S Act and Subchapter S Revision Act of 1982 is known as a Subchapter S corporation.

The French Government has been giving increasing attention to startup firms since 1976. Three problems for smaller businesses have been addressed: self-financing, external capital financing, and access to medium- and long-term bank credit (33). The first problem is being addressed through a tax allowance for startup firms equal to one-third of the firm's taxable profits in the fiscal year of their establishment and in the 3 subsequent tax years. The usefulness of this incentive for the small firms using biotechnology in its present stage of development is questionable. Few NBFs are experiencing profits, so few would be able to use the tax allowance. The second problem, external capital financing, is addressed in France through the establishment of regional financing companies (Societés de Financement Regional) and incentives for these financing companies to acquire holding in new firms. The last problem, access to bank credit, has been and still continues to be a problem for smaller companies in France. As noted earlier, the Government of France has established a mutual guarantee company, INODEV, to guarantee bank credit for the purposes of innovation (33). In addition, small and medium-sized businesses (i.e., businesses that have fewer than 2,000 employees, are not legally dependent on a larger business, and have less than 50 percent of their shares held by quoted companies) are entitled to an additional deduction of 50 percent of the cost of equipment and tools used in R&D. However, the small firm sector is not expected to play as innovative a role in France as it has in the United States.

In the Federal Republic of Germany, there is no special tax treatment of small businesses other than a provision applicable to research foundations and associations (30).

The United Kingdom has few tax provisions available to investors or owners of small businesses that would encourage the formation of startup firms. To the extent that the NBFs are important in determining a country's ability to capture world market share in biotechnology products, the United Kingdom would be at a disadvantage. A U.K. resident company which is controlled by five or fewer persons (a person is defined as an individual and near relatives) or by its directors is known as a close company. There is exemption for certain companies which, although closely controlled, have a 35-percent public shareholding and are quoted on a recognized stock exchange. A close company is subject to special tax provisions, of which the most important before March 26, 1980, was that all or part of the company's undistributed after-tax income, after allowing for certain business requirements, could be apportioned (i.e., attributed to its shareholders according to their respective interests in the company and treated as their income). For accounting periods ending after March 26, 1980, only a close company's investment income can be apportioned (37). Therefore, the income of a close company is, to the extent attributed to shareholders under these provisions, subject to the progressive rates of personal income tax and investment income surcharge. Companies whose pretax profits do not exceed $40,000 (£22,900) pay a corporate tax rate of 40 percent instead of the usual 52 percent (37).

Various countries have national programs of regional tax incentives to encourage industries to develop in particular geographical locations. France is divided into four zones, Zones A through D, for incentive purposes. Zone D is the Paris Basin area and the Lyon region, and for this area, there exist no incentives. The other areas have varying amounts of grants and other incentives available (33). In the United Kingdom, enterprise zones are to be designated to encourage the creation of new businesses in economically declining areas. Generous depreciation allowances will be granted in these areas on the cost of certain new buildings in these zones. There also exist regional tax incentives in the Federal Republic of Germany, but the incentives only apply to the West Berlin area. In the United States, there are no Federal programs to encourage industry development in certain sections of the country. Increasingly, however, local and State governments are offering their own tax incentive programs.

Tax incentives relevant to established companies in the United States and other countries

Tax incentives for established companies include R&D tax incentives, capital formation tax incentives, and corporate taxation.

R&D TAX INCENTIVES

The depreciation allowances that apply to the capital assets used in R&D by established companies are the same as those discussed in the R&D tax incentives section for small firms above. Additional tax incentives for established companies are noted below.

Large established companies in the United States can utilize the same R&D tax credits as those used by small firms. An early assessment of the recent U.S. R&D tax credit suggests that it is not likely to induce significant increases in the growth rate of R&D in the short run, but the tax credit may have been one of a number of factors helping to *maintain* R&D budgets in the tight financial situation of 1980-82 (31).

Table 54 shows initial calculations relating U.S. firm size to tax credits earned in 1981. The assumptions underlying this table are: 1) about 63 percent of total R&D budgets is actually eligible for inclusion as R&D expenses for the credit; and 2) half of 1981 eligible expenditures occurred in the second half of the year (because only the second half of 1981 is covered by the credit). The tax credit as a percent of total 1981 R&D falls from about 2 percent on average for firms with fewer than 1,000 employees to about 1 percent for firms with 25,000 employees or more. The inverse relationship between firm size and tax credit as a percentage of R&D reflects the inverse relationship between firm size and rate of growth of R&D. The initial results tend to suggest that the tax credit for R&D is relatively more important to small than large companies.

Japan allows companies that are members of a Government Research Association* such as the one formed for biotechnology research to take a 100-percent depreciation allowance on all fixed assets used in connection with their Research Association activities. Only established companies are members of Research Associations. The Federal Republic of Germany provides a 7.5 percent tax-free cash subsidy for investment in R&D facilities for investments exceeding $206,050 (DM500,000).

Some countries allow businesses to deduct payments to research institutes for contract research. The United Kingdom allows deduction for payments made to research institutes approved by the Secretary of State or the Minister of Technology (1). The United States allows corporations to deduct the cost of equipment given to universities. Also, a manufacturer of new R&D equipment in the United States can donate equipment to universities and obtain a deduction of cost plus one-half the difference between price and cost, up to a limit of twice cost. Payments to universities for contract research or basic research by firms may be included in eligible expenditures for computing R&D tax credit.

CAPITAL FORMATION TAX INCENTIVES

The corporate capital gains tax rate and investment tax credits are discussed below as they relate to capital formation for established compa-

*Research Associations are government-sponsored groups of established companies in Japan performing joint research in specified fields.

Table 54.—Estimated Relationship Between Tax Credit Earned and U.S. Firm Size[a]

Number of employees in company	Number of companies	R&D expenditures (millions of dollars) 1980	1981	Change 1980 to 1981	Tax credit as a percent of R&D expenditures
Not available	24	$ 102	$ 130	$ 28	1.46%
Under 1,000	113	185	240	55	1.91
1,000 to 4,999	286	1,260	1,563	302	1.56
5,000 to 9,999	99	872	1,031	158	1.28
10,000 to 24,999	108	2,781	3,282	500	1.25
25,000 and over	147	22,686	25,862	3,176	0.99
Total	777	$27,886	$32,107	$4,221	1.06%

[a] Based on figures published in *Business Week's* "R&D Scoreboard 1981."

SOURCE: National Science Foundation, *An Early Assessment of Three R&D Tax Incentives Provided by the Economic Recovery Act of 1981*, PRA report 83-7, Washington, D.C., April 1983.

nies. In a broader sense, all of the tax incentives discussed in this chapter have some influence on companies' decisions concerning investment.

Corporate long-term capital gains are taxed in the United States at a maximum rate of 28 percent. In the Federal Republic of Germany and Japan, corporate capital gains are taxed at ordinary corporate income tax rates. In the United Kingdom, corporate long-term capital gains are effectively taxed at 30 percent (30,37). France allows long-term capital gains and losses of the same fiscal year to be offset against each other. Any remaining net after-tax gain (after off-setting) is credited to a special reserve, where it is allowed to remain for an indefinite period of time. If capital gains in the special reserve are distributed as cash dividends, a complementary tax equal to the difference between the long-term capital gains tax and the corporate tax is assessed. If the amount is a loss (after off-setting), it may be carried forward for 10 years to offset future long-term capital gains (36).

The United States and Japan have investment tax credits. In the United States, the credit is equal to 10 percent of qualified investment in depreciable property up to 70 to 100 percent of the tax liability for the year the equipment was placed in service; the excess may be carried over. In Japan, the credit is equal to 10 percent of the purchase price up to 20 percent of total corporate tax liability in the year of purchase for certain industries; the excess may be carried over for 3 years.

CORPORATE TAXATION

The top-bracket corporate tax rate on retained earnings or distributed earnings in the United States for established companies is 46 percent. The corporate tax rate in Japan is 40 percent on retained earnings and 30 percent on distributed earnings. In the Federal Republic of Germany, the corporate tax rate is 56 percent on retained earnings and 36 percent on distributed earnings. In United Kingdom, the corporate tax rate on retained earnings is 52 percent. In France, the corporate tax rate is 50 percent (42).

For international comparisons, effective corporate tax rates should be used rather than the statutory rates just cited. The effective rates take into account different definitions of taxable income and treatments of depreciation. Available studies suggest that effective corporate tax treatment in the Federal Republic of Germany, France, and the United States is relatively equal, with Japan and the United Kingdom having lower effective corporate tax rates; however, these studies need to be updated.

In Switzerland, different cantons have different corporate tax rates: some allow taxes that are paid to other tax authorities as a deduction; others have different loss carry-forward provisions; still others will tax capital gains at a separate rate or not tax the gains at all. The effective corporate tax rates (including Federal defense taxes) in Switzerland range from 8.85 percent to 36.89 percent, depending on the size of profits and the particular canton (38). These tax rates are among the lowest in Europe, and Switzerland is favorable in its treatment of established companies. Switzerland does not have any special treatment for small businesses, only for companies that invest in the equity of other companies and derive most of their income from dividends.

Findings

As a factor determining competitiveness in the commercial development of biotechnology, financial resources to support entry into this new field are of critical importance in all countries, especially now when the technology is new and its applications are just being developed. Financial resources available to commercialize biotechnology are greatest in the United States and Japan and somewhat

less in the four other countries examined: the Federal Republic of Germany, United Kingdom, Switzerland, and France.

In the United States, a variety of funding sources are available to support the commercialization of biotechnology in both NBFs and established companies. Most major U.S. corporations have sizable internal sources of funds and are therefore less likely than NBFs to use external sources of funds to support R&D efforts in biotechnology. If external funds are needed, however, they are most likely to be obtained through debt financing.

Funding needs of NBFs depend on the market selected for entry. Funding needed to support entry into the contract research market is very low. Higher, but still quite low, are the funds needed to manufacture in vitro MAb diagnostic products; indeed, such product lines should be profitable within 2 to 3 years. Greater financial resources are required to enter the pharmaceutical market involving products for internal human use because of the expense of testing and clinical trials to obtain FDA approval. Nevertheless, about 55 percent of the NBFs in the United States plan to enter this market.* The amount of financial resources needed to enter the specialty chemicals market varies depending on the product. Most specialty chemicals do not require regulatory approval; however, FDA approval is required for specialty chemicals considered foods or food additives. Because research is near term for many of the products, 3 to 5 years, and most do not require approval, the financial costs of entering this market fall betwen those for the contract research and commodity chemicals markets. Very great financial resources are needed if an NBF wishes to enter the market for applications to plant agriculture requiring the manipulation of many genes, such as nitrogen fixation or photosynthesis, because a great deal of basic science remains to be done before commercial applications can be achieved, so a firm must plan on many years of research without financial return. Entry into the commodity chemicals market also requires major financial resources, because economies of scale are essential for economic production, and production plants for commodity chemicals cost millions of dollars. The commodity chemicals market is a risky one to select because it involves competition over a few cents difference in price. Additionally, the biotechnology that would be used needs substantial basic research.

The major sources of financing available to NBFs in the United States may be broadly categorized as:

- revenues from contract research and interest on cash previously obtained from public or private offerings,
- various sources of venture capital, and
- public stock offerings.

Research and product development agreements between NBFs and established companies are generally cost reimbursement contracts with additional incentives for reaching agreed upon milestones. Prepayments and advance payments may be obtained, and licensing agreements may bring royalties to the NBF from marketable products of the research. The funding that NBFs receive from research contracts is likely to diminish in the future as large corporations establish greater in-house capabilities in biotechnology. The funds available from corporate sponsors will increasingly be for truly innovative research, which historically has been done by small firms. As contract research funds decrease, however, many NBFs may find themselves in financial jeopardy.

Venture capital sources include venture capital from major corporations, R&D limited partnerships, venture capital funds, and SBICs. SBICs have provided relatively little venture capital to NBFs, although recently an increasing number of equity investments in new firms including NBFs have been made by SBIC bank affiliates. Many equity investments have also been made by major corporations in NBFs. Such investments appear to be motivated more by the corporations' desire to gain "a window on the technology" than by the hope of financial gain from their investments.

Some venture capital firms are set up by major corporations to invest corporate funds in new ventures. Because the firms are independent entities, the corporation is protected from loss. If suc-

*The commercial applications of biotechnology being pursued by NBFs are discussed in *Chapter 4: Firms Commercializing Biotechnology*.

cessful, the venture firm returns some profits to the parent corporation. Other venture firms have no connection to major corporations. Venture capital firms can provide seed money (used to write business plans for new firms), but most often, they fund startups, underwrite public offerings, and invest in R&D limited partnerships as limited partners. A few of these firms have invested a significant amount of their money in NBFs.

R&D limited partnerships are a very important source of funds for NBFs; next to public offerings, R&D limited partnerships have so far provided the most funds for NBFs. Although such partnerships have been available for some time, NBFs are responsible for popularizing their use. Such partnerships have enabled NBFs to attract the substantial funding needed to fund research and early product development and have also been formed for novel purposes, such as supporting the cost of clinical trials.

The number of public stock offerings in biotechnology in 1982 declined to about half the number in 1981, paralleling a similar decline in the number of public offerings in all U.S. industrial sectors. Furthermore, the amounts raised by NBFs in 1982 public offerings were less than NBFs had hoped for. The disappointing return on public offerings probably reflected increased public knowledge about biotechnology and more realistic appraisals of the time necessary before investments in biotechnology are likely to pay off. Thus far in 1983, there is a boom in the new issues market and a large number of NBFs are using the market as a means to finance expansion. Between March and July of 1983, 23 NBFs raised about $450 million (18). The stock market is also providing newly public NBFs with second- and third-round financing. Some of these firms, however, may encounter future financial constraints if they continue to rely on the stock market, because many investors are interested in relatively short-term returns.

In European countries and Japan, there is significantly less venture capital available than there is in the United States, and venture capital has therefore not been a major funding source for biotechnology R&D. Furthermore, because of a lack of venture capital in these countries, the number of NBFs in Europe and Japan is tiny compared to the number of NBFs in the United States. Some governments, such as those in France, Japan, and the United Kingdom, have attempted to stimulate the formation of venture capital, but the results have been disappointing. Outside the United States, direct government funding of industry is proportionately a far more important funding source for the commercial development of biotechnology than it is within the United States. In Japan, corporate funds supply most of the financing for biotechnology.

The United States tends to use tax incentives more than direct government funding to encourage industrial development. In the United States, the tax measures aimed at capital formation and R&D are important to NBFs in their present stage of development. As scale-up proceeds, tax measures aimed at R&D capital assets will become more important. The United States tax code offers no special incentives, beyond those available for investment generally, for investment in depreciable structures or for equipment used for research and experimental design. Currently, France and the United Kingdom have accelerated write-offs for R&D capital assets, and West Germany has an investment grant allowing a company to recover up to 20 percent of the cost of R&D capital expenditures. Japan also has extremely favorable depreciation allowances for capital assets used in R&D for members of Government Research Associations such as the one formed for biotechnology.

Available studies suggest that Switzerland, followed by Japan and the United Kingdom, have the lowest effective corporate tax rates. The effective rates in the United States, the Federal Republic of Germany, and France are higher and about equal.

In most countries, proceeds from patents are treated as either capital gains income or ordinary income. In the United Kingdom, however, proceeds from patents are taxed as corporate income

(at a rate of 52 percent). Royalties are taxed as ordinary income, except in France under certain circumstances. From a tax viewpoint, the United Kingdom has the most adverse treatment of income derived from innovational activity, because proceeds from patents are taxed at corporation tax rates and the long-term capital gains tax rate in the United Kingdom is the highest of the competitor countries.

The United States has the most favorable tax treatment for raising capital for smaller firms. This is an important advantage in fostering the growth of startup and small expanding firms. The people contacted in NBFs agreed that this feature of the U.S. tax system aided the formation of their companies, especially compared to the tax treatment abroad. Recently, OECD published a study comparing the treatment of small businesses among its members and concluded that the European governments had few policies directly aimed at small businesses (33). The European governments are trying to develop policies to encourage entrepreneurs, but there are cultural as well as economic obstacles to be overcome.

Issues and policy options

ISSUE 1: How could Congress help new biotechnology firms obtain the financing necessary for production scale-up?

Many NBFs in the United States are currently sustaining large losses because of the very large investment in R&D relative to operating revenues required to develop a biotechnology product. Most NBFs at present have few or no products to generate revenues and will have difficulty financing production scale-up. Furthermore, as more and more NBFs carrying large losses approach production stages in the future, financing difficulties are expected to increase. If NBFs do not have the financing necessary for production scale-up, the commercialization of biotechnology in the United States may be hindered.

Although many NBFs are currently using public stock offerings and R&D limited partnerships to obtain funds for scale-up, it is not at all certain that these sources of financing will remain available to them. The public market is not generally considered a reliable source of funds for investments characterized by long time horizons and high risk; and R&D limited partnerships may not be a reliable source of funds given current legal uncertainties and uncertain IRS interpretations which affect the tax status of the partnership. If future returns on investments are lower than expected by current investors or if the time horizons for biotechnology scale-up are longer than expected, these sources of financing might become less available.

It might be argued that sufficient investment capital is available to commercialize biotechnology in the United States and that the Government need not intervene with specially targeted guaranteed loans or special tax provisions to further stimulate the U.S. biotechnology effort. However, the commercialization of biological technologies appears more costly both in time and investment than other high technologies. For this reason, Government support may be necessary to maintain the current competitive status of the United States. To help NBFs obtain the financing necessary for production scale-up, Congress could adopt one or more of the following options.

Option 1: Provide guaranteed loans for production scale-up.

A guaranteed loan program, much the same as the 1950 V-loan program that supplied working capital for U.S. semiconductor firms,* could be formulated for biotechnology. Under a V-loan program for biotechnology, the Federal agency guaranteeing a loan would be obliged to purchase a stated percentage of the loan if the borrower defaulted. The loans would be granted at less than

*The development of the semiconductor industry is discussed in *Appendix C: A Comparison of the U.S. Semiconductor Industry and Biotechnology*.

prevailing interest rates and would thus decrease the cost of capital for the individual firm. Because the guarantees would not be tied to a particular loan but to a particular level of debt, they would serve as a system of revolving credit. As periodic repayments reduce the outstanding debt, additional loans could be taken out as long as repayment kept the debt within the face amount of the authorization. The V-loan program of 1950 authorized a total of $2.9 billion over its life, which permitted loans totaling about $11.6 billion. It also returned a profit to the Federal Government of about $24.5 million, because the Federal guaranteeing agent was entitled to a portion of the interest paid on the loan.

Funds for biotechnology earmarked for scale-up projects could be placed in a "Biotechnology Development Bank" or allocated to an interested agency such as the National Institutes of Health, National Science Foundation, or the SBA. The funds could be authorized for a specific amount and aimed at a particular level of debt, thus allowing *successful* biotechnology firms to pay back the loans to the level of debt only. Once the level of debt was paid back, the firms could obtain additional funds from the agency/Bank.

Option 2: Allow rapid depreciation for capital assets required for production scale-up.

The current depreciation schedule for plant and equipment assets in the United States is a set of statutorily provided depreciation periods: 15 years for most structures, 5 years for most equipment, and 3 years for R&D equipment. This schedule is faster than earlier schedules and provides a greater incentive than was provided before for the purchase of long-lived equipment such as bioreactors. A depreciation schedule that would allow an even more rapid recovery of capital costs incurred in production scale-up would help alleviate some of the financial constraints faced by NBFs in production scale-up. The increased write-offs could be made available to investors through equipment partnership agreements or leasing arrangements. Such agreements would allow NBFs to obtain additional money instead of relying on tax provisions alone.

The Defense Procurement Act of 1950, which allowed participating firms to write off their capital expenditures in a 6-month period, could be used as a model for new legislation that would similarly benefit firms using biotechnology. The new legislation could allow NBFs to write off 100 percent of their expenditures for pilot plant equipment.

Currently, the United Kingdom and France have tax provisions applicable to scientific R&D equipment, allowing up to 100-percent write-offs in the first year. Congress could allow similar write-offs or accelerated depreciation for equipment used in biotechnology pilot plants.

Option 3: Refund the R&D tax credit to NBFs not earning enough taxable income on which to apply the R&D tax credit.

The R&D tax credit legislation currently allows unused tax credits to be carried over to each of the 15 taxable years following the unused credit year. For NBFs experiencing cash flow problems while scaling-up production, a tax credit refundable in the year sustained would help alleviate these financial constraints. In addition, in present value terms, a refundable tax credit would be more valuable to NBFs in the year earned than a tax credit carried forward to the years in which enough taxable income would be earned to take advantage of the credit.

The major disadvantage of this option would be the loss of revenue to the U.S. Treasury in times of high deficits. In addition, political and equity-related objections might be raised concerning Government rebates to businesses.

ISSUE 2: How could Congress encourage broader use of R&D limited partnerships in biotechnology?

R&D limited partnerships have been an important source of financing for NBFs. As noted above, NBFs incur high R&D costs relative to their revenues and have few marketable products. NBFs have found R&D limited partnerships useful vehicles by which to attract the substantial funding needed to fund research, early product development, and in the case of some pharmaceutical products, clinical trials required by FDA. Such partnerships may allow more NBFs to enter markets such as that for pharmaceuticals, where extensive regulation makes the costs of entry high.

Given the very large amounts of capital which will be required to support the further commercial development of biotechnology and the variability of the stock market as a source of funds through public offerings, R&D limited partnerships are probably critical to the survival and growth of NBFs. To encourage broader use of R&D limited partnerships and increase their role in providing financing for NBFs, Congress might consider the following options.

Option 1A: Amend section 1235 of the IRS code so that it applies to plant variety protection certificates.

The most favorable tax treatment of income for R&D limited partnerships is provided under section 1235 of the IRS Code. Section 1235 treatment applies to a transfer of property consisting of all substantial rights to a patent by any holder. Under section 1235, any royalties received as a result of transfer of a patent qualify as long-term capital gains rather than ordinary income. Because they are legally distinct from patents, plant variety protection certificates are currently excluded from section 1235 treatment. Their exclusion from section 1235 treatment may have limited the use of R&D limited partnerships for biotechnology research in plant agriculture—an area where some of the most important applications of biotechnology are likely to occur. Adopting this option would very likely encourage the formation of R&D limited partnerships for plant-related biotechnology.

Option 1B: Amend section 1235 of the IRS code so that universities are included in the definition of holder.

Under section 1235, a holder is defined as any individual whose efforts created the patentable property or any other individual who has acquired interest in the patentable property in exchange for money paid to the creator prior to the actual reduction to practice of the invention. A holder cannot be the employer of the creator. This definition of holder may discourage some university/industry R&D limited partnerships. The present definition makes it difficult for an R&D limited partnership to acquire rights to a patent directly from the inventor when a university has such rights through its employment agreement with its scientists. Amending section 1235 to include universities in the definition of holder, in addition to allowing universities to obtain additional money, would enable wider use of R&D limited partnerships.

Option 2: Allow R&D limited partnerships to qualify for tax credits under the Economic Recovery Act of 1981.

Under the Economic Recovery Act of 1981, tax credits are provided for any incremental R&D expenses incurred above a 3-year moving average. The language as it is currently written and statements in the legislative history, suggest that R&D limited partnerships do not qualify for these credits. If they did, the credits could be passed on to the limited partners, thus making R&D limited partnerships more attractive to investors.

On the other hand, it can be argued that R&D limited partnerships are already attractive to investors. The additional incentive to investors that would be provided by enabling limited partnerships to qualify for the R&D tax credits might be small. The loss to the U.S. Treasury must also be considered.

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Chapter 13

Government Funding of Basic and Applied Research

Contents

Tables

Figure

Chapter 13

Government Funding of Basic and Applied Research

Introduction

Federally funded basic research in the United States has been essential to the development of biotechnology. The United States currently has a strong and diversified basic research capability, the foundation for which was laid during World War II by the Office of Scientific Research and Development (OSRD). The National Institutes of Health (NIH) was established to succeed OSRD's Commmittee on Medical Research in 1930.

Within a few years after World War II, several patterns of U.S. Government funding for basic research had been established. First, funding of scientific research would further the broad aims and priorities of the U.S. Government as defined by Congress and the President. Second, nongovernmental laboratories (e.g., research universities) would perform much of the research of interest to the Federal Government; in-house Government laboratories would also perform such research. Third, direct relationships between Federal agencies and university researchers would be established; funds for university research would be awarded to individual investigators or small teams of investigators rather than to the institutions themselves (legally, funds are administered through institutions in the name of investigators). Fourth, university research and graduate training in the United States would be closely related functions. These patterns, with elaboration, have persisted until the present (21).

The launching of Sputnik in 1957 triggered a spectacular increase in the U.S. research effort. From 1953 to 1967, national expenditures in current dollars for research and development (R&D) increased by more than 350 percent, and current dollar R&D expenditures by the Federal Government increased almost 425 percent. In 1967, Federal Government expenditures represented 62 percent of total national expenditures for R&D. After 1967, the rate of growth in R&D expenditures declined, and by 1976, the Federal Government's contribution had dropped to an estimated 53 percent of total national R&D expenditures (21).

National basic research expenditures by the Federal Government have decreased more sharply in constant dollars than in total R&D outlays. Between 1968 and 1976, basic research expenditures declined in constant dollars by an estimated 15 percent. Since universities perform the greatest share of basic research, they have suffered the most from constraints on Federal research funding. In real dollars, fewer basic research funds were spent in universities in 1976 than in 1968 (21). In spite of this leveling off of Federal support, the basic research effort of the United States is prodigious and led to the recent developments in biotechnology.

One aspect of the development of biotechnology demonstates the unanticipated results of a long-term commitment by the U.S. Federal Government to basic research. The "war on cancer" stimulated investigators to study the properties of viruses that cause tumors.* A great deal of work was done to locate the genes in several tumor viruses, such as SV40 virus, that cause tumors in hamsters and mice. These viruses are particularly recalcitrant to classical genetic procedures for mapping genes. This problem led to the use of bacterial restriction enzymes—enzymes that cut DNA at specific locations—to construct physical maps of genes. Physical mapping of an entire genome (a complete set of genes of an organism) using restriction enzymes was first accomplished on SV40 DNA. It was the knowledge of the mechanism of action of these restriction enzymes, generated originally from cancer research, that led to the cloning of genes.

*See *Appendix C: A Comparison of the U.S. Semiconductor Industry and Biotechnology.*

As biotechnology is commercialized, different emphases will be placed on various aspects of the continuum that stretches from basic to applied research. The objective of basic research is to gain a better understanding of the fundamental aspects of phenomena without goals toward the development of specific processes or products. The objective of applied research is to gain the understanding necessary to meet a recognized and specific need, process, or product (13). Bridging the gap between basic and applied research is "generic applied" research, which is more specific than basic research, but longer term and more risky than most applied research.* The Federal commitment to basic and generic applied research in the United States will be a necessary element in the commercialization of biotechnology in the coming years.

Donald Kennedy has characterized the process that moves from basic, to generic applied, to applied research as the "trajectory of innovation" (10). Within this trajectory, particular kinds of institutional sponsors play defined roles:

- *Phase One* (Basic Research). Characterized by loose, informal organization, open communication, quick publication of all the details of an experiment. Usually takes place in university departments or laboratories such as those at NIH, or sometimes in a special organization such as Bell Laboratories. Most often publicly funded, oriented toward the discovery and explanation of phenomena.
- *Phase Two* (Generic Applied Research). Focused on processes, the application phase. Takes place in various settings: applied institutes, some university departments, nonprofit organizations (e.g., Stanford Research Institute, Battelle). Mixed public and private funding. Environments variable with respect to proprietary secrecy.
- *Phase Three* (Applied Research). Innovative emphasis on products, the development stage, attention given to practical application. Funding by private risk capital, environment tends to be closed for proprietary reasons, essentially all work takes place in private laboratories.

Biotechnology is moving rapidly along the trajectory of innovation. The role of Federal funding in the process has been and will continue to be critical to the U.S. competitive position in biotechnology.

Assessing the U.S. competitive position in biotechnology research is difficult for several reasons. First, the definition of biotechnology used in this report is a definition specific to the commercialization of biotechnology, and thus is more likely to fit traditional definitions of applied research. Second, basic or fundamental research in biotechnology can include research on topics as diverse as cancer, developing new vectors to improve recombinant DNA (rDNA) techniques, increasing oxygen solubility in aqueous systems, understanding immune function, and neurobiology. Basic research by its very nature is wide ranging; many elements drawn from basic research of various kinds go into the innovation and development of a particular patentable product. Third, the use of rDNA techniques or rDNA research may be but a small component of a particular research project, or the description of the particular research may not have contained key words that warranted its inclusion in an agency classification of biotechnology research. In addition, as rDNA techniques are more widely used, much of basic research at the cellular and subcellular level will use these techniques; thus, much of basic biomedical research will use the techniques of biotechnology. Fourth, even in the United States, biotechnology is defined differently among funding agencies. Added to problems of definitions are differences in granting procedures by various agencies, as well as different accounting procedures for indirect costs (indirect costs are part of the cost of doing research and therefore must be included). And, finally, overall funding levels give some indication of the total research effort but do not reveal the quality of the research. Nevertheless, most experts would agree

*Generic applied research is a part of the continuum between the two poles of basic and applied. This research may be characterized as follows: 1) it is not committed to open-ended expansion of knowledge as university basic research typically is, but is less specific (more widely applicable or "generic") than the typical industrial product or process development effort; 2) it has more well-defined objectives than basic research, but is longer term than typical product and process development efforts; and 3) it is high risk, in the sense that the stated objectives may fail and the resources committed may be lost for practical purposes.

that the two are closely correlated and that the United States leads the world both in its investment in science and in the quality of its science. The totals for Federal funding for biotechnology research are shown in table 56 and will be discussed in the sections to follow.

Since the focus of this chapter is an assessment of the relative strengths of basic, generic applied, and applied research in biotechnology in the United States, Japan, the Federal Republic of Germany, the United Kingdom, Switzerland and France, the estimates of government funding for biotechnology research in other countries that are available have been included in this chapter. Given problems with respect to definitions, currency exchange fluctuations, and lack of complete data, these figures must be interpreted with caution. For detailed analysis of agency budgets within the United States, the reader is referred to the American Association for the Advancement of Science and National Science Foundation (NSF) documents listed in the references (1,13).

The three sections of this chapter that follow are intended to provide a perspective on the U.S. commitment to biotechnology research by discussing basic, generic applied, and applied biotechnology research, respectively, within individual U.S. Government agencies. A separate section considers instrumentation initiatives by the U.S. Government that have bearing on biotechnology research. Near the end of the chapter, research expenditures in biotechnology and channels of research funding in Japan, the Federal Republic of Germany, the United Kingdom, Switzerland, and France are presented in a comparative overview. The final section of the chapter identifies issues and congressional policy options pertaining to U.S. Government funding of biotechnology research and instrumentation initiatives.

Table 56.—U.S. Federally Funded Research in Biotechnology[a]

		Amount of funding (millions of dollars)		
		Basic	Generic applied	Applied
NIH:				
Molecular biology, generic manipulation, hybridoma, monoclonal antibodies	FY 1982	$378.0	—	—
Immobilized enzymes	FY 1982	—	$ 2.0	—
NSF:				
rDNA research	FY 1982	12.8	—	—
Bioprocess engineering	FY 1982	—	1.7	—
Other biotechnology-related research (broadly defined)		38.6	—	—
USDA:				
ARS plant biotechnology	FY 1983	7.2[b]	—	—
ARS animal biotechnology	FY 1983	6.4[b]	—	—
CSRS competitive grants (CRGO)	FY 1982	5.0	—	—
SAES	1981-82	15.6[b]	—	—
DOD:				
DARPA	FY1983	—	2.2	—
Army/Navy/Air Force rDNA research	FY 1983	3.3	—	—
Other biotechnology	FY 1983	2.0	—	—
DOE:				
Photosynthesis, stress mechanisms of plants and micro-organisms, genetic mechanisms, methanogenesis, etc.[c]	FY 1983	9.9[b]	—	—
Conservation & Renewable Energy Program	FY 1983	23.7[b]	—	—
Other	FY 1983	2.0[b]	—	—
Biocatalysis research	FY 1983	—	0.5	—
Total		$510.9	$ 6.4	$5.0(SBIR)

[a]Unless otherwise specified, see text for explanation of figures.
[b]Some of this research may be generic applied research.
[c]Biotechnology, broadly defined.

SOURCE: Office of Technology Assessment.

U.S. Government funding of basic research in biotechnology

U.S Government agencies funding basic research in biotechnology are NIH, NSF, the U.S. Department of Agriculture (USDA), the Department of Energy (DOE), and the Department of Defense (DOD).

National Institutes of Health

In November 1983, the fiscal year 1984 budget of NIH was appropriated at $4.3 billion with some of the unauthorized programs still under continuing resolution. The number of new and competing project grants will be maintained at 5,000.* The 16,560 research project grants—5,000 competing and 11,560 noncompeting—will be the largest number of research project grants supported in the history of NIH. Budget estimates indicate that direct costs for noncompeting continuation grants will be reduced by about 1 to 2 percent and those for competing grants by 2 to 4 percent. A 4-percent reduction in average costs was applied to these grants in both 1982 and 1983.

Most of the basic research that has been and is done in biotechnology is NIH-funded research. Despite the budget pressures on NIH funding as a whole, the number of extramural projects using rDNA techniques has increased. Funding figures for NIH projects in biotechnology for the fiscal years 1978 to 1982 are shown in table 57. Since data are catalogued by NIH staff on the basis of grant applications or progress reports and indexed by staff who looked for key words such as "genetic manipulation," "hybridoma," "monoclonal antibodies," and "immobilized enzymes," the figures may be slightly misleading. For example, the term "genetic manipulation" includes some projects that do not involve rDNA techniques. Also, the figures are the total costs associated with the awards, including direct and indirect costs, and are not related to the proportion of rDNA research in the total research effort. With the exception of generic applied research on immobilized enzymes, the work is primarily basic research, so many of the industrial applications associated with new biotechnology may be in the distant future. Despite these classification problems, it is evident from the figures in table 57 that research using rDNA techniques is becoming more widespread and comprises a larger proportion of the total grants awarded each year.

Table 57.—NIH Projects in Biotechnology, Fiscal Years 1978-82

Fiscal year	Number of projects	Dollars awarded (millions of dollars)
Genetic manipulation:		
1978	546	$ 61
1979	847	103
1980	1,061	131
1981	1,400	164
1982	1,588	185
Hybridomas (term not created until 1980):		
1980	256	$ 22[a]
1981	479	49
1982	654	64
Monoclonal antibodies (term not created until 1980):		
1980	268	$ 22
1981	768	78
1982	1,274	129
Immobilized enzymes:		
1978	25	$ 1
1979	33	2
1980	26	2
1981	27	2
1982	25	2

[a]Data are probably not complete.

SOURCE: U.S. Department of Health and Human Services, National Institutes of Health, Office of Recombinant DNA Activities, 1983.

Funding figures for biotechnology research in NIH intramural programs are unavailable; however, this research is a much smaller portion of all NIH-sponsored research.

National Science Foundation

The total fiscal year 1984 budget request for NSF is $1.2 million, a 17.4-percent increase over fiscal year 1983. Research instrumentation and support for graduate students are high priorities. Within NSF's Biological, Behavioral, and Social Sci-

*New projects are those competing for first time; competing projects are those that are competing but have been funded before by NIH (a competitive renewal); and noncompeting projects are ongoing projects awarded for more than 1 year.

ences program, the physiology, cellular, and molecular biology program is increased 20 percent over fiscal year 1983. The Chemical and Process Engineering Division budget in NSF's Engineering program is also up 21.5 percent; this may have some effect on biotechnology (4).

The total NSF expenditure for grants having some rDNA component from 1975 through October 1982 was just over $57 million. From fiscal year 1975 through fiscal year 1980, about $35.3 million was spent. Funding for grants having some rDNA component in fiscal year 1981 was $9.8 million and in fiscal year 1982, $12.8 million.

U.S. Department of Agriculture

The fiscal year 1984 budget proposal calls for USDA's agricultural research programs to get along with essentially the same amount of money in 1984 as in 1983 (19).

The division of funds among USDA's bureaus—the Agricultural Research Service (ARS), the Cooperative State Research Service (CSRS), and the Forest Service—and the USDA research agenda have been the subject of several reports and studies. The latest, from the White House Office of Science and Technology Policy (5), has caused considerable debate. The findings from that report indicate that research at the land-grant colleges and universities lags far behind current developments in plant biology, that agricultural research funds should be more widely distributed, that much of the research conducted by ARS is duplicative, and that the agriculture system overall is no longer energy- nor resource-efficient. In addition, this and other reports have suggested that the competitive grants program within CSRS funds high-quality basic research within USDA and should be expanded in order to create a critical mass of long-term high-quality research. Hearings on this issue are expected in the next year.

In fiscal year 1984, there will be an increase of $4.6 million for the competitive research grants within CSRS in order to initiate a program in animal science. Some of these grants may include biotechnology research. In fiscal year 1981 (latest year for which data are available), of the $15.8 million total being spent for competitive research grants, approximately $5 million was spent on biotechnology research (17).

The Agriculture Committee on Biotechnology of the National Association of State Universities and Land-Grant Colleges (12) has estimated that during 1981-82, $34.7 million was committed to biotechnological research by State Agricultural Experiment Stations (SAES). (This estimate was derived from a survey of SAES that totaled the number of persons plus full-time equivalents working on biotechnological research.) The distribution of this total is 42 percent State, 45 percent Federal, and 14 percent private funding.

ARS has funded a total of $13.6 million in biotechnology research in fiscal year 1983; $7.2 million of this was devoted to plant biotechnology and $6.4 million to animal biotechnology (27).

Department of Energy

DOE has several programs involved in biotechnology research. DOE's Office of Basic Energy Sciences, which funds fundamental research in plant sciences and microbiology (photosynthesis, stress mechanisms of plants and micro-organisms, genetic mechanisms, methanogenesis, genetics of anaerobic micro-organisms, and regulatory aspects of metabolic pathways), had a budget of $9.9 million in fiscal year 1983 and will have $11.0 million in fiscal year 1984. Work on anaerobic digestion, algal production, and genetic manipulation is funded through DOE's Conservation and Renewable Energy programs (including DOE's Solar Energy Research Institute); the budget for these programs is $23.7 million. Other programs support biotechnology research relating to pollutant control, beneficiation of coal, and microbial enhanced oil recovery. The aggregate of these latter activities totaled between $1.5 million and $2.0 million in fiscal year 1983 (14).

Department of Defense

The Federal agency with the greatest increase in the fiscal year 1984 budget proposal for R&D funding is DOD—up 29.7 percent over fiscal year 1983 in current dollars. Although most of this increase will fall in the development areas of re-

search, a 9-percent increase in basic research is also proposed (18). Within this framework, there are some data available on biotechnology R&D.

The total funding for rDNA basic research over all three military services for fiscal year 1983 is $3.3 million; $2.9 million of this is funded with $0.4 million obligated but not yet funded (2). DOD is currently amassing data on fiscal year 1983 funding for biotechnology activities (research on cell culture, monoclonal antibodies, etc.). DOD estimates that in-house research is probably at a level of $1 million per year and that contract research in biotechnology is at least as great as that. More accurate figures should be available in fiscal year 1984 (2). These figures represent a very small proportion of the total military basic research budget ($787.5 million for basic research in fiscal year 1983) (19).

U.S. Government funding of generic applied research in biotechnology

NSF, DOE, DOD, and NIH are the only U.S. Government agencies funding generic applied research in bioprocess engineering. Because of limited Federal support, bioprocess engineering could prove to be a critical bottleneck in the United States as biotechnology moves toward production scale-up. Not only is bioprocess engineering research underfunded relative to other types of engineering research, but trained bioprocess engineers are in short supply.*

The major U.S. Government funding group for generic applied research in bioprocess engineering is NSF's Chemical and Process Engineering Division. In fiscal year 1983, $1.7 million of its $4.5 million budget was used to fund projects in bioprocess engineering. In fiscal year 1984, there is no increase in its budget, but more of the budget, $2.7 million, is being allocated to bioprocess engineering (29).

DOE has a Biocatalysis Research Activity within its Energy Conversion and Utilization Technologies Program. Although this activity was funded up to $525,000 through fiscal year 1983, the administration's fiscal year 1984 budget request implies that biocatalysis research activities will be terminated. This research project, begun in 1981 at $130,000 was a generic applied research project designed specifically to capitalize on basic research conducted at universities. Its goal was to build the technical and engineering base of biocatalysis technology to enable U.S. industry to displace a significant level of nonrenewable resource requirements by the year 2000. The project supported applied research and exploratory development to help establish the technology base that the chemical process industry will need to develop cost-competitive products from genetically manipulated organisms based on renewable energy feedstocks. Unfortunately, this beginning toward a federally funded generic applied research base in bioprocess engineering has been terminated. Currently, however, discussions are underway in DOE's Office of Energy Research to begin a broader bioengineering initiative.

DOD's Defense Advanced Research Projects Agency (DARPA), with an overall budget for fiscal year 1983 of $719.5 million (projected to increase 9.7 percent in fiscal year 1984), has two program areas in biotechnology, one underway and one beginning in fiscal year 1984. Thie first program, a research effort in chemical and biological ultrasensors, began in fiscal year 1982 with a budget of $888,000. Funding for this program is expected to increase to $2.2 million in fiscal year 1983, stay level at about $2.2 million in fiscal year 1984, and increase to $2.9 million in fiscal year 1985. The research is being done through contracts with four universities, two private companies, and three Federal laboratories. The purpose of the second initiative, which is to begin in fiscal year 1984, is to study the mechanical properties of bio-

*See *Chapter 14: Personnel Availability and Training* for a discussion of the shortage of bioprocess engineers.

polymers. Funding in fiscal year 1984 will be $1.4 million, rising to $2 million in fiscal year 1985 and 1986, $2.7 million in fiscal year 1987, and decreasing to $1 million for phaseout in fiscal year 1988.

Projects are undertaken in DARPA if there is a perception that there will be downstream applications of interest to the military. Thus, the research DARPA funds is generic applied. If a particular initiative appears to be fruitful, additional funding will be targeted to basic research in the area. Programs are viewed as successful if the technology is transferred to secondary agencies within 5 years. Thus, most research initiatives are for 5 years, at which time they are phased out. New initiatives are continually being phased in as projects demonstrate merit (20).

Although most NIH research is basic research, NIH research on immobilized enzymes, which totaled about $2 million in 1982, could be characterized as generic applied.

U.S. Government funding of applied research in biotechnology

U.S. Government funding of applied research in biotechnology is provided principally through the Small Business Innovation Research (SBIR) program, a program that was established to promote research by small businesses because only about 1 to 2 percent of the total research budgets of Federal funding agencies were set aside for research by small businesses. The Small Business Innovation Development Act establishing this program was passed in 1982, so it is too early to evaluate it. Furthermore, each Federal agency is implementing the program slightly differently. In several of the agencies, however, there is potential for some funding of applied biotechnology research. The status of the SBIR program with regard to biotechnology in specific Federal agencies is detailed below. Also discussed is the Small Business Set Aside program.

Small Business Innovation Research program

The findings of both Government and private studies on technological innovation in small firms convinced the U.S. Congress of the need to increase the share of Federal R&D dollars going to small businesses. The new Federal SBIR program was created to meet this objective. The SBIR program provides a source of nonequity capital to small businesses in the United States. The SBIR program is designed as an expanded version of continuing smaller programs in DOD and NSF. When the program is fully phased in, nearly $430 million annually will be set aside for small high-technology firms, including many new biotechnology firms (NBFs).*

On July 22, the Small Business Innovation Development Act of 1982 was signed into law by President Reagan. The purposes of this act are to: 1) stimulate technological innovation from Government-funded R&D, 2) use small businesses to meet Federal R&D needs, and 3) increase private sector innovation derived from Federal R&D by coupling the SBIR to venture capital. In the first NSF SBIR solicitation, NSF awards totaled $5.3 million. Approximately $42 million in follow-on funding was awarded to the first recipients.

In order to accomplish the three objectives of the law, the SBIR program is structured in three phases. Phase I is a screening phase to evaluate the technical and commercial feasibility of proposals. Usually, the period of performance is months. The awards given in Phase I are up to $50,000. This money is most effectively used for either out-of-pocket expenses and the salary of a technician or for financial sustenance while developing a business plan and looking for venture capital. Only winners of Phase I awards can compete for Phase II awards, and only about 50

*NBFs, as defined in *Chapter 4: Firms Commercializing Biotechnology*, are small firms that have been started-up in recent years specifically to capitalize on new biotechnology.

percent of the Phase I winners receive Phase II awards.

Phase II provides funds for the projects found most promising after Phase I. These awards are generally used for the principal research effort. The period of performance is up to 2 years and the awards given are up to $500,000. In Phase II, the law requests (but does not require) the proposer to obtain a follow-on funding commitment from a third party, usually a large corporation or a venture capital firm. The third party is used not only because the small firms tend to be undercapitalized but also to provide an objective look at the management, market, technology, and long-term financial requirements.

Phase III consists of private investments to stimulate commercial production. This phase is not funded by the Federal Government.

The SBIR law requires that each Federal agency for the next 6 years set aside a specific percentage of its R&D budget for awards to small businesses. Federal agencies with external R&D budgets exceeding $100 million—i.e., the National Aeronautics and Space Administration (NASA), the Department of Health and Human Services (of which NIH is a part), NSF, DOE, USDA, the Department of Transportation, the Department of the Interior, the Environmental Protection Agency, and the Nuclear Regulatory Commission—must set aside 0.2 percent of their external R&D budget for small businesses in fiscal year 1983, 0.6 percent in 1984, 1 percent in 1985, and 1.25 percent in 1986-88. In those agencies with external R&D budgets exceeding $10 billion (DOD), the set aside begins at 0.1 percent and increases to 1.25 percent in the fifth year. Each agency sets its own guidelines for implementation and its own R&D areas for solicitations.

Because the SBIR law is so new, it is difficult to determine the extent to which it might affect technological innovation and the overall competitiveness of NBFs. Nevertheless, it is clear that the SBIR program gives the U.S. Federal Government an opportunity to influence technological innovation in the U.S. private sector. If biotechnology research areas are given adequate support by Federal agencies, innovations in biotechnology might very well be fostered.

U.S. DEPARTMENT OF AGRICULTURE

USDA has reserved almost $550,000 for its SBIR program in fiscal year 1983. There are five project areas. The two most likely to initiate biotechnology proposals are animal production and protection and plant production and protection. Solicitations were sent May 1, 1983. USDA anticipates making 10 to 14 awards.

DEPARTMENT OF ENERGY

DOE has set aside $5.5 million for the SBIR program for fiscal year 1983. One topic of the 25 in the solicitation schedule deals with bioprocess technology and applied microbiology. Of the 1,700 proposals DOE received, 100 were on this topic. Traditionally, DOE's relationships with small businesses have been through subcontracting of funds allocated to the National Laboratories and contractors in universities and elsewhere. The work has usually involved procurement of materials, construction, and fabrication rather than research. The SBIR program will provide DOE with another means of supporting applied research in small R&D firms (14).

DEPARTMENT OF DEFENSE

For fiscal year 1983, DOD has almost $17 million set aside in its SBIR program. Unlike all other Federal agencies, with the exception of NSF, DOD already relies on the small business sector for R&D contracts. In fiscal year 1981, DOD awarded 7.4 percent ($679 million) of its external budget to small businesses—almost twice the small business share of total Federal R&D. Because DOD does not classify R&D projects by industrial application or research area, the amount awarded to small businesses for biotechnology R&D is unknown.*

Because of the important contribution small firms have made to DOD's R&D effort, the Department designed its own SBIR program in 1981—the Defense Business Advanced Technology (DESAT) program—and has made awards to small businesses through that program as well as through regular procurement channels. In fiscal

*DOD's classification system is as follows: 6.1-Basic Research, 6.2-Exploratory Research, 6.3-Advanced Research, 6.4-Engineering, 6.5-Support, 6.6-Major Systems. These headings are not immediately recognizable as biotechnology.

year 1982, 1,103 proposals were received from the first solicitation under the DESAT program and 100 awards were made. The DESAT program will in all likelihood be replaced by the SBIR program.

All three military services plus DARPA participate in DESAT.

- *Air Force.* The Air Force is not pursuing any biotechnology-related R&D with small business or otherwise.
- *Navy.* In fiscal year 1982, the Navy granted 36 awards under the DESAT program; few if any of which were in biotechnology-related areas. Other awards were made to small business, but no agency or service is able to break down biotechnology-related contracts for small businesses only, unless they fall under a specific small business program. Most contract research carried out by the Office of Naval Research and the Naval Research Laboratory in the past has been unsolicited. Of the unsolicited business in the past, 48 percent was done by small business and 50 percent was done by universities.
- *Army.* Under the SBIR program, biotechnology and chemical defense "correspond to the U.S. Army's 'New Thrust' program designed to take advantage of U.S. technology unmatched by Soviet capabilities that can provide the leverage technologies needed for the future battlefield" (23). The Army's R&D efforts under the SBIR program will emphasize the application of novel technologies such as rDNA and hybridoma technology in the development of vaccines, antidotes, analgesics, and blood substitutes (mostly for casualties). About 3,000 proposals are expected to be received for this topic alone.
- *Defense Advanced Research Projects Agency.* In fiscal year 1983, DARPA has set aside $750,000 for its SBIR program. It is unlikely that more than one biotechnology-related contract will be awarded under the program this year, because there are 14 research areas to be covered and the average contract price is about $50,000. In fiscal year 1982, about 12 percent of all awards went to small businesses. Most proposals that come into DARPA are unsolicited. Earlier in fiscal year 1983, when the schedule for solicitations was being formulated, biotechnology R&D was given the highest ranking for research areas to be pursued. As the schedule went through the review process, however, the specificity of the proposals was changed and the proposals were broadened. A biotechnology effort will, however, be funded in DARPA, in the area of biopolymers. Some of the contract awards will no doubt go to NBFs.

DEPARMENT OF HEALTH AND HUMAN SERVICES

The fiscal year 1983 SBIR budget for the Public Health Service, of which NIH is a part, is $5.6 million. Within NIH, it is difficult to speculate about the amount of R&D money to go to NBFs. NIH uses what it refers to as an omnibus solicitation. This approach is designed to generate new business. NIH has little experience awarding applied research contracts to small for-profit companies. In fiscal year 1981, contracts totaling $40 million went to small businesses, mostly for research support (e.g., building animal cages). In fiscal year 1982, the amount increased to $70 million. However, only since January 1982 has NIH been making awards to other types of profitmaking organizations. Most of the forthcoming NIH research solicitations under the SBIR program are in the field of biotechnology.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

NASA's fiscal year 1983 SBIR program has a budget of $11 million. However, biotechnology as defined in this report does not fall within the mission of NASA and is therefore not a NASA research area.

NATIONAL SCIENCE FOUNDATION

NSF's SBIR budget for fiscal year 1983 is $5.5 million, approximately the same as the SBIR budget for the Public Health Service. In fiscal year 1982, NSF did not give any awards in biotechnology, and few good proposals were received by NIH. Congressman Don Fuqua sent a letter to NSF and NIH asking why so few proposals for biotechnology research topics were received (6). The response given was that many of the NBFs had

received funding from private sources for their first-round financing needs (6). Such firms were ineligible to receive Phase II funding without having participated in Phase I.

Small Business Set Aside program

The Small Business Set Aside program was created to help small businesses obtain Federal Government contracts and subcontracts by setting aside "suitable" Government purchases or competitive awards to small businesses. The set aside contracts (not grants) reserve an entire procurement or a portion of a procurement for the exclusive bidding of small business concerns. The program was designed to give small businesses equal opportunity to compete for Government contracts and subcontracts. It was not designed specifically with R&D contracts in mind and has had limited significance in stimulating technological innovation in small businesses (22).

U.S. Government instrumentation initiatives

The obsolescence of analytical instruments is an increasingly severe problem for U.S. universities. As instrumentation becomes more sophisticated, it also becomes more costly; furthermore, obsolescence occurs more rapidly. DOD has estimated that upgrading all qualified laboratories to "world class" status in instrumentation would take an infusion of $1.5 billion to $2 billion. Instrumentation is needed not only to carry out research but also to teach the next generation of researchers and industrial personnel.

Since reduced funding levels have caused universities to cut back purchases of necessary technical equipment, a special fund totaling $150 million over 5 years for the purchase of equipment has been set up in DOD. The purpose of the special DOD fund is to upgrade the equipment of universities. Each of the three military services contributes equally to DOD's special fund, and the Office of Naval Research coordinates its administration. The solicitations sent out by DOD stipulate that the requests are to be for major pieces of equipment that cannot be purchased with other funding. One goal of DOD's fund is to stimulate program projects, i.e., to encourage several researchers to work together. The research they would undertake would necessitate the purchase of equipment costing a minimum of $50,000 (this may be raised to $100,000). The primary criterion for evaluating proposals is the relevance of the proposed research to DOD's interests. The second criterion is the scientific merit of the research to be performed with the equipment. By the closing date of November 30, 1982, 2,478 proposals totaling $645 million had been received. The announcement of 204 awards was made in late April 1983, with awards averaging $148,000. The large response to the DOD initiative is one index of the need for updating instrumentation in universities (15).

For fiscal year 1984, major increases in NSF's R&D equipment and instrumentation initiative are proposed (see table 58). Rather than taking the form of a single dedicated line-item, the funding is distributed among the regular disciplinary elements of the budget. NSF stresses that a few manufacturers of equipment recently have agreed to provide substantial discounts for equipment purchased by NSF grantees. Efforts to broaden participation by manufacturers in this program are continuing.

DOE has a $4 million university equipment initiative in fiscal year 1984 for DOE contractors who need equipment costing more than that allowed in the DOD instrumentation initiative; these requests can have a minimum of about $100,000 (14).

Table 58.—NSF R&D Equipment and Instrumentation, Fiscal Year 1984 Request (obligations in millions of dollars)

	Actual FY 1982	Estimate FY 1983	Estimate FY 1984	Increase (percent) FY 84/82	FY84/83
Mathematical and Physical Sciences	$41.7	$ 56.4	$ 86.3	107.0%	53.0%
Engineering	6.4	8.7	18.3	184.4	109.2
Biological, Behavioral, and Social Sciences	14.3	16.2	24.6	72.0	51.9
Astronomical, Atmospheric, Earth and Ocean Sciences	19.6	22.1	36.7	87.2	66.1
U.S. Antarctic Program	6.0	6.6	12.1	101.7	83.3
Scientific, Technological and International Affairs	2.1	2.3	2.3	9.5	0.0
Total, NSF	$90.1	$112.3	$180.2	100.0%	60.5%

SOURCE: American Association for the Advancement of Science, *R&D in the FY 1982 Budget: A Preliminary Analysis*, Washington, D.C., March 1983.

International comparisons

A brief overview of Government research funding in the foreign countries expected to be the major competitors of the United States in biotechnology—Japan, the Federal Republic of Germany, the United Kingdom, Switzerland, and France—is presented below.

Government funding of biotechnology research in other countries

The amounts spent by foreign governments on biotechnology research (including basic, generic applied, and applied) are extremely difficult to estimate. Any estimate is at best a guess, and, except where indicated, breakdowns by basic or generic applied cannot be made. Currently available estimates for the countries identified as the major competitors of the United States in the area of biotechnology are as follows:

- *Japan.* Funding for biotechnology research in Japan is divided among the Ministry of International Trade and Industry (MITI), the Science and Technology Agency, the Ministry of Agriculture, Forestry and Fisheries, and three other Government agencies. This research is a mix of basic, generic applied, and applied. The figures are shown in table 59.
- *Federal Republic of Germany.* Estimates of spending for projects funded by the Federal Ministry for Research and Technology (BMFT, Bundesministerium für Forschung and Technologie) range from $49 million to $70 million (DM120 million to DM170 million). A large proportion of this research is generic applied.
- *United Kingdom.* The British Government is spending about $43.8 million to $52.5 million (£25 million to £30 million) per year on generic applied and applied research in biotechnology. If basic research is included, the figure probably ranges upward toward $60 million.
- *France.* Estimates for Government expenditures for biotechnology range from $35 mil-

Table 59.—Government Funding for Biotechnology Research in Japan, 1982 and 1983 (in millions)

	1982		1983	
	Yen	Dollars	Yen	Dollars
Ministry of International Trade and Industry	¥ 2,381	$ 9.56	¥ 2,503	$10.04
Science and Technology Agency	2,172	8.72	2,338	9.40
Ministry of Agriculture, Forestry, and Fisheries	1,874	7.53	2,017	8.10
Ministry of Education, Ministry of Welfare, and Environmental Protection Agency	7,557	30.35	7,906	31.75
Total	¥ 13,984	$56.16	¥ 14,761	$59.29

SOURCE: G. Saxonhouse, "Biotechnology in Japan" contract report prepared for the Office of Technology Assessment, U.S. Congress, June 1983.

lion to $60 million (F230 million to F395 million).

Organization of basic and applied research in other countries

The organization of basic research in the United States and other countries competing in biotechnology is described in *Chapter 17: University/Industry Relationships* and in *Appendix B: Country Summaries*. The organization of generic applied and applied research efforts in countries likely to compete with the United States in biotechnology is outlined below.

JAPAN

Because of Japan's continuing interest in bioprocess engineering and because MITI has identified biotechnology as a "next-generation" project, there is a great deal of activity in biotechnology research in Japan. Much of the research is carried out by MITI's Agency for Industrial Science and Technology. Some biotechnology projects that MITI is sponsoring are listed in table 60. This agency oversees several research institutes, including the Fermentation Research Institute (FRI). FRI was founded in 1940 to develop fermentation technology and has expanded to include any microbial application in industry and environmental protection. Additionally, FRI has a depository for patented micro-organisms. Its fiscal year 1982 budget was $4.4 million (¥ 1.1 billion). FRI and other institutes in Japan meet many of industry's needs for generic applied research in biotechnology. Their equivalent does not exist in the United States (16).*

FEDERAL REPUBLIC OF GERMANY

The Society for Biotechnological Research (GBF, Gesellschaft für Biotechnologische Forschung) is without doubt the most important of the federally owned research centers for biotechnology in West Germany and perhaps the most ambitious governmentally operated institution of its kind in the world. In 1982, GBF's operating expenses were $13.1 million (DM32 million). Generously funded by the West German Government, GBF is one of the best equipped facilities of its kind in Europe. Its bioprocess laboratory, for example, permits considerable experimentation with bioprocess technology as well as scale-up of biotechnological processes to the pilot-plant stage.

GBF was set up to perform a variety of substantive research tasks as well as to cooperate with other researchers working in the field of biotechnology. GBF's major functions include the following (9):

- to develop environmentally sound biotechnological processes in order to assure a suf-

*For further details, see *Chapter 17: University/Industry Relationships*.

Table 60.—Some Biotechnology Projects in Japan

Title of R&D project	Ministry with jurisdiction	Institutions conducting projects	Project period
Utilization of biomass	Ministry of Agriculture, Forestry, and Fisheries	Business Office, Agriculture, Fishery and Forestry Technology Council National Institute of Agricultural Sciences Forestry Experiment Station National Agricultural Experiment Station National Research Institute of Agriculture University and private research institutes	1980-90
Enzymatic reactors	MITI	National Chemical Laboratory Agency for Industrial Science and Technology	1979-83
Industrial enzyme use	MITI	Fermentation Research Institute Agency for Industrial Science and Technology	1980-84
Physiologically active macromolecules and production processes	MITI	Research Institute for Polymers and Textiles Agency for Industrial Science and Technology	1978-82
Biochemical pulp technology	MITI	Government Industrial Research Institute, Shikoku Agency for Industrial Science and Technology	1980-83

SOURCE: G. Saxonhouse, "Biotechnology in Japan," contract report prepared for the Office of Technology Assessment, U.S. Congress, June 1983.

ficient supply of chemicals, pharmaceuticals, and foodstuffs;
- to scale-up biotechnological processes from the laboratory to the pilot-plant stage, this being the basis for the development of full-scale industrial processes;
- to make new sources of raw materials available for the manufacturing of natural products by micro-organisms and to make plant and tissue cultures available;
- to make new pharmacologically significant natural products available and to investigate their modes of action;
- to make its scientific facilities available to non-GBF research groups, provided that their projects fit within the R&D program of GBF;
- to support other research groups in the fields of biology, chemistry, and medicine by supplying noncommercial natural products;
- to participate in joint projects, provided they are within the framework of BMFT's Biotechnology Program; and
- to provide advanced interdisciplinary training for scientists, engineers, and technicians.

In keeping with its overall mission, GBF is involved in a number of cooperative arrangements with industry and with academic institutions. GBF's resources and expertise are used by industrial and academic researchers, and GBF relies on other institutions, usually private industry, for services such as toxicological and pharmacological testing of new products. GBF is also engaged in joint activities with academic and international research centers. GBF fosters international scientific exchanges by receiving temporary visitors from other countries. An acknowledged objective of BMFT is to strengthen existing ties between GBF and private industry in order to facilitate technology transfer in the field of biotechnology (9).

Since 1979, the German Collection of Micro-Organisms (DSM, Deutsche Sammlung von Mikroorganismen) has been incorporated into GBF. DSM has served since October 1981 as an international depository of patented or patent-related micro-organisms pursuant to the Budapest Treaty.* More generally, DSM's mission is to collect micro-organisms of scientific and technological significance, to conserve them unchanged, and to make them available for R&D and teaching purposes. The proposed budget for operating DSM in 1982 was $833,000 (DM2 million).

UNITED KINGDOM

The United Kingdom has several Government-sponsored research centers that are involved in biotechnology development projects (see table 61). Some of the centers are entirely Government owned, whereas others have significant industrial commitments.

*See *Chapter 16: Intellectual Property Law.*

Table 61.—Government-Sponsored Applied Biotechnology Centers in the United Kingdom

Name of center	Funding (in millions)	Source of funds
Center for Applied Microbiology and Research (CAMR)	£2 ($3.5)	Department of Health and Social Security, sales of products, industry contracts
British Technology Group (BTG)	£13 ($22.8)	Government
Celltech	£12 ($20)	BTG (44%)[a] Technical Development Capital (14%) Prudential Assurance (14%) Midland Bank (14%) British & Commonwealth Shipping Co. (14%)
Agricultural Genetics	about £40 ($70)	BTG (about one-third), Ultramar, Advent Eurofund
Biotechnology Institute and Studies Centre Trust	N.A.[b]	Government through: Polytechnic of Central London, University of College London, University of Kent at Canterbury No committed industries

[a]BTG recently released 14 percent of its equity to the Rothschild Biotechnology Investments Group and Boots Co.
[b]N.A. = Information not available.

SOURCE: M. Vaquin, "Biotechnology in Great Britain," contract report prepared for the Office of Technology Assessment, U.S. Congress, December 1982.

One Government-sponsored center is the Center for Applied Microbiology and Research (CAMR). As shown in table 61, CAMR is financed in part through the Department of Health and Social Security and in part from sales of products and contract research. Its current operating budget is $3.5 million (£2 million), and there are plans for expansion. CAMR has been singled out by the British Government to play a special role in the development of biotechnology. It has well-developed and established contacts with both universities and industry and sees itself as an intermediary between basic university research and production on an industrial scale. CAMR's major commercial contract in biotechnology is with KabiVitrum (Sweden) to scale-up and develop a process for manufacture of human growth hormone using rDNA bacteria developed for Kabi by the U.S. firm Genentech. CAMR also has contracts with Cadbury Schweppes (U.K.), Unilever (U.K.), Technofirm Development, Ltd. (U.K.), and Celltech (U.K.).

The British Technology Group (BTG) is a public corporation sponsored by the Department of Industry with the aim of supporting the development of biotechnology by facilitating the transfer of technology from the laboratory to the marketplace (see fig. 31). BTG has committed about $22.8 million (£13 million) for biotechnology projects to date, with annual increases of $6.5 million projected. BTG has four major investment areas: research support, joint venture funding, startup financing of small firms, and equity and loan financing. It is not clear what portion, if any, of BTG's funds is being used for scale-up and development processes. In addition to and separate from BTG activities, the Department of Industry has initiated a 3-year $30 million "Biotechnology in Industry" program.

Celltech was founded in 1980 by the National Enterprise Board (now BTG), Technical Development Capital, Prudential Assurance, Midland Bank, and British and Commonwealth Shipping Co., with an initial outlay of $20 million (£12). Recently, the BTG and Technical Development Capital released 14 percent of their equity to the Rothschild Biotechnology Investments Group and Boots Co. The establishment of Celltech represented one of the first steps initiated by the British Government to involve industry in commercializing the results of research in public sector laboratories. While the company was being formed, it successfully negotiated exclusive access to all work in the Medical Research Council, where monoclonal antibodies (MAbs) were discovered in 1975. Although the firm, which intends to concentrate on the development of MAbs for human diagnostic and therapeutic applications, has yet to make a profit on its limited product sales, it has extensive plans for the future, including the development of a continuous cell culture bioreactor that would produce MAbs in higher volumes than current bioprocessing technologies permit.

Agricultural Genetics is a company similar in design to Celltech that will commercialize research of the Agricultural Research Council. BTG will provide about one-third of the capital ($8.6 million; £5 million). The industry sponsors are Ultramar and Advent Eurofund.

The Biotechnology Institute and Studies Centre Trust (BISCT) is a recently established organization that draws on the expertise of some of United Kingdom's foremost biotechnologists. Currently, BISCT is offering continuing education in the form of a 1-year postgraduate degree in biotechnology, short courses, and an advisory service for industry. It hopes to undertake research programs sponsored by industry in bioprocess engineering and applied microbiology (26).

SWITZERLAND

Switzerland has no publicly owned research institute specifically for biotechnology comparable to GBF in West Germany. Outside industry, research related to biotechnology, both basic and applied, is carried out primarily in the university system, which at present includes 10 institutions of higher learning.

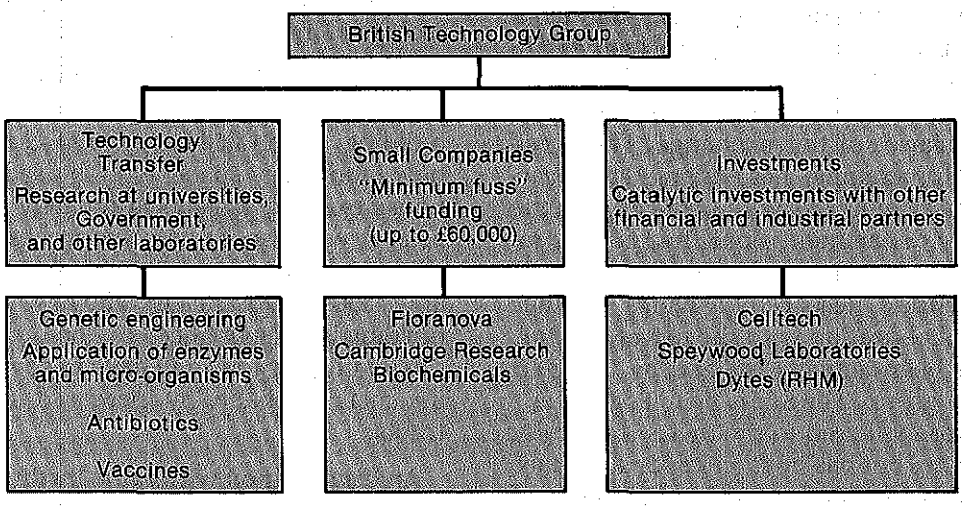
The leading Swiss center for research on the generic applied and applied aspects of biotechnology is at the Federal Institute of Technology (ETH, Eidgenössiche Technische Hoschschule) in Zurich, one of the two polytechnic universities managed by the Federal Government through the Swiss School Council (Schweizerischer Schulrat). Headed by a former research director of the Swiss pharmaceutical company Hoffmann-La

Figure 31.—British Technology Group Support for Biotechnology

BTG Support for Biotechnology

- Support research
- Joint venture funding
- Minimum-fuss finance for small firms
- Equity and loan finance

Total funds committed by BTG: £13 million



Biotechnology Subject Areas Being Supported

Agricultural applications	8 projects
Industrial applications	8 projects
Medicinal applications	17 projects
Veterinary applications	4 projects
Enabling technology	2 projects

Strategy for Further Investment

Seek out and promote:

- Opportunities for industrial investment in downstream applications of genetic engineering and cell fusion
  - — Low volume, high margin products
  - — Healthcare, food production and fine chemicals

Respond positively to:

- Technology transfer opportunities from universities and public sector laboratories
  - — Back a lot of starters
  - — Involve potential industrial partners as early as possible
- Opportunities for industrial investments in "biotechnology infrastructure":
  - — Laboratory reagents and equipment
  - — Fermentation hardware

Avoid:

- Early investment in "big biotechnology" projects
  - — e.g., heavy organic chemicals, bioenergy, and waste recovery

SOURCE: British Technology Group, Prutec Ltd., and Technical Development Capital, "Minutes of Evidence to Education, Science, and Arts Committee on Biotechnology," H. M. Stationery Office 289iii, April 26, 1982.

Roche, ETH proved receptive to the idea of biotechnology at a fairly early date, and its department of biotechnology was established in 1976. One of the department's achievements to date is the development of a new bioreactor design, which is being tested along with more conventional models in the ETH bioprocessing facility.

The channels for transfer of knowledge from the universities to industry appear well established in the area of biotechnology, although the large pharmaceutical companies may not yet be major beneficiaries of this exchange. The president of ETH, for example, has endorsed the practice of industrial contracts with professors in the biotechnology department. Joint funding by industry and the Commission for the Encouragement of Scientific Research provides another avenue for collaboration with the private sector, one that has been actively utilized by the ETH biotechnology group. The Swiss firm Biogen S.A.* is not only closely linked to the Swiss university research system, but has built an important share of its competitive strength on the productivity of these ties (8).

FRANCE

France has no Government-sponsored applied research centers like GBF in West Germany and the ETH-Zurich in Switzerland. The Institut Pasteur, a nonprofit organization jointly sponsored by the Government and industry, is the single most important facility in biotechnological research in France, but is primarily concerned with basic research. The Institut Pasteur receives 47 percent of its income from the French Government (Directorate General for Research). The rest of its income comes from the sale of services: royalties from Institut Pasteur Production (13 percent), industrial contracts (33 percent), and donations collected by the Association for the Development of Institut Pasteur (7 percent). Although the Institut Pasteur is mostly concerned with basic research (e.g., projects on vaccines and monoclonal antibodies), it does support the development aspects of biotechnology (e.g., projects on the use of cellulose for alcohol production and biological insecticides) with industrial contracts.

The Institut Pasteur has plans to open a new biotechnology building in 1985 or 1986. This building, which will have 3,000 square meters of new laboratory space, will be used partly to rehouse existing projects and partly for new projects. It will also contain bioprocess scale-up facilities (at present, the Institut Pasteur cannot do any scale-up work itself). The new biotechnology building is to be financed by the Government, but the Institut Pasteur will have to cover the operating costs, probably by increased industrial contracts.

An organization within the Institut Pasteur, G3, was started several years ago to encourage applied research in rDNA technology. G3 is funded by a set of Government groups: Institut Pasteur, the National Center for Scientific Research (CNRS, Centre National de la Recherche Scientifique), the National Institute for Agricultural Research (Institut National de la Recherche Agronomique), and the National Institute of Health and Medical Research (INSERM, Institut National de la Santé et de la Recherche Médicale). G3 has no capital, cannot employ directly, and does not own any laboratory space. It only has an operating budget. Now working with a staff of only 10, G3 plans to expand into the new biotechology building. The work program is proposed in part by the Government partners and in part undertaken at the request of industries. It is too early to predict whether G3 will contribute significantly to a generic applied research program in bioprocess technology (25).

*Biogen N.V., the parent company of the Biogen group, is registered in the Netherlands Antilles. Biogen S.A., one of Biogen N.V.'s four principal operating subsidiaries, is located in Switzerland, along with Biogen N.V.'s principal executive offices.

Findings

U.S. Government expenditures for basic research in biotechnology—the largest in the world—amount to approximately $511 million per year (mix of data from fiscal years 1982 and 1983). U.S. Government expenditures for generic applied research in bioprocess engineering and applied microbiology are estimated to be approximately $6.4 million (see table 56), although the amount could possibly range as high as $20 million or $30 million if the portions of USDA and DOE expenditures devoted to generic applied biotechnology research were known. U.S. Government funded applied research in biotechnology is virtually nonexistent, except for the SBIR program and some work being done in the National Laboratories. Most of NIH's solicitations for the SBIR program and about 5 percent of DOE's are for biotechnology; if all solicitations are funded, this could total about $5 million plus. The U.S. Army has also included a major initiative for biotechnology under its SBIR program. Since none of these grants has been funded, it is too early to estimate the amounts that will be devoted to applied biotechnology research.

Data on Government expenditures on biotechnology research in Japan are the best for purposes of international comparisons. The total amount being spent by the Japanese Government for biotechnology research in Japan is about $60 million, but Japan's definition of biotechnology is a broad one. A significant proportion of the Japanese Government's funding is for generic applied research in bioprocess engineering. The Federal Republic of Germany, United Kingdom, and France are probably spending similar amounts for biotechnology research (approximately $60 million to $100 million each), probably with relatively equal portions of basic and generic applied research.

The current pattern of U.S. Government funding for basic and generic applied research in biotechnology in the United States may compromise the U.S. competitive position in the commercialization of biotechnology. There is no doubt that past Federal support for basic research has produced a scientific infrastructure and knowledge base in the United States that is the best in the world. Furthermore, continued Federal support of basic research is critical for future innovation in a high-technology society. Because the U.S. Government has provided comparatively little funding for generic applied research, however, Americans may not be as efficient as the Japanese in applying the scientific base to the development of marketable goods and services. The Japanese Government's funding for generic applied research allows companies in Japan to make optimal use of the basic scientific knowledge of the United States and other countries and very efficiently develop this knowledge into marketable products. U.S. industry draws on the basic science knowledge base also, but the speed of the diffusion and development of this knowledge may be slower and ultimately more costly than it would be if more generic applied research were funded by the U.S. Government.

In comparison with other types of engineering research, as well as with molecular biology research, bioprocess engineering research in the U.S. is severely underfunded by the Federal Government. The personnel and academic research needs are enormous. If current funding levels for bioprocess engineering research are not increased, the United States' competitive position in biotechnology may not be as strong in the future as it is now. Bioprocessing expertise currently rests in private industry (chiefly in the pharmaceutical industry). Because private industry's bioprocessing research is proprietary, the diffusion of generic applied knowledge in this area is not as rapid as it might be. Industrialists generally agree that roughly 20 person-years of engineering research are required to go from the test-tube stage to the point where the design of a plant can begin. (Each person-year costs from $80,000 to $120,000). If existing processes or engineering techniques can be used, then about 8 instead of 20 person-years of engineering research are required. The 12 person-year difference is partially attributable to generic applied research that is now duplicated among companies at great cost. Generic applied research in bioprocess engineering could, at least partially, be supported by Fed-

eral funds. Federal support could ensure more rapid diffusion of generic applied knowledge, thus enhancing U.S. competitiveness in biotechnology.

In Japanese universities, there is a clear separation between basic and generic applied research. In addition, the Japanese Government supports generic applied research through institutes such as FRI. Japan currently is increasing its funds to basic research, although it relies to some extent on the basic research of the United States.

GBF, generously funded by the West German Government, is one of the best equipped applied biotechnology research centers in Europe. Its bioprocess laboratory, for example, is excellent. In its various activities, GBF also serves as a bridge between academia and industry.

The United Kingdom has a high standard of excellence and a cadre of highly trained basic research personnel. Recently, the British Government funded either wholly or in part several institutes and organizations to carry out generic applied and applied research and to train researchers in industry in the new techniques. These include CAMR, a center to carry out generic applied microbiology research and diffuse it to industry; Celltech, a company formed to exploit public sector microbiology research; Agricultural Genetics, a company formed to exploit public sector agricultural research; and BISCT, a biotechnology institute and studies center trust to offer continuing education, especially to industrialists.

Switzerland has an excellent basic research base in molecular biology, especially considering its small size. In addition, ETH in Zurich undertakes applied research and in 1976 established a biotechnology department. ETH and faculty at universities have a tradition of close interaction with industry in Switzerland.

In France, universities are regarded as teaching rather than research institutions. The Government funds its own laboratories through CNRS or INSERM. These laboratories are attached to several universities. The most important center for biotechnology research is the Institut Pasteur which is funded jointly by the Government and industry and carries out primarily basic research. G3, an organization established several years ago within the Institut Pasteur, was specifically mandated to encourage applied research in rDNA technology. It is too early to predict whether G3 will contribute significantly to the development of the field. The major lack in French biotechnology is a supply of trained researchers, because the biological disciplines have not traditionally been favored in France.

Basic, generic applied, and applied research are necessary for any country's competitive position in biotechnology. In terms of funding of basic research, the United States is clearly the leader with the largest and most extensive basic research enterprise in the world. The United Kingdom, West Germany, and Switzerland follow, and Japan is slightly behind them. France is sixth because it only now is beginning to exert a concerted effort to study molecular biology.

In contrast, the Japanese Government leads all countries in its commitment to generic applied and applied research. The West German Government also has an extensive commitment to generic applied research with the best equipped generic applied research laboratory in Europe. The United Kingdom and Switzerland follow. The United Kingdom is beginning to fund applied efforts with its support, for instance, of Celltech and Agricultural Genetics, and Switzerland, with ETH, has had a biotechnology effort since 1976. The United States ranks behind these four countries in its relative commitment to generic applied research as opposed to basic research, and is followed by France, which ranks sixth in all three categories of research.

Issues and options

ISSUE 1: How could Congress improve U.S. competitiveness in biotechnology by promoting generic applied research?

With its continual support of basic research, Congress has endorsed a Federal commitment to long-term funding of basic research that is essential to technological development and innovation in this country. It is crucial to the U.S. competitive position in biotechnology that this commitment to basic research continue.

Over the last three decades, the Federal commitment to generic applied research in biology and bioprocess engineering has declined relative to the commitment to basic research. Researchers in the United States have not been attracted to fields such as applied microbiology or bioprocess engineering because only small amounts of Federal funding have been available. Two critical factors underlie this decline: 1) there is no flexible, broad-based Federal system for carrying out such work; and 2) there has been a steady erosion of these generic applied science efforts in U.S. universities.

The governments of the major industrial countries of Western Europe and Japan all possess generally effective and sometimes extensive mechanisms for funding generic applied R&D. Furthermore, the university systems of these countries have not become as unaware of the needs of industrial technology as have the universities in the United States (7). To improve U.S. competitiveness in biotechnology by promoting generic applied research, Congress could adopt one or more of the following options.*

Option 1: Fund one or more biotechnology institutes within universities.

The interdisciplinary nature of biotechnology requires interaction among people with backgrounds in biology and engineering, but most American universities are not structured to facilitate this interaction. The creation at selected campuses of biotechnology institutes, in which faculty in both biology and engineering could be located in the same physical structure and work on common research projects, could facilitate this interaction. These institutes could carry out basic and generic applied research. Funding could come from Federal and State Governments and from industrial sources. Several States have already begun development of biotechnology centers; Federal funding might help leverage State funding to bring in more industrial support. Industrialists as well as academicians could work in the institutes; this arrangement would foster domestic technology transfer. In addition, students could be trained in both academic and industrial environments and industry personnel could be retrained at the institutes.

Option 2: Increase funding for university-industry cooperative programs within NSF.

NSF currently has two university/industry cooperative programs. One, the Industry/University Cooperative Research Projects program, encourages industry/university cooperation for basic research because it will fund up to half of the cost of a grant for basic research projects involving the cooperation of investigators from industry and universities. The program is advantageous to industry, because it allows industry to leverage its research funding effort, and, through cooperation, to gain a competitive edge in the innovation process. University researchers benefit from the program as well, because they improve their awareness of industrial problems and applications of basic research work.

The other NSF program, the Industry/University Cooperative Centers program, provides seed money for a university to set up a center in cooperation with industrial partners. Federal funding is phased out after 3 to 5 years. This program allows the establishment of settings that encourage university/industry cooperative research, while market demand helps to determine the type of research to be undertaken. Government funding adds incentive for industry to fund long-term, generic applied research. The infrastructure for

*See *Chapter 12: Financing and Tax Incentives for Firms* for indirect funding options for R&D.

the continued implementation of the program already exists within NSF.

The peer review system for reviewing university/industry cooperative research projects at NSF is separate from the system for reviewing other research projects. Thus, the generic applied nature of these cooperative research projects is taken into consideration, while high standards of research are assured.

Although increased Federal funding for university/industry cooperative programs within NSF could promote generic applied research, if the funding is not supplemental to needed increases in basic research in bioprocess engineering, the cooperative program could be damaging to the extension of fundamental knowledge in bioprocess engineering and applied microbiology.

Option 3: Establish special grants for interdepartmental cooperative research in biotechnology.

Currently, there is little communication between bioprocess or chemical engineers and basic biologists in universities. Special grants stipulating that a bioprocess engineer and a biologist be coprinciple investigators on a cooperative research project could make researchers in these disciplines more likely to conduct research on bioengineering or applied microbiology research relevant to the commercial development of biotechnology. The grants could be administered by NSF, since it has the technical personnel to administer such a program.

One potential problem with special grants, given current difficulties in obtaining funding, is that the researchers might cooperate in order to write the proposal then do essentially separate pieces of research once funding is obtained. Thus, the research conducted might not be truly cooperative. Avoiding this problem would necessitate carefully stated requests for proposals and careful monitoring of research.

Option 4: Develop generic applied research capability for biotechnology in the National Laboratories.

The National Laboratories are an existing resource, both in terms of physical plant and personnel, that would be expensive to duplicate. Currently, the National Laboratories do not have a great deal of expertise in biotechnology. Nevertheless, there would be several advantages to developing their generic applied research capability. These laboratories have a commitment to research, facilities to conduct research, an objective attitude towards industrial development, an array of personnel trained in relevant disciplines, and unique instrumentation development capabilities that could have a major impact on biotechnology development. DOE's Energy Research Advisory Board has just assessed the laboratories, and the White House Office of Science and Technology Policy is currently reviewing them. An assessment of the capability of the National Laboratory system to carry out generic applied research in biotechnology has not been a part of this report. This is an option for further study by Congress.

Option 5: Increase funding for the SBIR program.

Increased funding for the SBIR program would foster applied research not only in biotechnology but also in other high-technology areas. Furthermore, this program maintains the traditional philosophy of keeping much of applied research in industry and fostering entrepreneurship.

Two counterarguments to this option should be mentioned. First, although DOD and NSF have had programs similar to the SBIR program, the SBIR program has not been in existence long enough in other agencies to be evaluated. Second, because SBIR-funded research must have commercial potential within 3 years, it is too short term for problems that are generic applied, i.e., studies that fall between fundamental research and applied research. The SBIR program, as it is structured, is funding research that is further on the continuum toward product development than generic applied research. Although the program is important for biotechnology because it could help support small businesses that are doing biotechnological research, it may not be a viable op-

tion for increasing support of generic applied research in biotechnology.

ISSUE 2: Should the U.S. Government fund a germplasm screening program?

USDA (under ARS) has a network of centers for accession, storage, screening, and research on germplasm. The work at most of the centers is devoted to study of plants (the center at Fort Collins, Colo., being the largest). The center in Peoria, Ill., however, also includes micro-organisms in its collection. The Peoria center currently houses about 80,000 accessions of micro-organisms (pathogens are not included in the program) of potential interest to bioprocesses, especially for foods and drugs. It also houses 15,000 accessions of wild plant species and is screening these for industrial and medical potential. Of these, 8,000 wild species have been analyzed. Since the Peoria center is a repository for patented and industrially important micro-organisms, there is no specific program to screen these or other micro-organisms for potentially useful genes. The National Academy of Sciences is currently reviewing the USDA germplasm storage program in order to evaluate the relative efforts spent on accession and storage versus screening and analysis for potentially useful genes. A germplasm screening program might be an oversight issue for Congress as biotechnology develops.

ISSUE 3: How could Congress help U.S. academic institutions meet their needs for modern equipment and instrumentation?

There is an enormous need for modern equipment and instrumentation at universities, colleges, and secondary schools. Instrumentation is needed for teaching as well as research purposes, because teaching and research institutions have not been able to meet the needs for rapidly changing technology in instrumentation. In addition, as research grows more sophisticated and specialized, the instrumentation also grows more costly. To enable academic institutions to meet their needs for equipment and instrumentation, Congress could adopt one or more of the following options.

Option 1: Increase the special DOD fund for upgrading university equipment.

The purpose of DOD's fund, obligated in fiscal year 1982 and totaling $150 million over 5 years, is to upgrade university equipment. The solicitations stipulated that the equipment must be for basic research, must be multiuser, and must cost more than $50,000. By the closing date, proposals totaling $645 million had been received from U.S. universities. An increase in funding would help to alleviate the huge need manifested by the $645 million in proposals.

One disadvantage of relying exclusively on the instrumentation fund in DOD is that DOD awards are granted only to projects that are of interest to DOD. A second problem is that DOD's fund does not address equipment needs in the $10,000 to $50,000 range.

Option 2: Increase the instrumentation fund within NSF.

The NSF research instrumentation initiative is slated for major increases in fiscal year 1984, with the biological sciences component up 51.9 percent and engineering up 109 percent (some portion of which will be spent on bioprocess engineering). The NSF funds will concentrate on multiuser equipment. Various manufacturers of equipment have agreed to give NSF grantees reduced prices for purchase of this equipment.

The NSF research instrumentation initiative, although it moves in the right direction toward reducing instrumentation needs, is a part of the awards process. That is, more money will be available only for NSF grantees to use for instrumentation needs for NSF-funded research projects. Instrumentation initiatives similar in amount to DOD's but without the defense-related restrictions do not exist in the United States. An instrumentation initiative within NSF or some other agency could be steadily increased over the next several years to begin addressing the instrumentation needs of teaching and research institutions. Some funds could be earmarked for instrumentation needs primarily for teaching purposes.

Option 3: Legislate tax deductions for the installation and servicing of new or used equipment that companies have donated to universities

Tax deductions to encourage industry to donate equipment to universities and colleges already exist. Often, however, because they cannot afford the installation and service costs, universities are unable to use the equipment that is donated. A change in the tax law to stipulate that installation charges and even service maintenance charges would also be tax deductible would increase the university research benefit of the measure.

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Chapter 14

Personnel Availability and Training

Contents

Tables

Chapter 14

Personnel Availability and Training

Introduction

Adequately trained scientific and technical personnel are vital to industrial competitiveness in biotechnology. Countries lacking highly skilled personnel cannot have companies that compete internationally in highly technical operations such as the design and manufacture of a computer-controlled bioreactor, the discovery of a new biochemical pathway for the production of a specialty chemical, or the development of a microorganism that produces a desired protein.

An important factor in the success of companies attempting to commercialize biotechnology is the degree of sophistication of their research and development (R&D) personnel with respect to state-of-the-art developments in the field. Despite the fact that there is no "typical" firm or organizational structure among the firms using biotechnology, most corporate activity in new biotechnology at present is dedicated to R&D.* Thus, for example, a July 1982 report on a survey of California firms using new biotechnology estimated that 63 percent of the employees in these companies were professional and technical personnel involved in R&D (11).** The other employees were clerical workers (17 percent), managers (15 percent), and floor-level production and maintenance workers (5 percent).

An indication that the commercial development of biotechnology is highly dependent on skilled personnel is the fact that companies are offering special inducements to highly qualified personnel. Many companies have given their scientists and engineers considerable freedom with respect to the pace and direction of their work. U.S. firms using biotechnology stress the independence and flexibility of the work environment in order to attract qualified personnel from academic environments (11). In Japan, companies that persuade Japanese doing academic research abroad to return promise them a flexible research environment (35).

As background for the analysis that follows, the first section of this chapter discusses the quantity and types of scientific and technical personnel needed for the commercial development of biotechnology. The second section compares and contrasts the availability of especially important categories of personnel in the United States and four other countries commercializing biotechnology—Japan, the Federal Republic of Germany, United Kingdom, and France—while the third section compares the training systems in biotechnology-related areas in these countries. Also presented is the information that is available on Switzerland. In the concluding section, congressional issues and policy options with respect to the training and retraining of U.S. personnel in biotechnology are outlined. Because the amount of government funding of specific research areas can attract or discourage students from entering those areas, the reader may wish to review *Chapter 13: Government Funding of Basic and Applied Research*.

*See *Chapter 4: Firms Commercializing Biotechnology* for a description of the firms involved in the development of biotechnology in the United States and other countries.

**This survey identified 50 companies and interviewed a simple random sample of 10 firms (20 percent). All were new biotechnology firms, as defined in *Chapter 4: Firms Commercializing Biotechnology*. The survey's definition of biotechnology was "the use of living organisms or their components in industrial processes."

Size and future growth of the biotechnology labor force

It is very difficult to estimate the size of the biotechnology labor force. Theoretically, the number of personnel in supply and technological support firms, which is approximately four to five times that of firms commercializing biotechnology (11), should be included in the estimate. This chapter, however, focuses exclusively on the personnel requirements for professional and technical personnel of firms commercializing biotechnology. It does not consider the requirements of supply and technological support firms, the vast majority of which market products not only to companies commercializing biotechnology but to other companies as well.

A July 1982 report estimated total U.S. private sector employment in "synthetic genetics" to be 3,278,* including about 2,000 "professional and technical" employees (11). The same report estimated that U.S. private sector employment in "synthetic genetics" had grown at a rate of 54 percent annually since 1976 and projected that total employment would reach about 40,000 in 1992.

OTA estimates that about 5,000 employees are employed by companies in the United States in biotechnology R&D. In April 1983, OTA and the National Academy of Sciences (NAS)** conducted a survey to determine the personnel needs in biotechnology of companies in the United States. The questionnaire, reproduced in *Appendix E: OTA/NAS Survey of Personnel Needs of Firms in the United States,* was sent to 286 companies. Of the 133 that responded, 18 indicated that they were not engaged in biotechnology activities, and 20 others were determined not to be engaged in biotechnology activities from their answers to the questionnaire. To estimate the total number of firms engaged in biotechnology in the United States, OTA determined which of the 153 nonresponding companies were engaged in biotechnology by telephoning the companies, examining annual reports, reading newspaper reports, etc. OTA's estimate of the total number of companies engaged in biotechnology activities in the United States is 219.*

As of April 1983, the 95 companies that responded to the OTA/NAS survey employed 2,591 individuals in industrial biotechnology R&D. These 95 firms represent 43 percent of the 219 firms in the United States estimated to be engaged in biotechnology activity. Extrapolation of this number suggests that the number of individuals employed in biotechnology R&D in all 219 companies using biotechnology could be about 5,000.

The 95 firms that responded to the survey indicated plans to hire an additional 1,167 technically trained employees over the next 18 months.** No company indicated plans to reduce the number of technically trained employees in the next 18 months, so this figure represents an annual employment growth rate approaching 30 percent (not including any new companies formed in the next 18 months). A 30-percent annual growth rate in the number of R&D personnel probably will not be sustained over any length of time, so it is unlikely that the commercialization of biotechnology will lead directly to large increases in employment in the R&D sector. The need for marketing and sales personnel and the potential for spinoff industries are difficult to assess at this time. However, these sectors could be high-growth sectors for biotechnology.

*This number was arrived at by taking estimates of total worldwide shipment of biotechnology products estimated for the target year from OTA's 1981 report *Impacts of Applied Genetics: Micro-Organisms, Plants, and Animals* (40). This estimate was converted to employment of production workers by using case study data from the same OTA report. Next, this estimate was converted into total employment, including nonproduction workers, by utilizing data for established industries. Finally, total worldwide employment was subdivided and a weighted allocation made to the United States.

**NAS Committee on National Needs for Biomedical and Behavioral Research Personnel; Robert Barker, Cornell University, Chair of Panel on Basic Bicmedical Personnel.

*For a list of companies engaged in biotechnology in the United States, see *Appendix D: Index of Firms Commercializing Biotechnology in the United States.*

**For a tabulation of the numbers and types of employees these companies indicated they planned to hire, see question 4 in *Appendix E: OTA/NAS Survey of Personnel Needs of Firms in the United States.*

One reason that commercialization of biotechnology will not directly contribute to a rapidly expanding U.S. work force is that bioprocess technology is not labor intensive (11).* It is estimated that personnel requirements for bioprocessing, even after firms enter mass production, will be only 10 to 15 percent of the total biotechnology work force. Furthermore, with more sophisticated, computer-controlled continuous bioprocesses, the labor intensity of bioprocesses could decrease (11).

*Feldman cites a 1980 report by the National Institute for Occupational Safety and Health (NIOSH), in which NIOSH reported on a Schering-Plough (U.S.) process for producing human leukocyte interferon. Only six people were assigned to production, and probably all six were not needed to monitor the bioprocess (11).

The demands for biotechnology R&D personnel are estimated to be fairly small in foreign country calculations as well. Britain's Royal Society has estimated that about 100 graduate biotechnologists per year will be needed over the next 10 years to commercialize biotechnology in the United Kingdom; about four times that number of technicians and technical support staff will be needed (45). The French Biotechnology Commission has forecast a need for about 1,830 researchers and engineers in biotechnology in France over the next 5 years (44).

Availability of biotechnology personnel

Categories of technical expertise

The industrial development of biotechnology will require several specific categories of technical personnel, many of which are listed in *Appendix E: OTA/NAS Survey of Personnel Needs of Firms in the United States*. Especially important categories include specialists in genetic manipulation such as molecular biologists and immunologists, specialists in scale-up and downstream processing such as bioprocess engineers, biochemists, and microbiologists. Generalizations with regard to the relative importance of these various categories of technical specialization in the development of biotechnology can be drawn from the responses of the 95 companies that responded to the OTA/NAS survey.

SPECIALISTS IN GENETIC MANIPULATION: MOLECULAR BIOLOGISTS AND IMMUNOLOGISTS

The development of hybridoma and recombinant DNA (rDNA) technologies brought molecular biology into the marketplace. A sufficient supply of molecular biologists and immunologists who are specialists in genetic manipulation has been critical to the development of corporate biotechnology R&D in the United States. As shown in table 62, about one-third of the technical personnel employed by the 95 companies responding to the OTA/NAS survey are specialists in rDNA/molecular genetics or hybridoma/monoclonal antibody (MAb) technology (there are twice as many specialists in rDNA as in hybridoma technology). These specialists in genetic manipulation are expected to become increasingly important in the next 18 months, constituting 37 percent of new hirees.

Most molecular biologists trained in the United States at present are specialists in animal molecular biology. The development of agricultural applications of biotechnology will require specialists in plant molecular biology with knowledge of both plant physiology and molecular genetics. According to the OTA/NAS survey, specialists in plant molecular biology currently constitute only 3 percent of the U.S. biotechnology R&D labor force and will constitute 5 percent of all new hirees in biotechnology in the next 18 months.

SPECIALISTS IN SCALE-UP AND DOWNSTREAM PROCESSING: BIOPROCESS ENGINEERS, BIOCHEMISTS, AND MICROBIOLOGISTS

Specialists in scaling-up the production of genetically manipulated micro-organisms (and higher organism cells) and in separation and purification

Table 62.—Major Categories of Biotechnology R&D Personnel in Firms in the United States (OTA/NAS Survey)

Area of technical expertise	Present employees		Employees to be hired in the next 18 months	
	Number	Percent of total[a]	Number	Percent of total[a]
Areas related to genetic manipulation:				
rDNA/molecular genetics	586	23%	302	25%
Hybridoma/monoclonal antibodies	247	10	146	12
Plant molecular biology	76	3	63	5
Areas related to scale-up/downstream processing:				
Microbiology[b]	334	13	160	13
Biochemistry[c]	326	13	125	10
Bioprocess engineering	186	7	100	8
Areas related to all aspects of biotechnology:				
Enzymology/immobilized systems	219	9	59	5
Cell culture	187	7	66	5

[a]The total number of industrial personnel (currently engaged in R&D in new biotechnology) identified in the OTA/NAS survey was 2,591. The total number of personnel to be hired in the next 18 months, according to the survey responses, was 1,167 (see app. E).
[b]Microbiology, as used in this table, combines the OTA/NAS survey responses to industrial microbiology and general microbiology (categories g and s of the survey questionnaire reproduced in app. E).
[c]Biochemistry, as used in this table, combines the OTA/NAS survey responses to analytical biochemistry and general biochemistry (categories j and k of survey questionnaire reproduced in app. E).

SOURCE: Office of Technology Assessment.

of products will become increasingly important as companies developing commercial applications of biotechnology move into production. Although few companies have reached the scale-up stage for new biotechnology products to date,* a substantial amount of R&D in companies developing commercial applications of biotechnology is related to scale-up.

As shown in table 62, about one-third of the biotechnology R&D technical personnel at the 95 companies responding to the OTA/NAS survey are specialists in areas related primarily to scale-up and downstream processing: bioprocess engineering, biochemistry, and microbiology. Bioprocess engineers are needed to design, construct, and maintain scale-up equipment and bioprocesses. Biochemists (apart from enzymologists, discussed below) are involved in the recovery, purification, and quality control of protein products. Microbiologists are needed for the isolation, screening, and selection of micro-organisms having particular catalytic properties. Such specialists are also needed to determine the optimal growth and production conditions for micro-organisms in order to facilitate the design of environments that maximize the micro-organisms' productivity. In the context of the commercialization of biotechnology, bioprocess engineering, biochemistry, and microbiology are generally considered to be more applied science disciplines than are molecular biology and immunology.

As shown in table 62, the OTA/NAS survey of firms in the United States found that bioprocess engineers constitute approximately 7 percent of the current biotechnology R&D work force and will constitute 8 percent of all new hirees over the next 18 months. Specialists in microbiology constitute 13 percent of current employees and 13 percent of the employees to be hired in the next 18 months. Biochemists constitute 13 percent of current employees and will constitute 10 percent of new hirees in the next 18 months.

SPECIALISTS IN ALL ASPECTS OF BIOTECHNOLOGY: ENZYMOLOGISTS AND CELL CULTURE SPECIALISTS

Enzymologists and cell culture specialists are important for many aspects of biotechnology. Advances in the understanding of enzyme structure and function are important in developing the potential of biocatalysts for product formation. Cell culture is used at early R&D stages, but it is becoming increasingly important for the large-scale growth of higher organism cells, especially hybridomas. As shown in table 62, according to the OTA/NAS survey, enzymologists constitute 9 percent of current biotechnology employment in R&D; cell culture specialists constitute 7 percent

*In 1982, about 2 percent of all biotechnology workers in California were production workers (11).

of current biotechnology employment. Both categories of specialists constitute a smaller fraction of future biotechnology hirees (5 percent each) than they do of current employees.

Availability of biotechnology personnel in the United States

Of the countries studied, the United States has the largest number of specialists in genetic manipulation. The large supply of well-trained molecular biologists and immunologists in the United States is one reason for the rush of small company startups and the initial American lead in biotechnology. A primary reason for the large number of basic life science specialists in the United States is that for the past three decades, there has been substantial support from the U.S. Government, primarily from the National Institutes of Health (NIH), of basic research in the life sciences (26). In 1978, for instance, while the governments of most other developed countries were putting 2 to 4 percent of their R&D expenditures into health-related basic research, the United States was putting 11 percent of a much larger R&D base into health research (26). U.S. Government funds have strengthened the foundation of basic life science research, produced trained graduates, and generated an infrastructure for U.S. industrial growth in molecular biology (12). The dominance of the United States in the life sciences is supported by scientific and technical article publishing data. In 1979, U.S. authors published 40 percent of the world's articles in biology and 43 percent of the world's articles in biomedicine (26).

The results of the OTA/NAS survey of U.S. industrial biotechnology personnel needs reflect, with few exceptions, the United States' abundance of personnel trained in basic biological science. Relatively few of the 95 companies responding to the survey indicated that they were experiencing shortages of biochemists, pharmacologists, and toxicologists, who will be needed for the purification, recovery, and testing of biotechnology products. Furthermore, relatively few companies cited shortages of personnel in the areas of hybridoma and cell fusion technology.*

*For a tabulation of responses, see question 1 in *Appendix E: OTA/NAS Survey of Personnel Needs of Firms in the United States.*

Despite the abundance of personnel in the basic biological sciences in the United States, participants at two recent National Science Foundation (NSF) workshops* expressed concern that the United States currently may not have enough well-trained bioprocess engineers necessary for design and monitoring of biological scale-up processes (27). A shortage of highly trained bioprocess engineers in the United States, workshop participants suggested, could be a bottleneck to the rapid commercialization of biotechnology in the United States. The NSF workshop participants also pointed to an insufficient supply of industrial microbiologists. Between 1979 and 1981, the number of industrial microbiology positions listed in the United States nearly doubled, while the number of doctorates in "microbiology and bacteriology" has remained constant for the past 15 years (4). As shown in table 63, the results of the OTA/NAS survey also suggest that the United States may be experiencing shortages of bioprocess engineers: 11 of the 26 U.S. companies planning to hire Ph. D. bioprocess engineers in the next 18 months are experiencing shortages. The OTA/NAS survey results with respect to shortages of microbiologists are more equivocal.**

Shortages in bioprocess engineers, and possibly, industrial microbiologists, may be due in part to the fact that in the past three decades, there has been relatively less Federal support for applied microbiology, applied biochemistry, and bioprocess engineering research than for basic research in molecular biology, biochemistry, and immunology. Thus, university research activities have been guided by Federal funding toward basic biological research and away from these applied disciplines. The shortages may also reflect the fact that U.S. industrial support for university R&D in applied biology and bioprocess engineering has declined in the past three decades (12). After World War

*"Prospects for Biotechnology," University of Virginia, Apr. 5-6, 1982; "Developing the Biotechnology Component of Engineering," North Carolina Biotechnology Center, Apr. 24-25, 1983.

**Results concerning personnel shortages from the OTA/NAS survey are equivocal because the responses of the firms that indicated that they were not experiencing personnel shortages could indicate merely that the firms have not begun a search for personnel or instead indicate that they are not having any difficulty finding trained personnel. Furthermore, the 95 firms that responded to the survey represent less than half of the total number of companies commercializing biotechnology in the United States and may not be representative of the level of scale-up taking place as a whole.

Table 63.—Shortages in Major Categories of Ph. D. Biotechnology R&D Personnel in Firms in the United States (OTA/NAS Survey)

Area of technical expertise (Ph. D.)	Number of firms		
	Experiencing shortages and plan to hire in the next 18 months	Experiencing shortages and do not plan to hire in the next 18 months	Not experiencing shortages but plan to hire in the next 18 months
Bioprocess engineering	11	1	15
Recombinant DNA	10	1	29
Gene synthesis	7	3	7
Plant molecular biology	4	4	15
Industrial microbiology	3	4	14

SOURCE: Office of Technology Assessment.

II, U.S. chemical companies switched from biomass to petroleum feedstocks and consequently decreased their demand for bioprocess engineering and applied biology programs. Conditions in Japan, the Federal Republic of Germany, and the United Kingdom have differed markedly from those in the United States; in these countries, both public and industrial support have helped maintain a strong academic base for the microbial and bioprocess industries over the past several years (12).

The late David Perlmann wrote in 1973 (8):

> The interest in the U.S. has shifted in the past 20 years toward molecular biology. Few students are being trained for the fermentation industries. In the long run, this has worked to the disadvantage of the industries. Unless present trends in the U.S. are reversed, we can expect that in the future it will be desirable to send our students to Japan to learn the techniques that will assure the continuation of the fermentation industries in the United States.

This situation does not appear to have changed much in the last 10 years.

The OTA/NAS survey also showed that 10 of 39 companies planning to hire Ph. D. specialists in rDNA in the next 18 months are experiencing shortages. Much of the R&D activity now in the commercialization of biotechnology is in this area, and, thus, the demand for these specialists is high. However, as companies move toward production, the demand for scale-up and downstream processing specialists will increase, while the demand for the more basic scientists will not. Thus, the current shortages of bioprocess engineers and industrial microbiologists are considered to be more serious.

The shortages in biotechnology personnel in the United States may be partially counteracted by a flow of skilled foreign personnel into the United States.* A representative of one U.S. company stated that of the company's R&D staff of 130, 13 were foreign nationals (9 Ph. D.s). The foreign nationals were from Taiwan, India, Canada, and Hong Kong, and had expertise in nucleotide chemistry, applied microbiology, and bioprocess engineering. U.S. companies using biotechnology might be hiring an even greater percentage of foreign technical personnel if cumbersome and strict immigration regulations did not exist.

Availability of biotechnology personnel in other countries

The number of scientists and engineers engaged in R&D activities in the United States, Japan, the Federal Republic of Germany, the United Kingdom, and France is shown in table 64. As can be seen from that table, in 1977, the United States had more R&D scientists and engineers than any of its principal competitors in biotechnology. Japan had the second largest number, with half that of the United States. The size of a country's R&D labor force is one measure of a nation's R&D capacity. It is only an approximate measure, however, because it does not take into account such factors as the level of sophistication or specialization, utilization, or productivity of a country's R&D personnel. Furthermore, these data cannot

*Reliance on foreign R&D personnel has been common in other U.S. high-technology industries. Many semiconductor and computer companies hire foreigners in order to compensate for shortages of U.S. electrical engineers. At Intel (U.S.), for instance, 50 percent of the engineers holding M.S. degrees and 64 percent of the engineers with Ph. D.s are foreign (15).

Table 64.—Number of Scientists and Engineers Engaged in R&D by Country, 1977

Country	Number of scientists and engineers	Scientists and engineers as percentage of work force
United States	573,900	0.58%
Japan	272,000	0.50
Federal Republic of Germany	111,000	0.44
United Kingdom	80,700[a]	0.31
France	68,000	0.30

[a]1975.

SOURCE: National Science Foundation, *Science Indicators, 1980*, Report of the National Science Board, Washington, D.C., 1981.

be dissected into the percentage of biological personnel.

There are few statistics documenting numbers of specific types of biotechnology personnel in countries other than the United States. For that reason, shortages and surpluses in foreign countries are difficult to identify. Nevertheless, distinct patterns with respect to the availability of biotechnology personnel in foreign countries can be discerned through an examination of available government policy documents and other supporting evidence.

JAPAN

Several experts noted that in the early 1980's, Japan experienced a shortage of experts in genetic manipulation. This shortage was undoubtedly due to the inadequacy of the basic biological sciences in the universities.* Japanese universities have received limited Government support for basic research, so most Japanese universities have not developed extensive research programs in the basic biological sciences. Japan's public universities have been a relatively minor source of highly trained personnel in rDNA and hybridoma techniques (35). Thus, Japanese companies have had to look to other sources of trained basic biological scientists. Some companies have started in-house training programs. Japanese companies have also hired Japanese researchers from abroad, sent employees to be trained abroad and at Japanese universities, and recruited midcareer researchers from other Japanese companies (35). The last option is particulary unique for Japan, a country noted for a lack of personnel mobility. The extensive effort exhibited by Japanese companies seems to have overcome the personnel shortages documented a few years ago.

The supply of bioprocess engineers and industrial microbiologists is larger in Japan than in any of the competitor countries. Japanese Government officials monitoring biotechnology have indicated that the supply of personnel to handle the challenges of scale-up in Japan is not an area of concern (19,35). In fact, a major proportion of biotechnologists in Japan have their background in microbial physiology, an area of neglect in every country examined here except Japan (29).

The specialties of bioprocess engineering and industrial microbiology are strong in Japanese universities in part because the specialty chemical and other industries using traditional bioprocesses in Japan have kept the demand for graduates in these specialties high. After World War II, when chemical companies throughout the world largely switched to processes using petroleum feedstocks, Japanese chemical companies retained some processes using biomass feedstocks and came to dominate the international amino acid market. Furthermore, applied biology departments at Japanese universities have kept in close contact with industry representatives. Each year, 75 students in applied biochemistry graduate from Tokyo University alone; half go on to graduate studies, and half of these go beyond their M.S. degrees. Most are employed by Japan's leading bioprocess companies (35).

FEDERAL REPUBLIC OF GERMANY

The Federal Republic of Germany has sufficient personnel to compete with the United States and

*There is little communication between the basic and applied science departments in Japanese universities. Only the applied science departments have traditionally maintained close relationships with industry. For a more extensive description of the Japanese university system and its relationship with industry, see *Chapter 17: University/Industry Relationships.*

other countries in biotechnology. It is possible that there are some shortages of molecular biologists with expertise in rDNA and hybridoma research. However, according to Norman Binder, the cabinet head of the German Ministry of Science and Technology (BMFT, Bundesministerium für Forschung und Technologie), the training of people in rDNA and hybridoma technology is now a high priority in West Germany (21).

The Federal Republic of Germany's supply of personnel in specialties related to scale-up and bioprocessing appears to be adequate. Like Japan, the Federal Republic of Germany maintained a steady supply of both industrial and government funding for applied microbiology and bioprocess engineering after World War II. According to BMFT, however, the number of both bioprocess engineers and industrial microbiologists in Japan surpasses the number in West Germany (21).

Like the United Kingdom (see below), the Federal Republic of Germany is concerned about a brain drain of biotechnology R&D personnel to other countries. According to the Max Planck Society's senate and the present Minister of Research and Technology, shortages of suitably qualified workers in West Germany are partially due to a brain drain to the United States (9,37). The brain drain of scientists from West Germany, however, appears to be less serious than that from the United Kingdom.

UNITED KINGDOM

Like the United States, the United Kingdom boasts both qualified personnel and excellent training and education programs for personnel in the basic life sciences. In the 1950's and 1960's, there was considerable expansion of basic life science research in British universities. By 1972-73, health-related R&D, supported mostly by the Medical Research Council (MRC), had risen to 5 percent of the British Government's R&D budget, nearly twice the percentage of Japan, the Federal Republic of Germany, or France (26).* MRC's past investment in biology is now paying off. Molecular biologists and immunologists supported by MRC are internationally prominent in the development of rDNA and hybridoma technologies. Nevertheless, there may be shortages of molecular biologists if the industrial development of biotechnology expands rapidly (2).

Like Japan and the Federal Republic of Germany, the United Kingdom has a good academic base for training bioprocess engineers. Nevertheless, the United Kingdom appears to be experiencing a shortage of bioprocess engineers (2). A brain drain from the United Kingdom is viewed as partially responsible for this shortage. Many British biotechnologists are leaving for the United States, Switzerland, and other countries of the European Economic Community, because sufficient posts do not exist in the United Kingdom at present and salaries in the United Kingdom are not competitive with those in other countries (45). When the Swiss company Biogen S.A.* advertised for 30 molecular biologists, half of the 600 applications they received were well-qualified British (45).

Analysts estimate that a total of between 100 and 1,500 experts in some aspect of biotechnology have left the United Kingdom over the past several years (30). Governmental institutions are taking active measures to counteract the brain drain. The Research Councils, the United Kingdom's public research institutes, have adopted an active policy of encouraging scientists from the United Kingdom who have spent time in industry abroad to return home. The Science and Engineering Research Council (SERC) maintains a list of British biotechnologists outside the United Kingdom and may be taking measures to encourage them to return (30), and MRC has announced publicly that it will provide laboratory space and allow reentry into the career structure without penalty for scientists who return to the United Kingdom (45).

SWITZERLAND

The access to distinctive universities and the high standard of living in Switzerland attract highly qualified personnel from around the world to participate in Swiss biotechnology. Although the availability of personnel may not be impor-

*Since 1973, Government expenditures in the United Kingdom for health-related research have dropped and are now equivalent to those of the other foreign countries studied here (26).

*Biogen S.A. is one of the four principal operating subsidiaries of Biogen N.V., which is registered in the Netherlands Antilles. Biogen N.V. is about 80-percent U.S.-owned.

tant for the large pharmaceutical companies which conduct a large proportion of their R&D in other countries, it is crucial to the Swiss advancement of biotechnology in other sectors. The attraction of talent from other industrialized countries may help the competitive efforts of Swiss companies in biotechnology in the future.

FRANCE

France has a serious shortage of qualified personnel that could well undermine the country's basic and applied science base and prevent France and its industries from competing successfully in the world biotechnology marketplace. Specialists in the fields of general and industrial microbiology, rDNA and hybridoma technologies, enzymology, plant and animal cell culture, and bioprocess engineering are few (3). Although some French research centers boast internationally recognized teams, such as the enzymology and bioprocess technology teams at the technical University of Compiegne or the immunology groups at the Institut Pasteur (44), these are isolated clusters of expertise. Thus, France will have difficulty matching the total output of the large and balanced national research bases of other competitor countries.

The scarcity of personnel in France cuts across several sectors of R&D in these technologies and applies equally to different categories of personnel, from scientists and bioprocess engineers with advanced degrees to skilled laboratory and production technicians. In order to correct this situation, the French Government has given special attention to the education and training of qualified personnel. The research law passed in July of 1982 called for the active involvement in the educational process of public sector researchers outside universities (46). And the Programme Mobilisateur presents educational guidelines for all stages of schooling from secondary to postdoctoral levels, placing special emphasis on an interdisciplinary approach within the universities (24). The education of a specialist in rDNA technology, nonetheless, takes many years, as does the implementation of such training programs. As a short-term solution to its present lack of personnel, therefore, France imports foreign experts (24).

Personnel training

The availability of the scientific and technical personnel necessary for the commercialization of biotechnology is highly dependent on a country's educational infrastructure. The discussion here compares various aspects of training, all of which are important to the development of biotechnology: 1) secondary school education, 2) biotechnology-related undergraduate and graduate education, 3) transnational training opportunities, and 4) mid-career retraining opportunities.*

Secondary school education in the United States and other countries

Secondary school education in science and mathematics in the United States trails that in Japan and many European countries. High school students in Japan are required to complete 2 years of mathematics and 2 years of science before graduating (42). Secondary school students in many European countries, even students specializing in classics or languages, similarly get far more extensive training in mathematics and science than do students in the United States (6).

Several recent studies have identified a decline in the quality of science and mathematics education in U.S. secondary schools, attributing it to a lack of good teachers, instrumentation, Federal support, and local community support in the form of bonds and taxes (6,10,16,31,47). Furthermore, many leading scientists, engineers, and politicians in the United States fear that the decline is leading the United States to become a nation of technological illiterates and is compromising the U.S.

*For general information on science and engineering education and personnel internationally, see (39).

position in international competition in high-technology areas (1,38,49).

Undergraduate and graduate education in the United States and other countries

There is near unanimous agreement that the development of biotechnology will require personnel capable of operating in an interdisciplinary environment with various levels of expertise in both biology and engineering (29). Because of traditional barriers between basic biological science and engineering departments in most higher educational institutions, the challenge of providing interdisciplinary undergraduate and graduate education for personnel in biotechnology is a challenge common to all industrialized countries.

UNITED STATES

The United States has an adequate supply of personnel in nearly all the fields of basic biological sciences relevant to biotechnology, with the possible exception of plant molecular biology. For the training of plant molecular biologists, new and modified curriculum offerings may be needed. Most classical plant breeders in the United States are trained at agricultural research stations and land-grant colleges; thus, their training does not traditionally include molecular biology. Because the new genetic technologies grew out of biomedical research at universities and NIH, few traditional plant breeders have the training that would allow them to do experiments using rDNA technology. Nevertheless, interest in plant molecular biology is increasing dramatically. Botanists are learning the new techniques, and biomedically trained researchers are applying their expertise to plants. Because of the separation of agricultural researchers and plant molecular biologists in the United States, however, there are problems of communication between these groups which may slow research advances (34).

There is a growing concern that a shortage of plant molecular biology professors in the United States could result from a drain of Ph. D. plant molecular biologists from U.S. universities to industry (25). As numerous companies have started efforts in plant molecular biology and existing companies have expanded into plant molecular biology, industry has been competitively recruiting university researchers. As shown in table 65, according to the OTA/NAS survey, all of the companies wanting to employ Ph. D. plant molecular biologists intend to hire from academia, and half intend to hire from industry as well.

Bioprocess engineering education in the United States, now almost exclusively provided in university chemical engineering departments at the graduate level,* is closely tied to training opportunities in chemical engineering (12). Between 1970 and 1980, the number of Ph. D.s graduating in chemical engineering declined by nearly 25 percent, and the bioprocess subset of the chemical

*At the undergraduate level, there are only two accredited bioengineering (distinct from biomedical engineering) programs in the United States, one at the University of Illinois at Chicago and one at Texas A&M.

Table 65.—Sources of New Ph. D. Biotechnology R&D Personnel In Selected Categories in Firms in the United States (OTA/NAS Survey)

Area of technical expertise (Ph. D.)	Companies planning to hire from industry		Companies planning to hire from academia		Companies planning to retrain current staff	
	Number	Percent of total[a]	Number	Percent of total[a]	Number	Percent of total[a]
Recombinant DNA	15	38%	35	84%	3	7%
Gene synthesis	9	64	13	93	3	21
Industrial microbiology	11	67	13	81	2	13
Bioprocess engineering	19	86	11	50	2	9
Plant molecular biology	9	50	18	100	3	17

[a]Refers to percent of companies that both indicated plans to hire in the specialty area *and* revealed the sources from which they would hire new personnel. Many companies indicated more than one hiring source for each specialty area.

SOURCE: Office of Technology Assessment.

engineer category probably declined proportionally. At most, only about 10 percent of the recent M.S.s and Ph. D.s in chemical engineering are ready to enter the bioprocess industry without additional formal training (13).

The decline in the number of Ph. D.s graduating in chemical engineering in the United States in part reflects declining graduate student enrollment. Because industry salaries are quite high for bachelor's degree engineers, fewer and fewer people have gone to graduate school. Another reason for the decline is a shortage of engineering professors. Most American universities do not pay salaries commensurate with industry. Currently, there are 1,600 faculty vacancies at U.S. engineering schools in all disciplines (43). Participants at a 1982 workshop on biotechnology sponsored by the University of Virginia and NSF agreed that the shortage of faculty in engineering is a more pressing problem for the long-term educational stability of the United States than the declining engineering graduate student enrollment (28).

According to the OTA/NAS survey of firms using biotechnology in the United States, Ph. D. bioprocess engineers are in high demand by industry (see table 63). If incentives for Ph. D. bioprocess engineers to remain in the academic field are not improved, the loss of these Ph. D.s to the private sector may reach the point that the American Society for Engineering Education refers to as "industry eating their seed corn" (32). If the United States is to produce high-quality Ph. D. engineers, salary money and research funding for engineering faculty, as well as a restructuring of bioprocess engineering education emphasizing interdisciplinary training may be necessary.

JAPAN

In Japan, training in basic biology research is relatively weak. The director of the new Bioindustry Office of Japan's Ministry of International Trade and Industry (MITI) has listed as one of his primary concerns the state of basic biology research in Japan. However increased Japanese Government funding for such research is not apparent. The University of Tsukuba, the heart of a new $5 billion "science city" 37 miles north of Tokyo, has the largest budget of Japan's 95 national universities, but has no plans to expand its graduate enrollment in biology (22).

The distinction between basic and applied science departments at Japanese universities is great. At Tokyo University, for example, basic and applied science departments are located on separate campuses and have little interaction. Furthermore, professors in pure science areas such as biology are proud of their independence from industry (35). There is little direct correlation in Japan between university basic sciences curricula and corporate personnel needs. Special interdisciplinary biotechnology programs combining basic and applied sciences have not been instituted at Japanese universities.*

Because of Japan's need to generate and transfer basic science to industry more rapidly, the Japanese Government is attempting to end the isolation of Japan's basic research. Japan's Science and Technology Agency (STA) funds "Leading Technology" (Senatsu Gijutsu) projects, that allocate research responsibilities between university and corporate laboratories, but this funding has not yet been applied to the biotechnology field. STA is also funding a new program called the New Technology Development Fund (Shingijutsu Kaihatso Jigyodan) that was established to help companies commercialize university-generated research. The Government has also proposed building two new biotechnology centers open to private sector corporations through universities. Each researcher will conduct research in his or her own laboratory, but exchange of information between the corporate and academic researchers will take place on a regular basis (35).

National laboratories supported by the Agency for Industrial Science and Technology of MITI encourage the flow of personnel into interdisciplinary generic applied research. The national laboratories provide a place for university professors, Government researchers, and corporate researchers to work together. These laboratories have been especially important in the development of agricultural sciences and applied microbiology, because there are few private institutes

*See *Chapter 17: University/Industry Relationships.*

carrying on significant research in these areas (35).

FEDERAL REPUBLIC OF GERMANY

In the Federal Republic of Germany, three types of nonindustry laboratories conduct basic research in biotechnology: 1) laboratories belonging to universities, 2) laboratories dependent on BMFT for operating expenses and on the German Research Society (DFG, Deutsche Forschungsgemeinschaft) for project support,* and 3) laboratories in institutes supported by the Max Planck Society (Max-Planck Gesellschaft zür Forderung der Wissenschaften), which in turn receives support from BMFT.

Although laboratories supported by BMFT and DFG, such as the Cancer Research Center at Heidelberg, carry out important biotechnology-related work, institutes funded by the Max Planck Society are responsible for the bulk of basic research advances in biotechnology. The Max Planck Institute for Plant Breeding Research in Cologne, which recently received an unrestricted grant from Bayer, boasts some of the best plant genetics teams in the world. BMFT would like to see closer cooperation between the Max Planck institutes and industry (21).

The center for generic applied research in biotechnology in the Federal Republic of Germany is the Society for Biotechnological Research (GBF, Gesellschaft für Biotechnologische Forschung). GBF is a Government-supported private institution that was founded to conduct generic bioprocessing research to meet the needs of industries (23). In 1972, 89 percent of its $13 million (DM31.6 million) came from BMFT (14).

Among the factors cited to explain Germany's slow entry into biotechnology is an educational system that prevents the kind of interdisciplinary cooperation that is viewed by most experts as essential to the development of this field (21). Because of the traditional separation of technical faculties from arts and science faculties in West Germany, bioprocess technicians, usually located in technical schools, rarely come into contact with colleagues holding university appointments in biochemistry or microbiology (21). In August 1981, BMFT policy called for greater interdisciplinary cooperation among biologists, chemists, medical experts, and engineers (21).

*See *Chapter 13: Government Funding of Basic and Applied Research.*

UNITED KINGDOM

The United Kingdom's system of funding research in biology and the medical sciences at universities has produced highly trained personnel in rDNA and hybridoma technology for industry. Furthermore, the country's Plant Breeding Institute is considered a model for interdisciplinary research on plants. Unlike the United States, therefore, the United Kingdom is probably not suffering interdisciplinary training problems in plant molecular biology.

Many British universities have programs in bioprocess engineering. Bioprocess engineering has been taught at the postgraduate level at University College in London and Birmingham to biologists and biochemists for nearly 20 years. Furthermore, at least 10 to 15 university centers are now involved in postgraduate biotechnology education, and these centers are receiving extra money from the University Grants Committee. One of these, the Centre for Biochemical Engineering and Biotechnology, was set up by three universities both to acquire new laboratory space and to launch new courses. Imperial College in London set up the Centre of Biotechnology with four new faculty positions. This center will work with other departments of the college involved in biotechnology to launch a biotechnology masters course. Funding for bioprocess graduate research and training in Britain's universities is also being provided by SERC. SERC has plans to fund four new specialized biotechnology courses in universities, which will all contain elements of bioprocess engineering. SERC will fund a maximum of 60 places for graduate students, and industry is encouraged by the Government to finance more places (45).

British universities have 30 to 40 teaching staff who teach biotechnology (including bioprocess engineering) on a full-time basis and a much greater number of teaching staff who devote varying proportions of their time to teaching biotechnology. According to bioprocess expert Malcolm Lilly, the United Kingdom has more teaching biotechnologists than the United States

and is also ahead of other European countries. Thus, there appears to be no current shortage of biotechnology faculty at British universities. Nevertheless, Government officials are worried that a lack of bioprocess engineering faculty may be a problem for the United Kingdom in the future because of the fairly small numbers of chemical engineers getting higher degrees in bioprocess engineering in recent years (45). To counter any shortage in teaching capabilities, the United Kingdom plans to involve industrialists in teaching bioprocess engineering courses at the universities.

FRANCE

In France, those pursuing higher education in scientific and engineering education go either to universities, to the more prestigious grandes écoles, or to Government-funded laboratories. French universities do not have graduate interdisciplinary courses in microbiology, rDNA technology, enzyme engineering, or bioprocessing techniques (33), and their creation will be difficult because of the lack of funds and a shortage of faculty. Four grandes écoles have interdisciplinary courses in biotechnology, but they produce only about 40 graduates a year total. However, other grandes écoles are now introducing courses in biotechnology (44). The Institut Pasteur, which is 49-percent Government-owned, regularly accepts doctorate students in biotechnology fields.

Other important loci of graduate training for biotechnology personnel in France, apart from the grandes écoles, are public research centers (grandes organismes), a very important part of the French research establishment. The grandes organismes have approximately 600 technical workers in biotechnology-related fields (nearly one-half of all of France's personnel in biotechnology), but they will probably find it difficult to create interdisciplinary training programs. At the largest and most significant organisme, the National Center for Scientific Research (CNRS, Centre National de la Recherche Scientifique), for example, there are communication problems between the scientific and engineering departments (44).

Transnational training in the United States and other countries

A trend evident in many scientific and technical fields, including biotechnology, is the training of increasing numbers of foreign students in the United States. In 1982, foreign students constituted 2.6 percent of the total U.S. university enrollment, and 23 percent of the foreign students enrolled at U.S. universities were studying engineering. In 1981, for the first time, more foreigners than Americans received doctoral degrees in engineering in U.S. graduate programs (15). The proportion of foreign students in American postdoctoral engineering programs was more than 60 percent. Furthermore, foreign students constituted a third of all postdoctoral students in American science and engineering programs (26). These numbers illustrate the esteem with which U.S. science and engineering education is held throughout the world (43).

In the areas of molecular biology and immunology, foreign nationals are actively seeking training at U.S. institutions. Hoechst's (F.R.G.) 10-year, $70 million contract with Massachusetts General Hospital, for example, was, in part, established to train Hoechst's personnel at Harvard Medical School (21).*

NIH has several programs that sponsor research by foreign nationals in NIH laboratories. Under the "visiting program," NIH sponsors and pays visiting scientists studying at NIH labs. In 1983, 810 foreign nationals were enrolled in this program. Of these visiting scientists, 158 were from Japan, 97 from India, 62 from Italy, 27 from France, and 6 from the United Kingdom. Under the "guest researchers program," foreign nationals are sponsored by their native country. In 1983, 32 Japanese were enrolled, 23 Italians, 21 French, 10 Indians, and 4 British (36).

Japanese personnel trained in the United States are now being actively recruited by Japanese

*This arrangement is discussed in *Appendix H: Selected Aspects of U.S. University/Industry Relationships.*

firms. In a 1982 Keidanren survey* of 60 Japanese companies using biotechnology, 35 percent of the companies were active in recruiting researchers already studying or working abroad (35). When the Japanese company Suntory hired new employees for about one-third of the 126 research positions in its Biomedical Research Institute established in 1979, for example, many of the new employees were Japanese who had been working abroad (35).

The larger more established Japanese companies sponsor transnational training of their employees. Sixty-two percent of Japanese companies responding to the 1982 Keidanren survey indicated that some scientific and engineering personnel would be sent abroad for training in specialized technologies (35).

Foreign nationals are being trained not only at university and government centers in the United States, but at U.S. companies looking for supplemental sources of revenue. Five corporate researchers from Japan recently attended a 3-month course at Genex in rDNA technology offered at $120,000 per person. According to the Japanese companies, they learned "highly specific knowledge . . . and key points for developing specific products by using the rDNA technology" (18).

Amid all the evidence that foreign countries are making use of U.S. training facilities, data show that U.S. doctoral graduates are going abroad for postdoctoral study less frequently. During the decade of the 1970's, postdoctoral training abroad decreased by nearly 50 percent (26). In biotechnology especially, postgraduate training abroad appears to be an area poorly funded by the United States. Professor Arnold Demain, for example, has indicated that 8 of the 11 students currently enrolled in his graduate program in industrial microbiology at Massachusetts Institute of Technology (MIT) are foreigners, all sponsored either by their government or company. Money to send Americans overseas to do postdoctoral work in industrial microbiology, however, is not available (7).

*Keidanren, the Japan Federation of Economic Organizations, is a national organization composed of about 700 of the largest Japanese companies. It enjoys the regular and active participation of the top business leaders working closely with a large professional staff to forge agreements on behalf of business as a whole. It often surveys its members on issues of economic importance.

Midcareer retraining in the United States and other countries

To address the challenges of biotechnology, industrial scientists and engineers can probably be retrained. Retraining in the United States is often viewed as the responsibility of the individual scientist or engineer and not that of the employer, with some exceptions (see below). A problem is that it is very difficult for a scientist or engineer in midcareer to take a year off to go back to school.

Reflecting concern over this situation, four senior professors at MIT recently published a report advocating "lifelong cooperative education" (48). The report's major recommendation was that engineering schools and neighboring industries collaborate in making off-campus graduate programs available to working engineers. Although the report was addressed specifically to the electrical engineering department of MIT, it could also be addressed to a larger community, and many of its recommendations may apply to biotechnology. For example, MIT Professor Daniel Wang recently stated that chemical engineers who "don't know the faintest thing about how proteins are isolated," if taught some basic protein chemistry, could develop new techniques for large-scale purification (17). Historically, chemical engineers in the United States have been retrained by pharmaceutical companies to be bioprocess engineers (7).

As shown in table 65, a relatively small percentage of the 95 companies responding to the OTA/NAS survey intend to retrain their workers to fill vacancies in areas of biotechnology personnel shortages. For most categories of Ph. D. personnel, hiring from academia is considered the optimal choice. In the case of Ph. D.s in bioprocess engineering, however, 86 percent of the companies planning to hire Ph. D. bioprocess engineers intend to hire them away from other companies, 50 percent plan to hire from academia; only 9 percent of the companies plan to retrain.* One

*These percentages exceed 100, because some companies indicated more than one hiring source.

reason for the very small amount of retraining in biotechnology may be the small size of many of the U.S. companies using biotechnology. The small companies that account for much of the biotechnology research activity in the United States probably do not have the resources to retrain personnel in-house.

Some foreign countries are pursuing the retraining of personnel more actively than the United States. The retraining of workers in Japan, more than in any other industrialized country, is viewed as the responsibility of the corporation. The Japanese permanent employment programs, prevalent in a majority of companies in the Japanese biotechnology-related industries, make it economically feasible for a firm's employees to be optimally trained at company expense (35). Japanese employees' salaries are in part based on the number of years they have been employed by the firm, so employees have strong incentives not to leave the firm for which they are working. Because employees in Japan are more likely to stay with their firms than employees in the United States, a far larger proportion of total training is sponsored by the Japanese private sector than in the United States (35).

The provision of corporate funding for worker retraining in biotechnology is common in Japan. According to the 1982 Keidanren survey, 53 companies indicated that they planned to use in-house training to meet, at least partially, their personnel needs (35). Some Japanese corporations, by commissioning research on a particular topic, are able to send their researchers to train at a university laboratory with a professor and his or her staff. At national universities, each professor is limited to approximately six or seven corporate trainees a year, but at private universities, there is no such restriction. As discussed above, training of Japanese workers at institutions in other countries is also common.

Japan's ability to overcome weaknesses in its labor force rapidly, due largely to corporate financing of worker retraining, is truly extraordinary. In 1981, for example, no more than 10 private Japanese firms had more than 10 researchers working on rDNA projects. A year later, the Keidanren survey in March 1982 revealed that 52 out of the 60 leading Japanese firms surveyed had 10 or more research workers in the area (35). It is partly because of the large-scale retraining of industrial personnel that Japan has been able to overcome a weak biological science base to remain a leading international competitor in the commercial development of biotechnology.

The European leader in the industrial retraining of its biotechnology work force is the Federal Republic of Germany. The German chemical industry association, DECHEMA, has an expert group on biotechnology, a standing body to bring academics and industrial scientists into regular contact. It organizes continuing education courses in various aspects of biotechnology (e.g., the use of immobilized enzymes, measurement needs, and control of bioreactors) (21).

The British and French Governments are adopting active policies to encourage retraining. In the United Kingdom, some Research Councils are offering short courses for midcareer scientists. Currently, MRC establishments are providing training in cell fusion and rDNA technology to the employees of Celltech and some larger companies, including Glaxo, ICI, and Seralab (45). In France, the Institut Pasteur runs postgraduate courses in biotechnology, long courses in both microbiology and immunology, and short specialized training courses (44).

Findings

The OTA/NAS survey of 95 companies using biotechnology in the United States suggests that approximately 5,000 workers are now doing biotechnology R&D in the 219 companies using biotechnology in the United States. Though the number is expected to increase about 30 percent over the next year, it is unlikely that a 30-percent annual growth rate can be maintained over the next decade. The commercialization of biotechnology is unlikely to contribute directly to large increases

in employment. Bioprocess technology, an essential part of industrial biotechnology activities, is not labor intensive.

About one-third of the technical personnel currently employed in 95 surveyed companies using biotechnology are specialists in basic science areas related to genetic manipulation: rDNA/molecular genetics and hybridoma/MAb technology. Specialists in these categories will continue to be important to biotechnology R&D, and more hirees are expected. Another third of the technical personnel currently employed by the U.S. companies using biotechnology are specialists in areas of applied science related to scale-up and downstream processing: microbiology, biochemistry, and bioprocess engineering. Of these categories, only hirees in bioprocess engineering will increase over the next 18 months. About one-fifth of the biotechnology work force are specialists in areas important to all aspects of biotechnology: enzymology and cell culture. The balance of people are specialists in such fields as pharmacology and toxicology.

The United States currently has a competitive edge in the supply of scientific personnel able to meet corporate needs for R&D in rDNA and hybridoma technology. This edge is primarily due to generous Federal support for university life science research since World War II. Nevertheless, the supply of Ph. D. specialists in plant molecular biology and in applied disciplines such as bioprocess engineering and industrial microbiology may be inadequate for U.S. corporate needs. It may be difficult to alleviate rapidly the shortage of engineers because of the shortage of Ph. D. engineers serving as university faculty and the lack of governmental training programs. To an extent, foreign technical personnel are alleviating some of the industrial shortages.

With the exception of France, the other competitor countries have adequate supplies of basic biological scientists. French companies are importing foreign specialists. German and Japanese companies, where slight shortages do exist, are making efforts to train some of their personnel abroad and to retrain workers. Some Japanese companies are making successful efforts to repatriate Japanese workers trained overseas.

Japan, the Federal Republic of Germany, and the United Kingdom, unlike the United States, maintained a steady supply of both industrial and government funding for applied microbiology and bioprocess engineering after World War II. Japan's supply of scale-up personnel appears to be sufficient. However, the United Kingdom and West Germany are suffering from a brain drain to foreign countries (in particular to the United States), and shortages of scale-up personnel may occur.

The United States has very few undergraduate or graduate interdisciplinary programs in biotechnology. Consequently, in the agricultural fields, for example, there are communication barriers between classical plant breeders and plant molecular biologists. Bioprocess engineering education in the United States is provided almost exclusively at the graduate level and is closely tied to training opportunities in chemical engineering with few interactions occurring between biologists and engineers. Funds for Ph. D. and postgraduate education in bioprocess engineering in the United States have been inadequate for the training of sufficient numbers of specialists for industry and academia. Furthermore, the high industrial demand for Ph. D. bioprocess engineers is likely to create a shortage of university faculty in the field.

Universities in the United Kingdom, in contrast to their counterparts in the United States, have long had interdisciplinary programs in biotechnology, and the British Government is encouraging the formation of overarching biotechnology programs in those universities where they do not already exist. Though France, the Federal Republic of Germany, and Japan have systematic barriers to interdisciplinary programs, their governments are utilizing national research institutes to facilitate interdisciplinary research in biotechnology.

The funding by foreign governments and companies for the training of domestic workers overseas is far more extensive than that of organizations within the United States. In fact, in biotechnology-related areas, the U.S. Government appears to fund more the training of overseas

nationals in the United States than the training of U.S. nationals abroad.

Switzerland, which has not been extensively discussed in this chapter, appears to have no trouble meeting the personnel needs in either its universities or companies developing biotechnology. Particularly in relation to the size of the country, Swiss academic institutions show unusual strength in both basic and applied research relevant to biotechnology. Swiss companies seeking to develop and expand their expertise in these technologies may choose to work with the qualified Swiss researchers in the university or may recruit foreign scientists, with apparently little difficulty, to work in Switzerland (20).

Retraining of corporate workers in biotechnology is being pursued more actively in foreign countries than in the United States. Japanese companies, in particular, make a regular practice of sending their workers to be retrained at Japanese and foreign universities and research institutions. Only a very small percentage of companies using biotechnology in the United States intend to retrain their workers in areas of personnel scarcity.

Issues and options

ISSUE 1: How could training for biotechnology at the graduate and postdoctoral levels be improved?

The United States appears to be suffering shortages of Ph. D. plant molecular biologists, applied microbiologists, and bioprocess engineers in its biotechnology-related industries. Although improved science education at the secondary school and undergraduate level could enhance the development of biotechnology in the future, the graduate level seems to be the best place to address the shortages of certain types of personnel.

For the past several years, U.S. Government funding for research in the areas of plant molecular biology, applied microbiology, and bioprocess engineering has been far less than funding for research in animal and bacterial molecular biology and immunology. Increasing Federal funding for research grants in plant molecular biology, applied microbiology, and bioprocess engineering, by encouraging more investigators to enter these fields, could help alleviate shortages of personnel. Since fields of faculty endeavor are at least partially determined by the availability of research grants, increased funding for research might encourage training and indirectly prevent future shortages of faculty. Options for directing research funds toward areas of personnel shortages are discussed in *Chapter 13: Government Funding of Basic and Applied Research.*

Another area where more Federal research funding could potentially reduce personnel shortages is that of interdisciplinary research. The interdisciplinary nature of biotechnology requires research collaboration among people with backgrounds in biology, engineering, and chemistry. Options that Congress could take to encourage interdisciplinary research are discussed below.

OPTION 1: Authorize increased funding for USDA, NIH, and NSF graduate and postdoctoral training grants in plant molecular biology, applied microbiology, and bioprocess engineering.

The lack of training grants is probably the single most outstanding reason for U.S. shortages in selected areas of biotechnology personnel. There are no NIH or NSF training grants for industrial microbiology or process engineering. The U.S. Department of Agriculture (USDA) this past year gave only five training fellowships in plant science. NSF until recently had no training grants at all in plant science, although in May of 1983, NSF's Biological and Behavioral Directorate approved 24 postdoctoral fellowships for study in plant cell biology.

In fields such as molecular biology, competitive training grants have been one of the most effective uses of Government funds for graduate and postdoctoral education. Training grants encour-

age university departments to carry on a cohesive training program and allow money from faculty research grants to be used for research instead of salaries. The institution of adequate training grants in the areas of plant molecular biology, applied microbiology, and bioprocess engineering would be a long-term strategy to counter personnel shortages in these areas. Such grants could be administered by NIH (for applied microbiology and plant biology), USDA (for plant biology), and NSF (for all three).

OPTION 2: Continue to support special incentives to encourage young engineers to stay in academia.

The shortage of engineering faculty at U.S. universities could seriously hamper efforts to increase the number of qualified engineers, including bioprocess engineers, in the United States. The recently instituted Presidential Young Investigator Awards to be administered by NSF is an example of the sort of special incentives program that Congress could continue to support to counteract the shortage of engineering faculty. Two hundred of these awards, 100 of which are to go to engineers, are to be awarded each year for 5 years to scientists and engineers in academia who have fewer than 7 years postdoctoral experience. Each award could total up to $100,000 per year for 5 years. The first $25,000 per year is to come from NSF. Industry funding for the engineers, of up to $37,500 per year, is matched by NSF, giving the total amount of $100,000.

OPTION 3: Specify that a certain percentage of NSF graduate and postdoctoral grants be used for training in other countries and authorize NIH and other relevant agencies to initiate researcher exchanges with other industrialized countries.

Increasingly fewer U.S. Ph. D.s are doing postdoctoral work abroad, while the number of foreign Ph. D.s doing postdoctoral work in the United States is increasing. The U.S. Government supports the training of its nationals overseas far less than its industrialized competitors.

Foreign countries have many significant and growing research programs in biotechnology that U.S. researchers could fruitfully be visiting—e.g., Japan's Fermentation Research Institute and University of Tokyo; the Society for Biotechnological Research (GBF) in Braunschweig, Federal Republic of Germany; and the John Innes Institute and Plant Breeding Institute in the United Kingdom. Few Americans are studying at those institutions. Though NSF's Science and Engineering Directorates can give grants to students studying overseas, such grants are not generally given because they are usually more costly than regular grants.

NSF's Science, Technology, and International Affairs Directorate has an International Cooperation and Scientific Activities program that provides special funds for researchers to study abroad—funds that can supplement the grants of other programs within NSF. One advantage of authorizing more money for this program is that this program has had experience negotiating standards of bilateral student exchange with foreign governments, having negotiated a successful bilateral agreement with France. In most foreign countries, American students cannot study at the best institutions (usually national) without the proper contacts and encouragement of the domestic government.

Congress could also specify that the NSF international grants that are given have a clearer training component. Currently, even the international fellowship grants are evaluated on the basis of their proposed research, rather than the quality of training for the U.S. nationals. It should be noted, however, that setting aside a part of NSF international grants for graduate and postdoctoral training would probably reduce the current percentage of international grants given to junior professors.

NIH's unilateral programs to support the study and research of foreign postdoctoral personnel in the United States could also be expanded to support the study of American nationals overseas. Since the United States is not the sole source of advanced R&D capability, Congress could authorize NIH to formulate programs that result in reciprocal exchanges and postdoctoral research opportunities for American scientists and engineers in areas of foreign expertise.

ISSUE 2: How could Congress improve interactions between classical plant biologists and plant molecular biologists?

Many people would argue that the agricultural research system in the United States does not need to be improved because the United States has the most productive agricultural system in the world. Nevertheless, there are specific areas where some advances in plant science, aided by new biotechnology, may be crucial to feeding the world's population in the coming years. These advances can be made only with the interaction of classical plant breeders and plant molecular biologists. Yet, because of the historical separation of agricultural researchers and plant molecular biologists in the United States, these groups do not have established communication networks. Most of the classical plant breeders are trained at agricultural research stations and land grant colleges, whereas most of the plant molecular biologists were originally trained in biochemistry, bacterial genetics, and animal biology (funded extensively by NIH) and are now working at the universities where much of the molecular biology is done. The lack of interaction between these two disciplines puts the United States at a disadvantage in modern agricultural research.*

The agricultural surpluses that the United States has today could vanish in a single year and probably are temporary. Greater productivity will be necessary as we move into the 21st century. The United States is also depleting its water resources and its topsoil. Advances in biotechnology can contribute to the solution of these problems with the development of plants that need less water, have greater nutritive value, and are more resistant to the high saline content of irrigation water. The costs of production can be lowered if plants are pest-resistant, and fewer fertilizers will be needed if plants can fix their own nitrogen. These advances cannot be made without greater interaction between classical plant breeders and plant molecular biologists. The Federal Government is spending about $20 billion on an acreage diversion program. This money subsidizes the market price, but does not address the central agricultural production issue, the farmer's low profit margin. Diverting a portion of this money to research on plant genetics could go a long way toward reducing agricultural production costs.

OPTION 1: Legislate the creation of one or more plant research institutes.

A plant research institute was established under the Department of Energy's (DOE's) management and with cooperation from the State of Michigan in 1965. DOE's contribution to this effort was $1.65 million in fiscal year 1983 and will be $1.7 million in fiscal year 1984. This is a beginning toward solving some of the problems of communication among biologists of different disciplines, but it is only one effort.

The creation of several more plant research institutes could facilitate interdisciplinary research between classical plant biologists and plant molecular biologists, although there could be some problems. First, a large amount of money would be required. Second, scientists to work in the institute would have to be drawn from other institutions, thereby possibly causing a shortage of teaching faculty. Faculty shortages could be partially alleviated if the institute were located near a major research university or land grant college. Third, it is not obvious what agency would administer the institute. DOE is one choice because it already has experience with one institute. USDA is another choice, but recent studies (see preceding footnote) have suggested that the research stations it already administers have not kept up-to-date with the latest molecular techniques being applied to plants. NIH, which is well versed in molecular biology, is not an ideal agency to administer an essentially agricultural program. NSF might be a candidate to administer a new plant research institute because of its interdisciplinary staff.

OPTION 2: Establish grants for cooperative research between classical and molecular plant biologists from different institutions.

*The administration of basic research in agriculture has recently been reviewed by several agencies (5,34,41). Changes in the administration of USDA research will be extremely important to the direction of development of biotechnology in agriculture. A proposal within USDA to significantly increase the competitive grants in plant biology has recently been published (25). However, an assessment of the USDA technical and administrative infrastructure is beyond the scope of this report.

An increase in funding alone would facilitate interaction between classical and molecular plant biologists. Because of its interdisciplinary focus, NSF might be the agency to administer these grants.

Careful specification of requests for proposals and monitoring of the grants by technically qualified staff would be needed to ensure that the research that is funded is truly cooperative. Otherwise, some researchers experiencing difficulties in obtaining research funding might be tempted to cooperate in proposal writing in order to obtain a grant and then carry out independent research.

ISSUE 3: How could the retraining of industrial personnel in biotechnology be improved?

The OTA/NAS survey of companies using biotechnology in the United States shows that there is little retraining of personnel in this field. This situation is probably due, in part, to the fact that many of the U.S. companies using biotechnology are small and have neither the resources nor incentives to retrain personnel. These small companies depend on their ability to attract already highly qualified personnel. However, the pharmaceutical industry has shown that chemical engineers can be retrained in bioprocess engineering.

Continuing education sponsored by large U.S. companies, in general, takes place through short courses or joint research performed at universities. University/industry training and research agreements in biotechnology are being developed without the assistance of the Federal Government. But the Government could further encourage retraining in biotechnology by increasing funding for NSF's Industry/University Cooperative Centers Program, which provides seed money for a university to set up a research center with industrial partners. This option is discussed in *Chapter 13: Government Funding of Basic and Applied Research.*

Whether human resources in the United States are used and retrained adequately is a larger, national question that addresses the transition of the U.S. labor force from declining to growing industrial sectors. Suggestions to encourage more retraining have included revision of the tax code to encourage business loans to employees for retraining and an extension of unemployment insurance to include payment for retraining. The comparative evaluation of measures such as these that include other disciplines is beyond the scope of this study.

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Chapter 15

Health, Safety, and Environmental Regulation

Contents

Chapter 15

Health, Safety, and Environmental Regulation

Introduction

Regulation has been and will continue to be a factor in the development of biotechnology, especially for recombinant DNA (rDNA) processes and products. When the rDNA technique was first developed, its novelty and tremendous power to manipulate organisms raised the specter of potentially drastic consequences to human health and the environment through the creation and proliferation of organisms with unknown but potentially hazardous traits. In the United States, therefore, Congress moved to develop stringent regulation of rDNA. This movement was forestalled in part by the adoption in 1976 of fairly restrictive self-regulatory guidelines by the scientists (27).

As time passed, however, concern and fears diminished greatly. As scientists learned more about molecular genetics, perceived risks associated with probing the unknown diminished, and no evidence was discovered to support many of the early risk scenarios. Formal risk assessment studies also led to downward evaluation of potential risk. Molecular biologists gained the confidence of the public by bringing other experts and the public into the decisionmaking process that established the system of voluntary self-regulation. And, most importantly, there has been no evidence of any harm to human health or the environment from rDNA. Consequently, the requirements of the rDNA guidelines in the United States have been substantially relaxed.

Today, most experts believe that the potential risks of rDNA research were drastically overstated and that rDNA technology generally does not involve a risk beyond that already inherent in the host, vector, DNA, solvents, and physical apparatus being used (35). This is not to say, however, that biotechnology—like most new technologies—does not continue to raise special concerns or present special risks. In particular, questions have been raised about the long-term effects on workers' health from exposure to novel organisms and products and about the risks of deliberately releasing genetically manipulated organisms into the environment. In addition, some of the products that will be made by biotechnology may present special risks. For example, the U.S. Food and Drug Administration (FDA) has been concerned about bacterial endotoxins found in drugs produced by *Escherichia coli* (28).

Regulation will have a moderately important effect on the development of biotechnology and, consequently, on U.S. competitiveness in biotechnology. Special risks may lead to limited new regulation that could direct commercial efforts away from certain areas or at least slow advancements in those areas. In addition, most of the products that could be made by biotechnology and associated processes are already subject to considerable regulation, pharmaceuticals and chemicals being the best examples. This existing regulation also will affect corporate strategies and patterns of industrial development.

The costs and time involved in complying with regulatory requirements are the price society pays for safety. However, unreasonable restrictions and unnecessary burdens may delay or prevent important products from reaching the market or may increase the business risks of developing those products. Uncertainties, for example, about what the regulatory requirements will be or which agencies have jurisdiction, will also affect the risk, time, and cost of product development. Those countries that have the most favorable regulatory environment in terms of least restrictions and uncertainties will have a competitive advantage in the commercialization of biotechnology.

This chapter evaluates the regulatory environment for the commercialization of biotechnology in the United States and five competitor countries

being examined in this assessment—the Federal Republic of Germany, the United Kingdom, France, Switzerland, and Japan. Two specific factors are considered in the evaluation: 1) the restrictiveness of the regulation, and 2) the uncertainties with respect to possible agency jurisdiction or requirements. Congressional options for improving U.S. competitiveness in biotechnology through changes in the regulatory environment are presented at the end of the chapter.

In the analysis that follows four areas of regulation are considered:

- regulation directed specifically toward biotechnology;
- existing regulation that would apply to biotechnology products;
- environmental regulation relevant to biotechnology; and
- worker health and safety regulation.

The chapter concentrates on the guidelines for rDNA research adopted by the competitor countries and the approval requirements for pharmaceuticals (human drugs and biologics) and for veterinary medicines (animal drugs and biologics). The guidelines for rDNA research merit significant attention because they are the only type of governmental oversight developed specifically for biotechnology. The approval requirements for pharmaceuticals and veterinary medicines also merit attention because those products are subject to the most restrictive regulation, even when made by conventional means,* and because so much of the current activity in biotechnology is directed toward those types of products. In addition, with respect to regulation of products in other countries, most of the information OTA was able to obtain related to the approval process for pharmaceuticals and veterinary medicines. Sufficient information on foreign regulation of food, food additives, medical devices, and chemicals was not available for meaningful international comparisons; however, this information is included for the United States because of its availability and because of the interest in it.

Two inherent limitations could qualify the analysis in this chapter. The first results from the difficulty of determining and interpreting foreign laws and especially the rules and policies of the foreign agencies. Much of this material is not readily available in English or even in the native language. In addition, enforcement of laws and regulations in other countries generally is much more discretionary than in the United States.* Thus, there may be a wide gap between the written laws and regulations and the actual regulatory environment in which foreign companies operate. The second limitation results from the fact that the analysis does not consider the positive effects of regulation and a country's track record for safety. In other words, the restrictiveness of regulation theoretically should be balanced against some measure of the harm avoided. However, the necessary data are generally not available, and such an analysis is beyond the scope of the chapter.

*Significant regulation also exists for commodity and specialty chemicals (including herbicides and pesticides), but it is generally not as restrictive as for pharmaceuticals and some types of veterinary medicines. The use of genetically modified organisms in the environment will probably face some moderate degree of regulation. Agricultural products currently face little health, safety, or environmental regulation, but this situation could change in the case of genetically modified plants and animals.

*In fact, this discretion has led to claims of selective enforcement against U.S. companies, thus creating a nontariff trade barrier. For discussion of other nontariff trade barriers, see *Chapter 19: International Technology Transfer, Investment, and Trade.*

Regulation directed specifically toward biotechnology: rDNA research guidelines

The only oversight mechanism directed specifically toward biotechnology is the rDNA research guidelines. These guidelines grew out of the concerns in the mid-1970's about potential risks of rDNA research and the desire to proceed cautiously in the face of the uncertainties. Guidelines

similar to the National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) in the United States have been adopted by Japan, the Federal Republic of Germany, the United Kingdom, France and Switzerland. Over time, they have been substantially relaxed worldwide in a series of revisions that reflect decreasing concern about the risk. In fact, many types of experiments involving rDNA are now exempt from the guidelines. The guidelines are essentially self-regulatory.

The guidelines for rDNA research reflect the decision by experts and policymakers that rDNA research presents some special risks and uncertainties that require special attention. They are based on two underlying concepts:

- rDNA research should be conducted at increasing levels of physical and biological containment related to the degree of possible hazard, and
- the degree of oversight should relate to the degree of possible hazard.

The implementation of these concepts is fairly similar in the competitor countries, because the worldwide scientific community was involved in their development and because most countries followed the lead of the United States. Nevertheless, there are some important differences among the guidelines adopted in the various countries, and different countries are at different stages in the process of relaxing them.

This section surveys the rDNA research guidelines of the six competitor countries with respect to their scope, containment requirements, approval requirements, and enforcement mechanisms in order to assess their impact on competitiveness in biotechnology.* The commercial development of biotechnology in many of these countries, however, will depend less on the specific biological and physical containment measures required by their rDNA research guidelines than on the scope of activities reached by the guidelines (i.e., whether they cover large-scale research) and the structure set up for implementing and enforcing the guidelines. The analysis presented here is based on the more detailed description of the rDNA research guidelines of the six countries and the European Economic Community found in *Appendix F: Recombinant DNA Research Guidelines, Environmental Laws, and Regulation of Worker Health and Safety,* which the reader is urged to examine.

*Provisions relating specifically to worker health and safety are discussed in the section of this chapter entitled "Regulation of Worker Health and Safety."

Scope

In the United States, Japan, and France, the guidelines technically apply only to government-funded rDNA research, while in Switzerland, the Federal Republic of Germany, and the United Kingdom, they apply to all rDNA research. (Actually, all the guidelines also apply to large-scale rDNA work to varying degrees, as discussed below.) While U.S., Japanese, and French private laboratories might seem to have some advantage over private laboratories in the other countries because they could dispense with safety measures perceived to be unnecessary, this "advantage" is probably illusory. Industry perceives compliance with the guidelines to be in its best interest, and there has been no publicized evidence of noncompliance.

Perhaps the single most important issue for companies using biotechnology is the rDNA guidelines' treatment of large-scale research (i.e., work with cell cultures in volumes exceeding 10 or 20 liters), which is a necessary step in successful commercial development. The guidelines in Japan are easily the least favorable in this regard. Recombinant DNA research with volumes exceeding 20 liters can be conducted in Japan only after Government permission, and that permission has been quite difficult to obtain.* It should be noted, however, the situation in Japan is expected to change shortly.** Under the U.S. guidelines, the large-scale work need only be reviewed by each

*Six companies have obtained permission for large-scale work (14).

**The Council for Science and Technology, which advises the Prime Minister and oversees rDNA work by private institutions in Japan, is expected to recommend the elimination of the prohibition of large-scale work without special Government approval. Instead, large-scale bioprocess facilities would classify into two categories, LS1 and LS2. LS1 facilities would be covered by rules similar to those for conventional microbiological laboratories. LS2 facilities, which would involve work with more hazardous micro-organisms, would be covered by more stringent rules. The Prime Minister is expected to act favorably on the recommendation in August 1983.

Institutional Biosafety Committee (IBC), although NIH has made specific recommendations regarding physical containment, which were recently incorporated into the U.S. guidelines. Large-scale research in the United Kingdom is treated on a case-by-case basis by the supervising authority, the Genetic Manipulation Advisory Group (GMAG).* But in explaining the need for a different kind of review of large-scale research, GMAG has suggested that large-scale research will not be subject to as stringent containment measures as smaller scale research. The French rDNA guidelines exclude large-scale research from their coverage, but the Government's oversight agency will apparently consider such activity on a case-by-case basis. The West German guidelines do not mention large-scale research. The Swiss guidelines permit scaling-up without special approval; it is unclear whether the small-scale rules continue to apply or whether, as with the NIH guidelines, large-scale research is subject to the safety measures decided on by the IBC.

Containment requirements

Each country's rDNA guidelines specify requirements for physical and biological containment of the research organisms. Except for the United Kingdom, each country assesses risk in the same manner—according to the source of the DNA used in the experiment and the pathogenicity of the host-vector system. The United Kingdom determines risk by considering the survivability and likely harm of the organism containing rDNA. Whether this risk assessment method gives the United Kingdom an advantage or disadvantage depends on the particular experiment. The United Kingdom does have an advantage with respect to rDNA production of insulin and interferon, which are classified at a lower containment level there than in the United States (8). Each country uses four levels of physical containment. Most research is now conducted at the lowest physical containment level.

*GMAG's status was recently reviewed by the Health and Safety Executive, and the subsequent report recommended relocation of the group from the Department of Education and Science to the Department of Health and Social Security. GMAG has been moved and is now called the Health and Safety Commission Advisory Group on Genetic Manipulation.

The physical and biological containment measures required for an experiment vary slightly from country to country, but it is difficult to determine what effect on a country's competitive position any one requirement might have. It is difficult to determine, for example, what effect will come from the fact that at the United Kingdom's physical containment level II, a continuous air flow into the laboratory is required, while it is not required in other countries until the third containment level. The measures with the greatest impact are probably the biological containment rules in Japan, which severely restrict the types of organisms that can be used in host-vector systems. These restrictions may prevent commercially promising rDNA research from going forward.

Approval requirements

Notice and approval requirements depend on the risk of the experiment. Research in the United States at the highest risk level is subject to the approval of NIH and the appropriate IBC; at the next level, only IBC approval before initiation is necessary. IBC notification at the time of initiation is required for some lower level risk experiments, while many are exempt entirely. More than 85 percent of all rDNA work in the United States is done at the lowest containment levels (23), and virtually all monitoring of rDNA work is done by IBCs.

The recommendation of the European Economic Community (EEC) on rDNA research suggests that notice of experiments be given to the central authority in each member state, usually before the work begins. For some types of research, notice would not have to be made before work is begun. The United Kingdom, France, and the Federal Republic of Germany are members of the EEC.

In the United Kingdom, the Health and Safety Executive (HSE) is directed to inspect the facilities for rDNA research at the two higher containment levels, categories III and IV. For research at these levels, GMAG also must have notice and an opportunity to give advice. Advance notice is required for research at the category II level but not approval. Activities at the category I level can go forward provided only that the local safety com-

mittee notifies the central authorities once a year of new research. Companies in the United Kingdom also have to deal with two separate agencies: GMAG, which promulgates and monitors the rules, and the HSE, which enforces them.

Scientists in France must notify the French Control Commission (Commission de Contrôle) of planned research. This commission must approve certain high-risk research. Local safety committees monitor the research.

In the Federal Republic of Germany, the Central Commission for Biological Safety (Zentrale Kommission für die Biologische Sicherheit) must be notified of all research except that at the lowest level of containment. This requirement makes for one of the most restrictive approval processes in the countries surveyed. Experiments at the two high-risk levels require the entire commission's approval, while those at the second lowest containment level must be approved by one or two individual members of the commission. The Commission for Biological Safety must also authorize the use of host-vector systems not enumerated in the rDNA research guidelines and may approve reductions in levels of containment employed.

Switzerland, where rDNA research is now conducted under guidelines that are essentially equivalent to the April 1982 NIH Guidelines (34), differs from the United States in an important respect. The research is overseen by a commission created by the Swiss Academy of Medical Sciences. The commission, as a private entity, may be more willing than NIH to modify requirements for projects with which it is familiar.

In Japan, two different bodies monitor rDNA research, the Council for Science and Technology, which supervises activities by private institutions, and the Science Council (in the Ministry of Education), which monitors the activities of public institutions such as universities. The Science Council is not required to approve university experiments, which may go forward simply on the approval of the president of the university and the university safety committee. However, it must approve the use of hosts other than those specified in the guidelines. Only a limited number of hosts and vectors have been approved for use, which puts Japan at a competitive disadvantage.

Enforcement

In all of the countries except the United Kingdom, the only direct sanction for noncompliance with the rDNA research guidelines is the ability of the government to restrict or withdraw funding for an institution's or a scientist's rDNA research. The guidelines in the United Kingdom are promulgated under the Health and Safety at Work Act of 1974 and are backed-up by the general legal sanctions created by that act.

Effect on competitiveness

The commercial effect of the rDNA research guidelines is difficult to assess, because their effect depends on the specific research done and because commercial exploitation of rDNA research has only recently begun. With the exception of Japan and possibly the Federal Republic of Germany, no country's rDNA research guidelines place it in a noticeably disadvantageous position. However, the U.S. rDNA research guidelines are probably the least restrictive of the six competitor countries. The European countries and Japan have generally followed the U.S. guidelines but are often following earlier, more restrictive versions.

Existing regulation of biotechnology products

A comparative assessment of the regulation of biotechnology products in the competitor countries involves two stages. Since biotechnology products generally will be subject to existing regulation for generic products, it is first necessary to compare these general regulatory regimes. In other words, biotechnologically made pharmaceuticals, for example, will be subject to

the general regulations covering pharmaceuticals, regardless of how they are made; thus, comparing the pharmaceutical laws of the different countries will provide information about competitiveness. In this context, the following questions are particularly relevant:

- How much time and effort does it take to get products through the approval process?
- What is the usual or average cost for securing regulatory approvals?
- What are the import and export restrictions on approved and unapproved products?
- Will the regulatory authorities accept foreign test data in the approval process?

The second stage of the analysis involves looking at specific issues raised by biotechnology. Some of these are the following:

- Will new biotechnology products chemically identical to approved products made by other means still be required to go through the full regulatory review process?
- Will the classification of a pharmaceutical as a drug or biologic affect the time or cost of securing regulatory approval?

United States

Three Federal agencies will be most involved in regulating biotechnology products. They are the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and the Environmental Protection Agency (EPA).

FOOD AND DRUG ADMINISTRATION

FDA regulates drugs, biologics, food, food additives, and diagnostics pursuant to the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. §§301-392) and section 351 of the Public Health Service Act (21 U.S.C. §262).

Since the first commercial applications of biotechnology (i.e., pharmaceuticals) have been in areas subject to FDA jurisdiction, FDA is the agency having the most experience with biotechnology products. FDA has approached rDNA-produced products on an agencywide basis by creating a Recombinant DNA Coordinating Committee, composed of representatives of its centers and bureaus, the Office of General Counsel, and Office of Regulatory Affairs. FDA's Recombinant DNA Coordinating Committee has determined that rDNA products whose active ingredients are identical to ones already approved or to natural substances will still have to go through the new product approval process. Data requirements may be modified and often abbreviated, however, and each case will be handled on an ad hoc basis.* (In the case of many conventionally produced products, abbreviated review procedures are available when the active ingredient of the new product is identical to one already approved or to natural substances.) FDA will not require compliance with the NIH Guidelines as a condition of approval. For monoclonal antibody (MAb) products, no coordinating body similar to the Recombinant DNA Coordinating Committee exists; FDA's policy for these products has been set by the National Center for Devices and Radiologic Health (NCDRH) and the Office of Biologics. Actual product regulation will occur at the individual bureaus or offices as discussed below.

Human Drugs.—FDA's Office of New Drug Evaluation has taken the position that drugs made by rDNA technology, even if identical to currently approved drugs, are "new drugs."** Therefore, such drugs cannot be marketed until approved by FDA as safe and effective.

FDA's approval process for a new drug can take several years because it requires a series of animal and human tests. Clinical investigations can be carried on only after a drug's sponsor files a Notice of Claimed Investigational Exemption for a New Drug (IND). The IND contains the results of animal testing, a description of the planned clinical investigations, and other information. The preclinical investigations generally last from 1 to 2 years (20). The human studies then go through

*FDA has been concerned about bacterial endotoxins and immunogens contaminating the products and about the genetic stability of the rDNA organism. In the latter case, the product might be affected if the DNA underwent changes.

**A new drug is a drug whose composition is not generally recognized by qualified experts as safe and effective under the conditions of use set forth in its labeling or, even if so recognized, has not been used to a material extent or for a material time (sec. 201(p) of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. §321(p)). A drug is a substance intended for use in the diagnosis, treatment, or prevention of disease or which is intended to affect the structure or function of the body (sec. 201(g) of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. §321(g)).

three phases to establish safety, set dosage levels, and establish efficacy. This clinical testing often takes 5 to 6 years (20). During or after the clinical studies, the sponsor files a New Drug Application (NDA), which contains the results of animal and human testing, a statement of the drug's composition, a description of the methods and controls used in its manufacture, and other information. The time required for processing an NDA depends on the completeness of the data, the drug's performance, and the speed of FDA review. In 1980, the duration of the NDA phase for new chemical entities varied from about 1 to 7 years and averaged slightly less than 3 years (20).* Taking into account the research and development (R&D) costs of drugs that fail to reach the market, various economic analyses indicate that the R&D costs per marketed new chemical entity range from $54 million to over $70 million (11).

There are abbreviated approval procedures that FDA might eventually permit sponsors to use after it gains more familiarity with rDNA technology and if warranted by the risks. One is the Supplemental New Drug Application (SNDA), which is required when an NDA holder intends to market the drug under conditions materially different from those approved in the NDA. An SNDA could become available in the case where the manufacturer of an approved drug made by chemical synthesis decides to make the drug by using rDNA and bioprocess techniques. A second procedure is the Abbreviated New Drug Application (ANDA), which is available for generic versions of drugs first marketed between 1938 and 1962. An ANDA might be used by a manufacturer using rDNA techniques to make an approved drug made by conventional techniques by another manufacturer. The final procedure is a "paper" NDA, available for generic copies of drugs marketed after 1962. Such drugs require an NDA, but FDA is willing to accept published reports demonstrating safety and efficacy, thus saving the new sponsor the time and costs of clinical trials. A "paper" NDA could become available in the case where a manufacturer wants to make an rDNA-produced drug whose NDA is held by another manufacturer, if adequate data are available in the published literature to establish safety and effectiveness.

Human Biologics.—A biologic is a vaccine, therapeutic serum, toxin, antitoxin, or analogous product for the prevention, treatment, or care of diseases or injuries. The distinction between a drug and a biologic is largely historical and bureaucratic and is becoming even more blurred with the advent of biotechnology.

Although biologics also come within the definition of drugs in section 201(g) of the Federal Food, Drug, and Cosmetic Act (FFDCA), they primarily are regulated under section 351 of the Public Health Service Act and by FDA's Office of Biologics rather than the Office of New Drug Evaluation.* Section 351 creates a regulatory structure for biologics similar to that for drugs. However, it is a licensing procedure; both the product and the establishment where it is produced must be licensed. At the investigational stage, the Office of Biologics follows the requirements for INDs. After clinical trials, the procedure involves a license application for the establishment and for the product; together they provide essentially the same information as required by an NDA. Differences, however, occur in practice. The Office of Biologics generally has been perceived to be more flexible than the Office of New Drug Evaluation. It often uses informal, unpublished guidelines, or "regulatory memoranda."** On the other hand, it is the administrative practice of the Office of Biologics to require lot by lot approval of many biologics before they are released by the manufacturer, which is not usually required by the Office of New Drug Evaluation (1).

Biologics made by biotechnology will have to go through the approval process outlined above. In accordance with announced policy, rDNA-produced biologics, even if chemically identical to approved biologics, will have to go through the

*A General Accounting Office study of the U.S. drug approval process found that for 132 NDAs submitted to FDA in 1975, the average approval time was about 20 months (20).

*The Office of Biologics also regulates diagnostics related to blood bank products. All other diagnostics, including most of those incorporating monoclonal antibodies (MAbs), are regulated by FDA's National Center for Drugs and Radiologic Health (NCDRH). The first MAb diagnostic kits related to blood products and were approved by the Office of Biologics.

**It has published three about biotechnology. One covers MAb diagnostic kits for blood bank related products (31). Another covers MAbs for use in human therapy (33). A third covers the production and testing of interferon (32).

full approval process, but data requirements may be lessened. For MAbs, there has been no announced policy, but virtually all of those that would be used for therapeutic purposes would be truly new and therefore have to go through the full review process.

Medical Devices.—Medical devices are regulated by FDA's National Center for Devices and Radiologic Health (NCDRH), except for those in vitro diagnostic products used in connection with blood banking activities such as tests for hepatitis B surface antigen. Those products are regulated by the Office of Biologics.

The Medical Device Amendments to FFDCA in May 1976 required that all devices for human use marketed before the amendments be classified by FDA into one of three categories on the basis of recommendations by expert panels. Class I products are subject to general controls, such as good manufacturing practice regulations. Class II devices are required to meet performance standards in addition to the general controls. Class III devices require FDA premarket approval for safety and effectiveness. For devices marketed after May 1976, those that are "substantially equivalent" to a preamendment device are classified with that product, and those that are not substantially equivalent are placed in Class III. Under section 510(k) of the act, manufacturers are required to give FDA a 90-day notice before they can market a device, during which period FDA determines whether the device is substantially equivalent to a preamendment device.

Manufacturers of MAb diagnostic kits generally have been successful in using the 510(k) notice procedure to get their products to the market quickly. Although MAbs are different from and generally superior to polyclonal antibodies for diagnostic purposes, applicants have been successful in showing that MAbs are "substantially equivalent" to polyclonal antibodies marketed before May 1976. That is, the applicants have demonstrated to the satisfaction of NCDRH that the MAbs provide essentially the same (or better) results as polyclonal antibodies used for the same diagnostic purposes (1). Since the review panels of experts required by the statute have placed most preamendment diagnostic kits in Class II (1), the new MAb kits have been placed in Class II, which requires certain performance standards to be met, rather than Class III, which would require the manufacturer to demonstrate safety and efficacy.* The availability of the 510(k) application is highly desirable from a company's perspective because NCDRH must respond within 90 days.

Food and Food Ingredients.**—The distinction between food and food ingredients (substances added to food) is important in terms of the regulatory approval process. Food can be marketed without FDA clearance, but food ingredients are subject to the food additives provisions of FFDCA, which may require premarketing approval. FFDCA defines food broadly and circularly as food or any component thereof (sec. 201(f)). A food additive is defined as a substance that may, by its intended use, become a component of food or affect the characteristics of food (sec. 201(s)). This definition excludes, among other things, substances generally recognized as safe (GRAS) by qualified experts and certain prior-sanctioned (previously approved) substances. A new food additive requires premarketing clearance by FDA, and its sponsor has the burden of demonstrating its safety. Favorable action by FDA results in a published regulation stipulating the concentration and other conditions under which the additive may be used. GRAS substances technically can be marketed without prior approval by FDA, but also can be the subject of published FDA regulations.***

FDA's Bureau of Foods has not been confronted with any foods, food additives, or GRAS substances produced by rDNA techniques; however, on the basis of the announced policy of FDA's Recombinant DNA Coordinating Committee and discussions with the staff, the Bureau appears likely to take the following positions. If FDA were concerned about the safety of such a food, high lysine corn, for example, it could take various

*If a MAb kit were placed in Class III, the sponsor could petition for a reclassification to Class II; however, such reclassifications are supposedly difficult to obtain.

**This section uses the term food ingredient instead of the term food additive used in other chapters, because the term food additive has a particular meaning under FFDCA. As explained in this section, under FFDCA a food additive is one type of food ingredient (substance added to food).

***FDA publishes lists of what it considered to be GRAS substances and sometimes it will consider a substance GRAS only when used under certain conditions.

steps to prevent its sale or remove it from the market by proving it was "ordinarily . . . injurious to health" and, therefore, was adulterated within the meaning of section 402(a) of FFDCA. It might be able to require premarketing clearance if the corn were used as an ingredient in other foods, such as stew, because then it would be subject to the food additive requirements (21 C.F.R. §170.30 (f)). Recombinant DNA products that are similar or chemically identical to GRAS substances or food additives already approved for use will be required to go through the approval process by FDA's Bureau of Foods, although the Bureau will be flexible on data requirements.

Animal Feeds, Feed Additives, and Devices.—These products are regulated in a way similar to the way in which human foods, food additives, and medical devices are regulated; however, the regulation for animal products is less rigorous than that for human products. For animal feeds and feed additives, the requirements for demonstrating safety are less than for the comparable case of human food and food additives. In the case of animal feed additives, however, there is an additional requirement that they be shown to be safe to people consuming edible products from animals receiving the additive. For animal devices, there is no premarket approval requirement as there is for many human devices. At this time, there is no reason to expect any particular regulatory problems if these products are made by biotechnology.

Veterinary Medicines.—For veterinary medicines (animal drugs and biologics), FDA's authority is similar to its authority for human drugs or biologics with two exceptions. First, there is an additional requirement in the animal drug approval process, i.e., animal drugs must not leave unsafe residues or metabolites in edible tissues or other food products. Second, FDA does not have the primary regulatory authority over animal biologics; USDA regulates them under the Virus, Serum, Toxin Act of 1913 (VST Act) (21 U.S.C. §§151-158), even though they are also technically drugs under FFDCA. USDA's authority applies only to interstate marketing. According to a recent case, FDA has jurisdiction over intrastate marketing (10).

These jurisdictional distinctions have been blurred by rDNA and MAb technology. An FDA/USDA memorandum of understanding creates a standing committee to sort out regulatory responsibilities in this area (29).* The memo says FDA will regulate where the VST Act does not apply or does not offer an appropriate remedy.

The first product to be considered by the standing committee is bovine interferon. Both agencies claimed jurisdiction, and the committee has split along agency lines. Several attempts to resolve the impasse on scientific grounds have failed; however, efforts are continuing. In the meantime, the manufacturer has encountered additional costs and burdens by attempting to meet the requirements of both agencies (6).

Control Over Exports.—Under section 801(d) of FFDCA, unapproved food additives and medical devices can be exported if certain conditions are met.** Unapproved new human drugs or biologics and unapproved new animal drugs, however, cannot be exported except in the following two cases: 1) if the products are subject to an IND, providing the importing country's government has approved such imports; or 2) if the importing country's government formally requests through the U.S. Department of State that the product be exported (for purposes of clinical trials only) (21 C.F.R. §312.1(a)). As to unapproved animal biologics, there is some question about whether the VST Act applies to exports. Nevertheless, it is clear that FDA has authority over such exports, and, as indicated in the previously

*The FDA/USDA memorandum of understanding defines animal biologic products as those that "generally act through a specific immune process and are intended for use in the treatment (including prevention, diagnosis, or cure) of diseases in animals. Such products include but are not limited to vaccines, bacterins, sera, antisera, antitoxins, toxoids, allergens, diagnostic antigens prepared from, derived from, or prepared with micro-organisms, or growth products of micro-organisms, animal tissues, animal fluids, or other substances of natural or synthetic origin."

**An approved food additive can be exported if the exporter determines, without any need to inform or petition FDA, that the four conditions in sec. 801(d)(1) of FFDCA are met. The same is true for a Class I medical device, but an unapproved Class II or Class III medical device cannot be exported unless a petition has been submitted to FDA and FDA has found that the exportation is not contrary to the public health and safety of the importing country and has the approval of the importing country, under sec. 801(d)(2) of FFDCA.

discussed memorandum of understanding, FDA could exercise that authority.

The U.S. policy of restricting the export of unapproved drugs and biologics is essentially based on paternalism. Many countries do not have the mechanisms either to evaluate or to regulate the quality of the drugs they import. In addition, there have been cases of drug dumping—situations where drugs deemed unsafe or ineffective by the United States or other developed countries have been marketed in less developed countries (25).

This policy has several implications for U.S. companies using biotechnology, and the implications may differ depending on the size of the company. In part because of the export restrictions, several of the large U.S. pharmaceutical companies have established manufacturing facilities in foreign countries, where their products are approved or where the law permits the export of unapproved products. These actions result in the transfer of technology, lost employment opportunities for U.S. workers, and lost opportunity to help the U.S. international balance of payments. These consequences can be expected to continue with respect to biotechnology products. The existence of such facilities in foreign countries may provide the large companies with at least a short-term competitive advantage over small, new biotechnology firms (NBFs).* The vast majority of the latter companies do not have and probably cannot afford to establish foreign facilities.

The export restrictions will also have an important implication for NBFs and for U.S. competitiveness in general because they may foster technology transfer to foreign companies with which they have joint ventures. In their joint ventures with large foreign companies, some NBFs in the United States are required to provide bulk product produced by the micro-organism to the foreign partner, which would secure necessary approvals and purify, package, and market the drug in foreign markets. If the U.S. firm is unable to provide bulk product, the foreign partner then has the right to obtain the organism for its own use. The U.S. prohibitions on the export of unapproved drugs and biologics might be one reason why an NBF could not fulfill its agreement to supply bulk product to its foreign partner, thereby being required to transfer the organism and the technology.

In proposed revisions to the regulations governing the approval of new drugs, FDA has taken the position that bulk products, which it calls "drug substances," can be exported only if they are used in the manufacture of approved drugs and if certain labeling requirements are followed (30). FDA has proposed to define "drug substance" as "an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis . . . treatment or prevention of disease. . . ." (30). This definition would cover drug products produced by biotechnology, even if they required purification, packaging, and labeling, because such products usually will be active. At least one NBF in the United States has argued that section 801(d) of FFDCA should not be interpreted to prohibit the export of such substances for purposes of clinical trials (if the conditions of sec. 801(d) are met) and that such an interpretation will require it to transfer technology for the reasons mentioned in the preceding paragraph (9).

This entire problem concerning the export of unapproved drugs can be avoided in the future, however, without changes in the law or regulations. As mentioned previously, the current U.S. regulations allow the export of unapproved drug substances upon the formal request of the importing country's government. NBFs in the United States rightly point out that such requests are unlikely in cases where the government is actively seeking to encourage inward technology transfer. However, the NBFs' licensing agreements with foreign companies could be written so that the NBFs would not have to transfer the technology if the foreign company's government did not make the necessary request.

Imported Pharmaceuticals and Foreign Test Data.—Imported pharmaceuticals must meet FDA's IND and NDA requirements, even if approved for clinical testing or marketing in a foreign country. A question naturally arises regarding the acceptability of foreign test data.

*NBFs, as defined in *Chapter 4: Firms Commercializing Biotechnology*, are firms that have started up specifically to capitalize on new biotechnology.

Currently, FDA will accept foreign clinical data in support of an NDA, but it very seldom approves an NDA solely on the basis of foreign data, even if the study that produced the data meets FDA requirements for well-conducted studies. Under proposed revisions to its regulations, FDA would consider approving NDAs based solely on foreign clinical trials on a case-by-case basis if: 1) the data are applicable to the U.S. population and U.S. medical practice; 2) the studies have been performed by investigators of recognized competence; and 3) FDA is able to assure itself of the validity of the data (30).

If adopted, the revised data requirements would have at least two implications for this country's competitiveness in biotechnology. First, they would allow large U.S. drug companies to continue their practice of conducting much of their clinical work in foreign countries where drug approval has been quicker than in the United States, but also to secure quicker drug approvals in the United States. Second, they would lessen a U.S. nontariff trade barrier faced by foreign firms.

U.S. DEPARTMENT OF AGRICULTURE

Under the VST Act, the manufacturer of an animal biologic to be sold interstate needs premarket clearance by getting licenses for the product and the factory from USDA. The agency has broad authority to require any data it thinks necessary to judge product identity, purity, safety, and efficacy. USDA regulation is generally seen as significantly less costly and time-consuming than FDA regulation. However, USDA's position on biotechnological products appears to be consistent with FDA's, i.e., such products will need a new license, even if identical to other licensed products, although data requirements may be lessened.

ENVIRONMENTAL PROTECTION AGENCY

EPA has extremely broad authority over chemicals, herbicides, and pesticides. Chemicals are covered by the Toxic Substance Control Act (TSCA) (15 U.S.C. §§2601-2629). TSCA is intended to fill gaps in other environmental laws. It authorizes EPA to acquire information on "chemical substances" in order to identify and evaluate potential hazards and then to regulate the production, use, distribution, and disposal of those substances. Commodity and specialty chemicals made by biotechnology (except those regulated under FFDCA) will face the same kind of regulation under TSCA as those chemicals made by conventional means. TSCA will also be applied to organisms used in the environment, as noted in the "Environmental Regulation" section below.

Pesticides, herbicides, and related products are covered by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (47 U.S.C. §§136(a)-(y)). FIFRA creates a premarketing clearance procedure under which EPA reviews data on safety and then registers the pesticide, provided it will not generally cause unreasonable adverse effects on the environment. EPA has proposed a rule on data requirements for such registration (36). Sections 158.65 and 158.165 of the proposed rule cover biological pest control agents, including genetically manipulated ones.*

European Economic Community countries

The Federal Republic of Germany, the United Kingdom, and France are members of the EEC, or Common Market, which was established by the Treaty of Rome in 1958.** The regulations of the EEC and the national regulatory processes of these three countries that are relevant to biotechnology products are discussed further below.

EUROPEAN ECONOMIC COMMUNITY

Since 1965, the EEC has issued a series of directives aimed at harmonizing the member states' testing and approval processes for proprietary medicinal products and veterinary medicinal products. None of these directives specifically deals with biotechnological products. The directives are important for the development of biotechnology because, to the extent biotechnological products are proprietary or veterinary medicinal products,*** their approval for manufacture or

*These sections set extensive data requirements on product performance, toxicology, residue analysis, hazards to nontarget organisms, and environmental fate and expression.

**The other members of the EEC are Belgium, Denmark, Greece, Ireland, Italy, Luxembourg, and the Netherlands.

***Proprietary medicinal products are drugs, biologics, or similar products sold under brand or trade names. In practice, most member states regulate biologics differently from chemically synthesized drugs and the European Community directives have not been used to try to harmonize those regulations.

marketing will be governed by national procedures conforming to the directives.

Although the ultimate aim of the EEC directives is to replace national drug approval processes with a Community-wide system, such a system is unlikely in the near future. The speed with which the EEC does achieve a Community-wide drug approval system, however, will have a significant impact on the development of biotechnology, because such a system could cut costs, provide uniform regulation, speed up the approval process, and open access to new markets.

Currently, the existing directives deal only with drugs and veterinary medicines, not biologics. The directives also deal only with some aspects of the pharmaceutical approval process—marketing authorizations and certain testing requirements. A system has been set up for obtaining multiple authorizations for marketing in EEC member states, but control over exports outside the EEC is entirely up to member states.

Council Directive 65/65/EEC established the basic regulatory framework with respect to drugs (4). It requires an authorization from the competent authority of a member state before a drug can be marketed in that state. It sets forth the required information that must be submitted to the authorizing agency and provides that authorization of the product shall be based on a finding of safety, efficacy, and quality. Licenses are to be granted for a 5-year period, subject to extension. A similar directive exists for veterinary medicine (5).

Two questions that will be important to biotechnology companies that manufacture drugs and that seek EEC marketing authorizations remain unanswered. The first concerns the so-called paper NDA issue. The EEC permits a new manufacturer of an already approved product to rely on published data to establish the safety, efficacy, and quality of its version. It is unclear, however, whether this policy will apply to biotechnological products. Under most member states' existing regulations, a change in manufacturing process from chemical to biotechnological synthesis requires either a new market authorization or an amendment to an existing one. Since the EEC has not addressed the issue, the individual member states will determine whether published tests results can be relied on or whether new tests must be undertaken.

A variation of this same issue involves unpublished test results. Under current regulatory policies for drug approvals in both Europe and the United States, the documents submitted in support of an application for approval of a drug (the "dossier") are treated as confidential. Proposals are being considered in Europe, particularly in the Federal Republic of Germany, to change the scope of the confidentiality of the dossier. One proposal is to retain the confidentiality of the dossier for a certain number of years, and then allow access to the information after the payment of compensation to the original manufacturer who performed the tests.

FEDERAL REPUBLIC OF GERMANY

The Law on the Reform of Drug Legislation of 1976 sets forth the approval process for drugs, biologics, and veterinary medicines (7). It is designed to conform with the relevant EEC directives, and responsibility for its administration lies with the Federal Health Office (BGA, Bundesgesundheitsamt).

The licensing procedure for new drugs and biologics produced through biotechnological processes will be the same as for more traditional products. A manufacturer of pharmaceuticals must obtain individual marketing authorizations to distribute each drug or biologic that it manufactures and separate manufacturing authorizations for each of its production plants. Generally, the drug approval process takes 4 to 6 months from the time the application is filed. In the case of biologics, BGA defers to the Paul Ehrlich Institute, which provides authorizations for the manufacture of sera, vaccines, test allergens, test sera, and test antigens. Before deciding to approve a new drug or biologic, BGA must consult an independent commission of experts composed of physicians and representatives of the pharmaceutical industry. After an authorization for a drug or a biologic is given, BGA continues to monitor the competence of the managers and the adequacy of the facilities. An authorization may be withdrawn, revoked, or suspended if satisfactory standards are not maintained.

BGA regulations governing clinical testing of drugs and veterinary medicines track the applicable EEC directives. No specific prior approval of clinical testing is required, but BGA guidelines for such trials must be followed. The process for obtaining marketing approval and the information required in the application follows the EEC directives on proprietary medicinal products and on veterinary medicinal products.* In addition, the manufacturer must show that it holds a manufacturing license.

Anyone seeking to market an imported product must show that the product's foreign manufacturer has the equivalent of a manufacturing license and a marketing license in the country of manufacture; otherwise an explanation of why such authorization has not been granted must be supplied.

With respect to exports, it appears that a manufacturer intending to produce an item solely for export must comply with the requirements and obtain a manufacturing license but need not obtain a marketing license.

Certain biologics, specifically sera, vaccines, or test allergens, may only be marketed if each batch is approved by the Paul Ehrlich Institute. Approval is given only if a test shows that the batch possesses the required safety, efficacy, and quality, and has been manufactured and tested by methods which conform to the standard set by scientific knowledge currently prevailing.

Several aspects of the Federal Republic of Germany's pharmaceutical approval process are of particular significance to pharmaceuticals produced by biotechnology, because a change in manufacturing process from chemical synthesis to biotechnology would necessitate a reauthorization of these products. In certain cases, a manufacturer must apply for reauthorization of a drug despite an existing authorization. The circumstances in which such a reauthorization must be sought include a change in the composition of the active constituents either in type or quantity, a change in dosage form, or an extension in the field of application. For biologics such as sera, vaccines, and test allergens, a change in the manufacturing process also requires a reauthorization.

Two regulatory issues currently being debated in the Federal Republic of Germany are also relevant. The first is a regulation now in force that requires any person who markets a drug in the country to maintain a legal presence in the Federal Republic of Germany. The EEC has recently ruled that this requirement is illegal and has asked that it be abolished. Whether the Federal Republic of Germany will do so remains to be seen.

The second issue involves current proposals to modify the confidentiality of drug authorization dossiers. As in most of Europe, no manufacturer in West Germany has access to confidential information in another manufacturer's dossier unless it specifically receives permission from the original manufacturer, permission which is usually granted, if at all, only after the payment of substantial compensation. A second manufacturer of a drug that has already been approved may also rely on published material in lieu of relying on the dossier or conducting its own tests, but most important drugs are not the subject of published studies. Almost any scientifically reliable material will be contained in the confidential dossier that the first manufacturer submitted. Under active consideration are proposals that would maintain absolute confidentiality of the dossier for a given number of years, but then allow for access to the dossier with a statutorily prescribed compensation system. It will probably be some time before any such system is enacted (8).

UNITED KINGDOM

Because the United Kingdom is a member state of the EEC, its regulations conform to the basic requirements of the EEC pharmaceutical directives. Its current standards are embodied in the Medicines Act of 1968 and in the regulations adopted under this statute. No specific regulations governing the approval of biotechnologically pro-

*The application data must contain data showing: 1) the toxicological effects and pharmacological properties of the drug; 2) its effectiveness in the given indications; 3) the propriety of the suggested dosage; 4) side effects; 5) the drug is of appropriate quality; and 6) the production control methods correspond to scientific knowledge currently prevailing and are suitable for quality assessment. An application for an authorization for veterinary medicines and medicated foodstuffs must include residue tests and indicate how long it takes for residues to occur in edible tissues and how such residues are to be assessed.

duced pharmaceuticals have yet been adopted, so such products are subject to the general approval process set forth in the Medicines Act. The approval process for pharmaceuticals and related substances is similar to the U.S. system in several respects, but it is somewhat less restrictive and much more efficient in terms of the time for approval.

The Medicines Act of 1968 provides a comprehensive framework for the regulation of "medicinal products" which include drugs, biologics, and veterinary medicines. Its provisions are administered by the Health and the Agriculture Ministers of the United Kingdom, acting with the advice of the Medicines Commission. The day-to-day operation of the act is the responsibility of the Medicines Division of the Department of Health and Social Security.

The regulations governing the use of medicinal products focus on the safety, efficacy, and quality of the product. The system utilizes five types of licenses: licenses as of right, clinical trial certificates,* product licenses, manufacturers' licenses, and wholesale dealer licenses. These licenses apply to the manufacture, sale, storage, import, or export of any medicinal product. The requirements for the issuance of clinical trial certificates are considered to be among the strictest in Europe. Before a certificate can be granted, an applicant must present animal pharmacokinetic data, acute and chronic toxicity data, and information on potential reproductive toxicity. The basic documentation required to obtain a product license is similar to that required by the relevant EEC directives. Trial certificates valid for up to 2 years and product licenses valid for 5 years are issued for drugs on which clinical testing and production began after September 4, 1971. Either may be renewed.

Additional requirements are imposed with respect to "biologicals," which include vaccines, toxins, antigens, sera, and enzymes. Such biological medicines are licensed on a batch release system. The manufacturing license requires that each batch of product be subject to certain tests and that samples and the results of the tests be submitted to the National Institute of Biological Standards and Controls (NIBSC). The basic tests administered by NIBSC, which may have to be modified in the case of new biotechnological applications, include potency, purity, toxicity, pyrogenicity, and immunogenicity.

NIBSC has begun considering how its testing requirements may have to be modified for biotechnological products but has not formally adopted new requirements (2). Among the issues which NIBSC has identified as requiring modification of its procedures for biotechnologically produced products are establishment of the identity of large proteins produced by rDNA technology, adaptation of bioassay techniques, biological potency, contamination of biotechnologically produced products with macromolecules of bacterial origin, and chemical modification of the required products.

Several aspects of the pharmaceutical approval process in the United Kingdom will be particularly relevant to the development of biotechnology. The batch release system for testing biologics will apply to many biotechnologically produced products, but that will be the case in many countries. Also of importance for biotechnology is the treatment of already licensed drugs produced with new methodologies. In the United Kingdom, such drugs require product and manufacturing licenses. However, the full documentation that would be required for a completely new drug need not be provided. The precise amount of documentation will vary with the particular drug. In general, the United Kingdom will allow the substitution of published references for actual test results in those situations permitted under the EEC Council Directive 65/65/EEC (4). However, a second manufacturer is not permitted to rely on the confidential information submitted in the dossier of a first manufacturer. Thus, a new manufacturer of an already approved drug is required independently to demonstrate the safety, efficacy, and quality of the drug through its own research or that of independent researchers.

Imported drugs also require a product license. The manufacturer may be required to declare that any requirements imposed by the law of the country in which the drugs are manufactured

*Licenses of right and clinical trial certificates are self-limiting. The trial certificates terminate automatically once the trial process has ended. Licenses of right are transformed into product licenses once the drug has been reviewed by the Medicines Review Commission and found safe, effective, and of proper quality.

have been complied with and to permit the licensing authority to inspect his premises to ensure that they comply with any prescribed conditions of the license. Drugs produced solely for export also must be licensed, but the licensing authority is required to consider only quality, not the safety and efficacy of the drug.

FRANCE

The French approval processes for pharmaceuticals includes many of the same steps as the processes in the United States. The basic standards for approval are quality, safety, and efficacy of the pharmaceuticals, and the necessary tests are largely the same.

The authority responsible for the registration of new drug products is the Directorate of Pharmacy and Medicaments of the Ministry of Health, which administers the requirements of the Public Health Code, Book V, and the EEC protocols for analytical, toxicological, and pharmacological tests and clinical trials. The Ministry of Health uses the same basic standards of quality, safety, and efficacy required by the EEC.

A manufacturer must notify the Ministry of Health before commencement of clinical trials of a new product or for a new indication of an established product. The trials must be carried out under the supervision of an "approved expert"* and must follow procedures and present data in the format established by the Ministry of Health. Toxicological and pharmacological data must be submitted to the approved expert prior to commencement of the trials. Except for the analytical data, the information does not have to be generated by local French studies; however, the foreign data can only be accepted if it is justified by approved experts and conforms to EEC protocols. These rules apply also to clinical data generated by studies conducted abroad. Clinical trials must be performed in hospitals as controlled experiments.

Prior to obtaining a marketing license, a manufacturer is also required to request authorization from the Directorate of Pharmacy and Medicaments to manufacture the new drug product. If the product is to be manufactured abroad, the manufacturer must attach to the French marketing application the document granting it authority to manufacture the product in the foreign country. The marketing authorization itself is subject to the documentary requirements established by the EEC directives.

Once a manufacturer has submitted all relevant data to the Ministry of Health, the Minister must announce a decision on the application for marketing registration within 120 days. This period may be extended for another 90 days in exceptional cases. In practice, however, the processing time for an application averages 6 to 8 months. A second manufacturer cannot rely on the dossier of a first manufacturer to qualify its drug, so a new manufacturer making an already approved drug by biotechnological processes would have to show the drug's safety, efficacy, and quality all over again. However, as in other EEC countries, a manufacturer may rely on some published data to support its application.

Once registration has been approved, as in the rest of the EEC, the marketing license is valid for 5 years. It may be renewed for additional 5-year periods only if the manufacturer formally declares that no modification has occurred in the scientific data submitted in support of the original application. The Ministry of Health must therefore be notified of any new data.

A drug may be imported from another EEC country and, in exceptional circumstances, from a non-EEC country, provided that a marketing license has been obtained in France. A certificate is required proving authorization for sale or distribution within the exporting country. Authorization for the marketing of an imported drug is only valid for 6 months, but presumably may be renewed.

Drug products designed for animal consumption are also regulated by the Ministry of Health. The application procedures for obtaining authorization to market veterinary drugs are basically the same as those for human drugs.

*"Approved experts" are scientists with expertise in various aspects of pharmaceutical testing who are approved by the Minister of Health. The Minister maintains lists of these experts from among whom an applicant may select experts to review his or her data and supervise further testing. Approved experts need not be French.

Switzerland

The Intercantonal Convention for the Control of Medicaments is the authority for the regulation of drugs and related products. Under the Convention, the Intercantonal Office for the Control of Medicaments (IOCM, Interkantonale Kontrollstelle für Heilmittel) administers the drug regulatory system. IOCM has four principal tasks: quality control of marketed drugs, quality control of manufacturing, the licensing of new drugs, and the review and relicensing of existing drugs. IOCM has responsibility for pharmaceuticals,* veterinary medicines, and medical devices. Food and cosmetics are controlled by the Federal Office of Public Health under separate Federal authority. The quality control functions of IOCM are exercised through sampling of drugs at the time of their registration and periodically thereafter and through periodic inspections of pharmaceutical facilities.

The licensing of pharmaceuticals is much more streamlined than in other countries. There is no requirement for government approval before initiation of clinical trials. This is due both to the small size of IOCM and to greater reliance on the good faith of manufacturers and the common sense of medical practitioners participating in the clinical trials of new drugs.

Approval of the marketing of a drug is based on its efficacy and safety, which are judged by an independent board of university scientists. Approval can be refused not only if the drug is found not to be safe and effective, but also if its price is excessive. Licenses are issued for a 5-year period and may be renewed by the same board.** The drug approval process generally takes 6 to 10 months.

Of particular importance for biotechnology is the fact that less documentation is required for drugs that are not new chemical entities. Switzerland's streamlined drug approval process should mean faster action on new drug applications and on old drugs being produced through biotechnology.

For imports, it is necessary to have a certification that the drug is authorized for sale or distribution in the country of manufacture and that the manufacturer is subject to regular inspection. Drugs intended solely for export are exempt from registration, but voluntary registration can be made.

Japan

The approval process for drugs, biologics, and veterinary medicines in Japan is set forth in the Pharmaceutical Affairs Law (17). The law generally requires each manufacturer or importer to obtain a license for each manufacturing plant or business office and a separate approval for each drug manufactured or imported.* The manufacturer's or importer's license must be renewed every 3 years. The product approval has no set duration, but in practice many drugs are reviewed again after 6 years. The approval process is quite drawn out and complex because many agencies are involved. The time from submission of an application to approval is supposed to take 1 to 3 years but in practice takes longer (13).

The information that must be filed with the application for the approval of a new drug in Japan include data on origin, discovery, use in foreign countries, physical and chemical structure and properties, stability, various forms of toxicity and other dangerous side effects, pharmacological action, how the drug will be used in the body, and results of clinical trials (15). Most of the data is required to be published as an original article in a Japanese scientific journal. Data on animal tests for toxicity must meet certain special requirements. The application will be denied if the drug has no effect, efficacy, or efficiency as indicated in the application, if the drug is "remarkably dangerous" in comparison to its effect, or if the drug has been designated improper under the Ministry of Health and Welfare Ordinance (17).

An application to import a new drug must meet these standards. It must also contain a document

*This includes in vivo diagnostics, contraceptives, narcotics, anesthetics, antibiotics, some industrially produced homeopathic medicines, herbal remedies, radiopharmaceuticals, and certain blood products.

**In special cases, up-to-date analytical, preclinical, and chemical data as well as samples may be required if requested by IOCM.

*The separate approval for each drug is unnecessary if the drug is listed in the Japanese Pharmacopoeia and has been exempted by the Minister for Health and Welfare.

certifying that the exporting country approves its manufacture and copies of the import contract or similar document (16). The import or manufacture of biologics is prohibited unless special requirements concerning their processing, properties, quality, and storage are met (16). Each batch of biologics must be tested and approved by the National Institute of Health.

New drugs must be reexamined about 4 to 6 years after approval, largely so that the safety of the drug can be assessed in light of post-approval clinical tests and other scientific research. The reexamination is to determine whether the drug now displays any condition that would, if a new drug application were now filed, require its rejection, i.e., that the drug is not efficacious, is more dangerous than efficacious, or has been designated improper (17). The approval for a drug may be canceled if the drug cannot pass reexamination, if health or sanitation reasons so require, if the licensee fails to submit accurate reexamination material, or if the licensee has not produced the drug for 3 years (17). How this will affect drugs produced with biotechnology is unclear.

Environmental regulation*

Protection of the environment is one aim of the rDNA guidelines in each of the competitor countries; none of them have any other rules specifically directed to the environmental effects of biotechnology. Nevertheless, the more general environmental laws will apply to biotechnological processes, products, and waste products. The extent to which these general laws will apply to genetically modified organisms used in the environment is uncertain in all of the countries except the United States, where EPA has asserted jurisdiction under TSCA.

The environmental requirements in the rDNA guidelines are likely to have little effect on the competitive position of any country. The specific measures required for any physical containment level vary little from country to country. Moreover, most rDNA activities are now conducted at low containment levels that require essentially only that good microbiological practices be followed. Deliberate release of genetically modified organisms is generally prohibited, although procedures exist for exceptions from the prohibition. In the United States, deliberate release is not prohibited as such, but one who would do so under the guidelines must have the approval of IBC and NIH, after consultation with the Recombinant DNA Advisory Committee.*

It is difficult to determine what effect, if any, the more general environmental regulations of each country dealing with air and water pollution and waste disposal will have on biotechnology in that country. Since much of the environmental regulation in any country is performed on the local level, generalizations about national environmental controls can be misleading. States (Länder) in the Federal Republic of Germany, for example, are about to enact specific legislation to fill in the framework set up by Federal laws. Certain environmental legislation in Japan, though enacted at the national level, applies only to certain areas. Local authorities in France and the United Kingdom possess considerable responsibility for administering and enforcing environmental rules. Switzerland leaves most decisions on environmental regulation to the cantons, as it does decisions on other subjects. The United States has one of the more centralized systems for environmental control, but even Federal statutes allow for responsibility to be transferred to the States.

*For specific information regarding the six countries, see the section on environmental regulation in *Appendix F: Recombinant DNA Research Guidelines, Environmental Laws, and Regulation of Worker Health and Safety*.

*A lawsuit has been filed against NIH claiming that approval by the Recombinant DNA Advisory Committee is not consistent with the National Environmental Policy Act and claiming that an Environmental Impact Statement must be prepared (*Foundation on Economic Trends* v. *Heckler*, No. 83 Civ. 2714 (D.D.C. Sept. 14, 1983)).

All of the countries except Switzerland have fairly comprehensive and stringent environmental regulation. Switzerland's national regulation is directed only toward water pollution. Thus, its biotechnology companies may have a competitive advantage over those in the other countries because of less restrictive environmental regulation. Yet even the more stringent regulation in other countries would not necessarily handicap companies because the regulation is directed mainly toward toxic chemicals. The degree of traditional environmental problems that companies using biotechnology might create—air and water pollution and hazardous waste—does not now appear to be so great that environmental controls will significantly affect the commercialization of biotechnology. However, increasing commercialization of biotechnology eventually will require more consideration about the disposal of waste byproducts. All countries are now about equal in this area, but those who undertake to resolve uncertainties about the specifics of that regulation should enhance the competitive positions of their biotechnology companies.

The United States seems to be the farthest ahead in considering the risks and regulation of the deliberate release of genetically modified organisms. This may simply be the result of the fact that this area of biotechnology is further along in the United States than in the other countries. In any event, NIH recently has reviewed and approved several proposals to release organisms into the environment. Also, on June 22, 1983, two congressional subcommittees held a joint hearing on the topic of regulating such releases (22).

At the hearing, EPA took the position that such organisms are "chemical substances" as defined by TSCA* and therefore subject to regulation by EPA under TSCA (3). Although the matter is not free from doubt, a consensus has been developing among the experts that TSCA would apply (18).

TSCA gives EPA broad authority to regulate the products of biotechnology, and, assuming EPA's interpretation of the definition of "chemical substance" survives any subsequent legal challenge, TSCA would have great potential for regulating the deliberate release of genetically modified organisms. Under section 4 of TSCA, EPA can adopt rules requiring testing of chemical substances that "may present an unreasonable risk of injury to health or the environment" or will be produced in substantial quantities (and enter the environment in substantial quantitites or result in substantial human exposure) when existing data are insufficient to make a determination and testing is necessary to develop adequate data. Section 5 requires the manufacturer of a new chemical substance to notify EPA 90 days before beginning production and submit any test data it may have on the chemical's health or environmental effects. If the agency decides that the data are insufficient for evaluating the chemical's effects and that it "may present an unreasonable risk of injury to health or the environment" or will be produced in substantial quantities (and enter the environment in substantial quantities or result in substantial human exposure), it can propose an order to restrict or prohibit the chemical substance's manufacture or use. Under section 6, EPA can prohibit or regulate the manufacture or use of any chemical substance that "presents, or will present an unreasonable risk of injury to health or the environment." TSCA also provides for recordkeeping and information gathering about the environmental and health effects of chemical substances.

Despite its theoretical applicability, TCSA may leave much to be desired in terms of a practical program to regulate the use of genetically manipulated organisms in the environment. First, EPA has little expertise or experience in the area of genetic manipulation. Second, its toxic substances program has been significantly understaffed, according to a 1980 study by the U.S. General Accounting Office study (21). Third, TSCA may not give EPA sufficient regulatory power, if the risks presented by deliberate release are viewed as substantial. For example, section 5, which creates the premanufacturing notice requirement, does not require the generation of toxicological data. A recent OTA background paper found that nearly half of the premanufacturing notices submitted

*A "chemical substance" is defined in the relevant part under sec. 3(2)(A) of TSCA as "any organic or inorganic substance of a particular molecular identity," including "any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature. . . ."

to EPA do not have information about the chemical's toxicity (26).* Moreover, the burden is on EPA to take legal action if it believes that insufficient data exists for a new chemical substance.

USDA also has an environmental role to play with respect to biotechnology. It regulates importation and interstate shipment of plants, animals, and their pathogens (21 U.S.C. §§101-135; 7 U.S.C. §§151-167; 7 U.S.C. §150aa et seq.). Thus, some of the "raw materials" of interest to biotechnologists in the agriculture field are subject to USDA restrictions. For example, two potential mechanisms for transferring genes into plants are the bacterium *Agrobacterium tumefaciens* with its integrating Ti plasmid and the cauliflower mosaic virus. Both the bacterium and the virus are subject to the restrictions. Similarly, work with particularly dangerous animal viruses may be prohibited or severely restricted. For example, work on foot and mouth disease virus can only be performed at Plum Island, a high containment USDA laboratory located off the coast of Long Island, N.Y. USDA also bars entry into the United States of 22 other pathogens that might be of interest to companies desiring to produce animal vaccines.

*As to the importance of such information, OTA's background paper stated (26): "Certainly, the absence of toxicity data complicates EPA's efforts to decide whether a new chemical may present an unreasonable risk to health or the environment. But the importance of toxicity data for making decisions about particular chemicals varies. Those data are less important for chemicals that closely resemble others for which there is much information and experience. They are critical for unusual chemicals or chemicals for which there is limited information."

Regulation of worker health and safety*

The rDNA research guidelines in each of the six countries (but not those of the EEC itself) contain provisions for the safety and health of laboratory workers. Each country also has more widely applicable laws and regulations, but it is the rDNA guidelines that will have the most immediate impact on the biotechnology companies.

The substance of the various worker health and safety provisions in the national rDNA guidelines varies among the six countries studied, although most set forth rules to ensure that laboratory workers are knowledgeable about laboratory procedures, that emergency procedures are known and safety equipment is available, and that worker health is monitored for certain types of work. It seems fair to infer that the costs and burdens associated with these requirements are modest, because there has been little criticism or complaints about them from academia or industry (8).

The more general worker health and safety laws in the United States and in each of the five foreign countries have had no measurable effect as yet on the industries using biotechnology in each country. Each country imposes general duties on employers to maintain safe workplaces and to eliminate or control hazardous substances (although when these substances are specified, they do not include materials likely to be found in a biotechnology laboratory). The most that can be said is that each country has at least one authority able to impose further requirements to protect worker health and safety, but none has yet done so. Such requirements would be primarily process rather than product oriented.

The United States has studied the question of the possible risks posed to workers from long-term exposure to novel organisms and products. The Centers for Disease Control and the National Institute of Occupational Safety and Health (NIOSH) created an ad hoc working group on medical surveillance for industrial applications of rDNA. The group concluded that, while physical containment of rDNA-containing organisms and their products is the first line of defense, medical surveillance of industrial workers can play a valuable auxiliary role in protecting their health (19). Others have disagreed with this finding, questioning the need for surveillance and the ability to construct a meaningful program.

*For specific information regarding the six countries, see section on regulation of worker health and safety in *Appendix F: Recombinant DNA Research Guidelines, Environmental Laws, and Regulation of Worker Health and Safety.*

The NIOSH findings have not been implemented by the Occupational Safety and Health Administration (OSHA), the U.S. agency primarily responsible for worker safety and health. Under the Occupational Safety and Health Act of 1970, OSHA can promulgate workplace standards to protect workers from toxic substances or harmful physical agents. Under a recent decision by the U.S. Supreme Court (12), such standards must be "reasonably necessary to remedy a significant risk of material health impairment." Although this requirement would appear to prevent OSHA from acting on those purely conjectural risks associated with biotechnology, the agency could act on known biological risks (e.g., those presented by known pathogens), or physical risks (e.g., those presented by the use pressurized containment vessels). In any event, OSHA has not promulgated any standards for bioprocesses in general, nor has it taken any position on regulating biotechnology.

At this point and for the foreseeable future, worker health and safety regulation of biotechnology is minimal. Thus, it will give neither an advantage nor a disadvantage to any of the competitor countries.

Findings

Health, safety, and environmental regulation can affect the cost, time, and financial risks of getting products to market. Thus, such regulation can be expected to affect international competitiveness in biotechnology.

The only government controls directed specifically toward biotechnology are the rDNA guidelines adopted by the EEC and the six competitor countries. They are essentially voluntary and directed primarily at research, although they do apply to large-scale work to varying degrees. Their containment and oversight provisions have been substantially relaxed since they were originally adopted, and this trend is expected to continue.

The rDNA guidelines in the competitor countries are quite similar in their regulatory goals, requirements, and implementation because they are generally patterned after the U.S. guidelines, which were initially developed through the efforts of the international scientific community. Nevertheless, there are differences that allow the guidelines to be ranked in terms of their restrictiveness and potential impact on the competitiveness of the various countries.

The rDNA guidelines of the United States are the least restrictive of the guidelines in any of the competitor countries. The vast majority of the experiments that are done with the most commonly used host-vector systems are either exempt or can be done at the lowest containment levels. Prior approval, even by the IBCs, is required only for a limited category of experiments. The rDNA research guidelines of Japan and the European countries are more restrictive than the U.S. guidelines in one or more of the following ways:

- they require more stringent containment;
- they require more time-consuming approval procedures;
- they have fewer categories of approved host-vector systems; or
- they severely restrict large-scale work.

Japan has the most restrictive rDNA guidelines. A limited number of host-vector systems have been approved for use. More importantly, companies have had extreme difficulty in obtaining approval to do work with more than 20 liters of culture, but this is expected to change soon.

Of the remaining countries, Switzerland appears to have the least restrictive guidelines. Its Government has played no role in the guidelines, and there are no requirements covering large-scale work. However, Switzerland follows an earlier, and thus more restrictive, version of the U.S. guidelines. The guidelines in France and the United Kingdom appear to be roughly equivalent with regard to their impact on biotechnology. The Federal Republic of Germany appears to be slightly more restrictive, primarily because Government approval must be obtained before even moderate risk experiments can be started.

It is the existing regulation that will most affect biotechnology: product approval laws, environmental laws, and worker health and safety laws. The most important of these for biotechnology will be the product approval requirements, especially for pharmaceuticals and veterinary medicines because those products are the most stringently regulated or the subject of much of the current effort in product development. For this reason, and because of insufficient information on foreign regulation of the other products, the analysis for product approval in this chapter concentrated on the regulation of pharmaceuticals and veterinary medicines.

With respect to the product approval process, particularly for pharmaceuticals and animal drugs, the United States appears to be at a competitive disadvantage with respect to all of the other countries except Japan. The competitive disadvantage for the United States results mainly from the time and cost necessary to secure premarketing approval. In contrast, the United Kingdom has the most expedited pharmaceutical approval process, even though its substantive requirements are quite similar to those of the United States. Switzerland is the least restrictive of the countries in terms of substantive requirements. For example, it does not require Government approval before initiation of clinical trials. In contrast to pharmaceuticals and animal drugs, the regulatory requirements for animal biologics are less restrictive in the United States and roughly on par with those in other countries.

Another reason the United States is at a competitive disadvantage is that the United States, in contrast with the other countries, does not allow the export of unapproved pharmaceuticals. In addition, bulk drug products may also not be able to be exported. Given certain provisions in joint venture agreements between U.S. NBFs and their foreign partners, these requirements could enhance the transfer of biotechnology to foreign companies.

Specific requirements regarding biotechnology products are or will be set at the agency level within the existing statutory framework. In the United States, FDA has taken the lead in developing and publishing informal statements. Since these statements help dispel uncertainties, they will help product development. In its policy statements, however, FDA has taken the position that rDNA products whose active ingredients are identical to ones already approved or to natural substances will still need to go through the new product approval process. However, data requirements may be modified and abbreviated. This appears not to be the situation in other countries, although there have not been definitive pronouncements by the regulatory agencies.

One area of uncertainty that could hinder U.S. competitiveness in biotechnology to some degree is the question of jurisdiction over animal biologics. FDA and USDA are engaged in a jurisdictional dispute that could delay product approvals.

Environmental and occupational safety and health regulations are not likely to give any of the countries a significant competitive advantage in biotechnology. This regulation is likely to play a minor role, except in the area of deliberate release of genetically manipulated organisms into the environment. For that application of biotechnology, uncertainties exist as to what, if any, kind of special regulation will develop. The United States appears to be the farthest along in considering the problem; thus, to the extent that decisions are made and the regulatory picture clarified for corporate planners, the United States may have a slight advantage.

Issue and options

ISSUE: How could Congress improve U.S. competitiveness in biotechnology through changes in the regulatory environment?

Regulation imposes costs, constraints, and delays on biotechnology companies that are justified when they promote such general goals as the enhancement of human health or quality of the environment. To the extent that such regulation is inefficient or unnecessarily restrictive or creates uncertainties that impede business planning, however, it will restrict biotechnological innovation and U.S. competitiveness in biotechnology without achieving the other goals.

OTA has identified several options that could improve U.S. competitiveness in biotechnology through changes in laws, regulations, and administrative policies regarding health and safety. Many of these are not specific or limited to biotechnology but nevertheless could significantly affect this technology. Furthermore, many of the actions could be taken by executive agencies, and, in fact, are being considered. Nevertheless, Congress may decide legislative action is necessary or more appropriate.

Option 1: Amend the Federal Food, Drug, and Cosmetic Act (FFDCA) to permit the export of unapproved drugs and biologics.

Of the six competitor countries identified in this assessment, the United States is the most restrictive regarding the export of unapproved drugs and biologics. The relevant provision of FFDCA is designed to prevent "drug dumping"—situations where drugs deemed unsafe or ineffective by the United States or other developed countries have been marketed in developing countries.

Those who advocate eliminating this provision of FFDCA argue that a U.S. company can have ethical reasons for wanting to export a drug that is unapproved by FDA. For example, it may be supplying a company that sells the drug in a country that has approved the drug for sale. Advocates of eliminating this provision also argue that the provision simply embodies U.S. paternalism toward other countries, which are capable of making their own health and safety decisions. Partly to avoid the U.S. ban on the export of unapproved drugs, the multinational drug companies have established foreign manufacturing facilities. This practice results in the transfer of technology and jobs from the United States and has an adverse effect on the U.S. balance of payments. For NBFs, which may not have the money to establish foreign facilities or the time before contract revenues and capital run out, the export restriction may be especially burdensome.

FDA has taken the position that bulk pharmaceutical products made by biotechnology are drugs because such products are biologically active; thus, the export prohibition of FFDCA applies. One U.S. company, Genentech, has asserted that its inability to sell bulk pharmaceutical products to its foreign joint venturers will result in its being required to transfer the technology to produce that bulk product to its foreign partners. This company has argued that bulk pharmaceutical products produced by biotechnology and not labeled as drugs should not be considered drugs under FFDCA and FDA regulations. Clearly, this question of interpretation could be resolved on the administrative level without congressional action. To change the general prohibition in FFDCA against the export of unapproved human and animal drugs and biologics, however, legislation would be necessary.

The arguments against amending FFDCA to permit the export of unapproved drugs and biologics are essentially moral ones. There have been documented cases of drug dumping in developing countries. Supporters of the existing restrictions argue that the United States has a moral duty to try to prevent such actions and that the developing countries are unofficially in favor of these export restrictions.

There are several different ways that legislation to permit the export of unapproved human and animal drugs and biologics could address these moral arguments. First, the legislation could exclude products that have actually been barred by FDA. Second, it could permit the export of unapproved drugs and biologics only if they have

been approved by at least one other developed country. Third, it could permit the export of unapproved drugs and biologics only to countries where the products has been approved. Finally, the legislation could be drafted so that unapproved drugs and biologics can be exported only to developed countries. The potential diplomatic problems that could arise by having to decide which countries are "developed" could be avoided or lessened by using the definitions of various international organizations, such as the International Monetary Fund.

Option 2: Pass legislation to merge the Virus, Serum, Toxin Act of 1913 into the Federal Food, Drug, and Cosmetic Act.

The reasons for the different statutes are primarily historical, and the distinctions between animal drugs and biologics, if they were not already anachronistic, have virtually been made so by rDNA and hybridoma technology. Nevertheless, USDA and FDA were engaged in a jurisdictional dispute over bovine interferon and may well continue to engage in disputes over future products. By trying to satisfy both agencies, U.S. companies using biotechnology are likely to incur additional costs and delays. In addition, the uncertainties over regulatory authority may hinder corporate planning for what product areas to pursue or may steer firms away from pursuing these kinds of products. As a result, U.S. firms may be at a competitive disadvantage with respect to foreign firms.

Although combining the regulatory jurisdiction into one agency, FDA, may make sense conceptually, there will be substantial institutional barriers to doing so. If USDA is unwilling to give up its jurisdiction, as it appears to be, it can count on substantial political support from inside and outside of government. In addition, despite the adverse consequences of this jurisdictional dispute, the biotechnology companies themselves may well prefer USDA to retain or enhance its jurisdiction over animal biologics because USDA regulation is viewed as substantially less burdensome and costly than FDA regulation. This option has been proposed several times in past years, but there has been little progress toward its implementation.

Option 3: Amend the patent law to extend the term of patents on products or processes that need regulatory approvals before marketing.

This option was considered extensively by the 97th Congress, in which legislation passed the Senate and failed to pass the House by a few votes. It was also the subject of an OTA report, *Patent-Term Extension and the Pharmaceutical Industry* (24). Legislation to accomplish this option (S. 1306, H.R. 3502) has been introduced in the 98th Congress.

Firms that are heavily involved in basic research support patent-term extension. They claim that R&D costs and risks are rising, yet the effective life of patents on the products resulting from the R&D is declining because of the increasing time necessary for securing regulatory approvals before marketing. Since this may cause returns on R&D investments to decrease, the firms assert that innovation will suffer. Several biotechnology firms have supported this option publicly.

Generic drug producing firms and consumer groups oppose patent-term extension. The generic drug firms, which derive most of their revenues from drugs equivalent to the pioneering ones whose patents have expired, assert that patent-term extension will delay their entry into the market or not make that entry worthwhile because of limited product life remaining. They also assert that patented products often maintain an exclusive market position after their patents expire because of nonpatent barriers to market acceptance of generically equivalent products. As a result, patent-term extension would cause competition to decline and prices to increase. The consumer groups support this position and also note that the pharmaceutical industry has been extremely and consistently profitable for a great many years, even while the regulatory burdens have been increasing.

The OTA report mentioned above found that "[t]he evidence that is available neither supports nor refutes the position that innovation will increase significantly because of patent-term extension." It did note, however, that the incentives provided by patents for pharmaceutical R&D would be enhanced.

Option 4: Address the uncertainties and concerns about the deliberate release of genetically manipulated organisms into the environment by passing new legislation or amending the Toxic Substance Control Act to clarify its applicability to living organisms.

There are risks associated with releasing nonindigenous organisms into the environment. Although most nonindigenous such organisms do not establish an ecological niche, many have done so with disastrous consequences. For example, over half of the insect pests in the United States today came from abroad; similarly, the micro-organism causing Chestnut blight was not indigenous to the United States.

The risks of releasing genetically manipulated organisms into the environment are not known. On one hand, changing the genetic makeup of an organism usually decreases its ability to survive. On the other hand, many of these organisms, such as microbes used for enhanced oil recovery, will have to be manipulated so as to be competitive with indigenous micro-organisms and to be able to withstand extreme environments in order to be able to accomplish the task. Some industry spokespeople, who believe that rDNA-containing micro-organisms do not present any special risks when properly contained in bioreactors, have expressed concern about the deliberate release of such micro-organisms into the environment.

The concern about releasing genetically manipulated organisms into the environment and the uncertainties about the Federal Government's authority to regulate such activities may impede developments in the use of biotechnology in areas such as microbial enhanced oil recovery, pollution control, and mineral leaching. It may even hinder genetic manipulation of plants,* although the risks involved are seen as much less than those for micro-organisms. Given the concern about risk and the uncertainty over the Federal Government's possible regulatory response, U.S. companies may have difficulty planning where to place limited resources for research and product development.

Opponents of this option are likely to question whether legislative action is needed to accomplish the goal of environmental protection. Although most experts acknowledge that there is uncertainty about whether TSCA covers organisms, a consensus seems to be developing that it does. More importantly, EPA has taken the position that TSCA applies. In addition, voluntary oversight is being exercised by the Recombinant DNA Advisory Committee, although the quality of that oversight is the subject of litigation.

*The U.S. Recombinant DNA Advisory Committee (RAC) recently approved a change in the guidelines that would permit field tests with plants containing rDNA with the prior approval of the local Institutional Biosafety Committee and a working group of the RAC under certain conditions.

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*Note: F.2d=Federal Reporter, Second Series.
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Chapter 16

Intellectual Property Law

Contents

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Intellectual Property Law

Introduction

Biotechnology will give rise to a vast array of new inventions. The inventions may be placed into two general categories: products and processes. Products will include organisms, such as genetically modified micro-organisms, cell lines, hybridomas, plants, and possibly even animals. Products also include parts of organisms and related material such as high expression plasmids, viral vectors, synthetic genes, probes, and restriction enzymes. Finally, there will be products of organisms, such as drugs, chemicals, biologics, and monoclonal antibodies (MAbs). Processes will include various ways to make new organisms or parts thereof or to use an organism to make some product such as insulin. Other examples of processes include various bioprocessing techniques, regeneration of plant tissue culture, breeding techniques, and methods of treating the human body. In addition, research and development (R&D) will give rise to new knowledge, which will be of value to whoever possesses it.

The ability to secure a property interest in an invention and to protect related know-how generally is perceived as providing an extremely important incentive for a private company to spend time and money to carry out research, development, and scale-up for the commercialization of new processes and products. Without the ability to prevent other companies from taking the results of this effort, many new and risky projects that could lead to important new products would not be undertaken. Empirically proving this notion, however, is difficult (47). It is beyond the scope of this chapter to delve into the debates among experts on that problem. This chapter will assume—as our society does—that the ability to secure property interests in or otherwise protect technological processes, products, and know-how will encourage development of technology. Therefore, one factor to evaluate in assessing U.S. competitiveness in biotechnology is how well the law of intellectual property of the United States and the five other major competitor countries—Japan, the Federal Republic of Germany, the United Kingdom, France, and Switzerland—allows inventors, private companies, and others to protect the results of their efforts.

The three categories of intellectual law most relevant to biotechnology are those dealing with trade secrets, patents, and plant breeders' rights. These are the focus of this chapter.* Copyright may also be relevant, because it protects the tangible expression of information, and a gene may be viewed as the tangible expression of information (36). Because this idea has not been widely accepted, and several commentators have criticized its usefulness (16,40,52), here it will not be discussed any further.

The categories of intellectual property law work together as a system. If one has disadvantages, a company can look to another. To the extent that a country has available many alternative ways for companies to protect biotechnological inventions, it is more likely to be competitive in biotechnology.

This chapter compares and contrasts the law relating to the protection of biotechnological inventions and related know-how in the United States, the United Kingdom, the Federal Republic of Germany, Switzerland, France, and Japan. The chapter begins by examining U.S. law in order to provide a basis for comparisons, raise the relevant issues, and explain some basic legal concepts.

*Two other areas of law are also relevant to biotechnology but will not be considered in this chapter: personal property law and contract law. Traditional personal property law will apply to cell lines and many other biological inventions because they are physical objects—just like cars and jewelry. Contracts create legally enforceable rights and duties between the contracting parties. Thus, biotechnological inventions can be protected by contract, and in view of some of the uncertainties in the intellectual property law regarding biotechnology, contracts can be important to biotechnology companies in many instances. These topics will not be considered further in this chapter, because OTA was unable to obtain information on how they would apply to biotechnology in other countries. Some commentators have addressed their applicability to biotechnology in the United States (10,40,42).

Foreign intellectual property laws are considered after the discussion of the U.S. law and also in appendix G. The strengths and weaknesses of the laws of the six countries are then analyzed by considering three basic questions: 1) what interests will the law protect; 2) how well will they be protected; and 3) what questions are unanswered? Policy options for Congress addressing the issue of how to improve U.S. competitiveness in biotechnology by strengthening U.S. intellectual property law are identified and discussed at the end of the chapter.

Intellectual property law of the United States

As noted above, three categories of intellectual property law are particularly relevant to biotechnology: trade secrets, patents, and plant breeders' rights.

Law of trade secrets

An inventor is regarded in the United States as having a natural right to keep an invention secret. This right is recognized by the law of trade secrecy. A trade secret is generally viewed as "any formula, pattern, device, or compilation of information which is used in one's business, and which gives him (sic) an opportunity to obtain an advantage over competitors who do not know or use it" (1).* Examples of trade secrets in biotechnology are a method for genetically manipulating an organism, a method for selecting among the organisms for those particular characteristics, and the organism itself.

The holder of a trade secret in the United States can enforce his or her interests in State courts by securing either an injunction or monetary damages against a person who takes or otherwise acquires the secret through improper means, or even against a person who acquired it through mistaken disclosure by the owner.** Criminal penalties may also be available in egregious cases in the majority of States. The underlying policy is that a person should not benefit by unfairly using another's efforts.

In the United States, virtually any biological invention, including cells and their components, or related information would be protectable by the law of trade secrets.*

It should be noted, however, there are some limitations on its scope. One important limitation arises from the fact that a trade secret must be continuously used in a business. This requirement raises questions about the results of basic research. Generally, the courts have held that if information is merely a preliminary idea, it does not qualify as a trade secret (41,51). Some degree of commercial value must be established if the information is to be considered a trade secret. A few States have taken a more expanded view of the concept of trade secret and protect information that also has only potential economic value. In those States—Arkansas, Idaho, Kansas, Minnesota, and Washington—the results of basic research clearly would be protected.

Another possible limitation on the scope of the law of trade secrets arises from the fact that the holder of a trade secret must know the information and attempt to keep it secret from others. In the well-known case involving disputed ownership of an interferon-producing cell line, *Hoffmann-La Roche, Inc.* v. *Golde* (28). Genentech (U.S.) and Hoffmann-La Roche (Switzerland) apparently argued that the University of California had no trade secret interest in the cell line because the university did not know about its ability to produce interferon (10).

The advantages of a trade secret to its holder are several. First, there is no time limit on trade

*In recognizing the existence of a trade secret, the courts do not use a hard and fast definition, but look at numerous factors, such as the extent to which the information is known outside of the business, the effort involved in developing and guarding the information, and the difficulty with which the information could be properly acquired by others (see 34).

**The cases also recognize secret information that does not qualify as a trade secret, but a person acquiring or using that information is liable only if he does so by "improper means" (1).

*Misappropriation of an organism or other tangible biological material constitutes misappropriation of the information it contains (see 53).

secret protection. It should be noted, however, that in a fast moving area like biotechnology, the "useful life" of a trade secret may actually be quite short. Second, a trade secret does not have to be a patentable invention. Third, maintenance and enforcement are generally less expensive for trade secret rights than for patents. Fourth, competitors are not apprised of the information, in contrast to the situation with patents (see below). Fifth, trade secret protection is valuable for certain inventions that would be hard to police if patented. For example, if a product is capable of being made by many different processes, keeping secret a new process for making the product might be preferable to patenting it. Sixth, if there is doubt as to the patentability of an invention, trade secrecy is a viable alternative. Finally, certain organisms and parts thereof, such as high-expression plasmids, may be better off held as trade secrets, since they could not be reverse engineered from the products that they produce, but, if patented, would be placed in the public domain.

Disadvantages of relying on trade secrecy include the following. First, the protection exists only as long as secrecy exists. The holder of a trade secret has no rights against someone who independently discovers and uses the trade secret and has no rights against someone who may have innocently learned the secret from someone who originally obtained it improperly. Second, reverse engineering (the examination of a product by experts to discover how it was made) is a legitimate way to discover a trade secret. The structure of a gene, for example, may be determined by reverse engineering a polypeptide that is on the market. Because of the complexity of biological processes and organisms, however, most of these will not be capable of being discovered by reverse engineering of their products. Third, trade secrecy is, by definition, incompatible with the desire of most scientists to publish the results of their research. If a company wishes to attract and retain good scientists, it may not be able to rely on trade secrecy to protect their work. Fourth, there is always the chance that a trade secret will be independently discovered by another, who then obtains a patent on it. The patent holder may then prevent the holder of the trade secret from using it. Finally, the acquisition of a trade secret by a competitor through misappropriation or breach of a confidential agreement may be difficult to prevent, discover, or prove. Micro-organisms are especially easy to steal, once one gains access to them, because of their small size and self-replicating nature. Further, the thief would not even have to understand exactly the valuable information contained in the micro-organisms; he or she has acquired the factory (i.e., the micro-organism) and the ability to grow it in any amount desired.

Patent law

U.S. patent law, Title 35 of the United States Code, is designed to encourage invention by granting inventors a limited property right in their inventions. A U.S. patent gives the inventor the right to *exclude* all others from making, using, or selling the invention within the United States without the inventor's consent for 17 years. In return, the inventor must make full public disclosure of the invention.

The policy behind U.S. patent law is twofold. First, by rewarding successful efforts, a patent provides inventors and their backers with an incentive to risk time and money in R&D. Second, and more importantly, the patent system encourages public disclosure of technical information, which may otherwise have remained secret, so that others are able to use it. The inducement in both cases is the potential for economic gain through exploitation of the patent right.

To qualify for patent protection in the United States, an invention must meet the following requirements:

- it must be capable of being classified as a process, machine, manufacture, or composition of matter;*
- it must be new, useful, and not obvious; and
- it must be disclosed to the public in sufficient detail to enable a person skilled in the same or the most closely related area of technology to construct and operate it.

*These categories are set out in §101 of Title 35 of the United States Code (35 U.S.C. §101). Sec. 101 is the basic section under which most inventions are patented. Patents under 35 U.S.C. §101 are often called utility patents.

Plants that reproduce asexually may also be patented under slightly different criteria.

The criteria for obtaining and enforcing patents on biotechnological inventions are quite similar in the six countries being examined in this report. The following eight subsections discuss the criteria of patentable subject matter, novelty, utility, nonobviousness, disclosure requirements, deposit requirements, claims, and enforcement in the United States in order to provide a basis for a comparative analysis of how each country's patent law will affect its competitiveness in biotechnology.

PATENTABLE SUBJECT MATTER

The categories of patentable subject matter under 35 U.S.C. §101—process, machine, manufacture, or composition of matter—are quite broad but they are not unlimited. The courts have held scientific principles, mathematical formulas, and products of nature to be unpatentable on the grounds that they are only discoveries of preexisting things—not the result of the inventive, creative action of human beings, which is what the patent laws are designed to encourage.

One of the major patent law questions arising with respect to biotechnology is whether living organisms are patentable subject matter. The U.S. Supreme Court addressed this question in 1980 in the landmark case *Diamond* v. *Chakrabarty* (21). In a five to four decision, the Court held that the inventor of a new micro-organism, whose invention otherwise met the legal requirements for obtaining a patent, could not be denied a patent solely because the invention was alive. The Court ruled that Congress had not intended to distinguish between unpatentable and patentable subject matter on the basis of living v. nonliving, but on the basis of "products of nature, whether or living or not, and human-made inventions" (22).

The U.S. Supreme Court stated that its decision in the *Chakrabarty* case was limited to a human-made micro-organism, leaving unresolved questions of whether eukaryotic cells or other higher organisms would be patentable subject matter. In theory, however, the *Chakrabarty* decision stands for the proposition that any organism is potentially patentable, because the crucial test used by the Court was whether or not the organism is human-made. As a result, eukaryotic cells, cell lines, tissue culture, and even plants are generally viewed as being patentable under 35 U.S.C. §101. The harder question is whether the U.S. Patent and Trademark Office or the courts would permit patents on higher organisms such as animals.*

There is no question, however, that virtually any other biotechnological invention would be patentable subject matter, providing that it meets the other requirements. Such inventions would include processes using micro-organisms, recombinant DNA (rDNA) molecules, subcellular units such as plasmids, methods for making these inventions, and biotechnological methods for treating human or animal disease (29).**

NOVELTY

The statutory requirement of novelty signifies that an invention must differ from the "prior art," which is publicly known technology. Novelty is not considered to exist, for example, if: 1) the applicant for a patent is not the inventor; 2) the invention was previously known or used publicly by others in the United States; or 3) the invention was previously described in a U.S. or foreign publication or patent (35 U.S.C. §102). The inability to meet novelty requirement is another reason why products of nature are unpatentable.

Two questions are particularly relevant to biotechnology. First, how can naturally occurring substances, such as genes, plasmids, and even organisms, be patentable? Second, what actions on the part of an inventor, such as discussing the invention with colleagues or publishing a paper about the results of research, can place the invention in a public domain, thus barring patentability because the invention will not be novel?

*The U.S. Patent and Trademark Office has stated that it will determine questions as to patentable subject matter on a case-by-case basis following the test set forth in *Chakrabarty* (49).

**A U.S. Patent and Trademark Office official estimated that there are currently 500 genetic manipulation related patent applications pending, that the office is receiving applications at the rate of 200 per year, and that the rate is increasing (46). These applications are classified in Class 435, Subclass 172 in the U.S. Patent Classification System (46). This classification is *not* coextensive with OTA's definition of biotechnology.