Appendix B
Country Summaries

OTA identified five foreign countries as the major potential competitors of the United States with respect to the commercialization of biotechnology: Japan, the Federal Republic of Germany, the United Kingdom, Switzerland, and France. This appendix summarizes information about those countries presented elsewhere in this report. It also describes the activities in biotechnology of Sweden, the Netherlands, Australia, Israel, Canada, the U. S. S. R., and Brazil.

Japan

INTRODUCTION

The commercialization of biotechnology in Japan is accelerating over a broad range of industries, many of which have extensive experience in bioprocessing. Leading Japan's drive to commercialize biotechnology are large established Japanese companies such as Takeda Pharmaceutical, Shionogi Pharmaceutical, Mitsubishi Chemical, Sumitomo Chemical, Toray Industries, Suntory, and Ajinomoto. The general chemical and petrochemical firms especially are leaning strongly to biotechnology, and some of them are making rapid advances in research and development (R&D) through their efforts to make biotechnology a key technology for the future.

The Japanese Government, which fell behind in starting to form a national support structure, has embarked on building a foundation for R&D and is demonstrating ambitious movement by forming Government and private collaborative projects with the motto "catch up, get ahead" (8). As biotechnology product markets begin to develop, Japan's expertise in the art of bioprocessing will provide Japanese companies with significant competitive strengths.

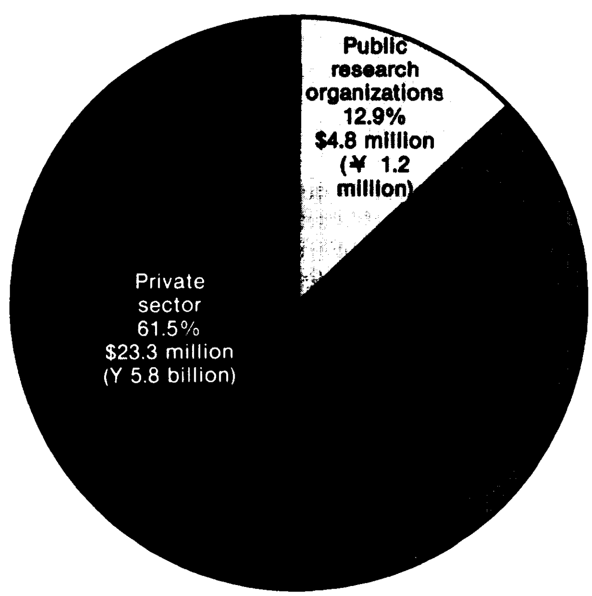
INDUSTRY

All of the large private sector Japanese companies using biotechnology have come from established industries. In this respect, Japan differs from the United States, where more than 100 new biotechnology firms (NBFs)* have been started specifically to exploit biotechnology.

Japanese companies did not start investing in new biotechnology until after 1980, when publicity spread about its potential applications to the pharmaceutical industry. Since then, led by the promise of interferon and monoclinal antibodies (MAbs) in cancer treatment and the potential of producing unlimited quantities of each through biotechnology, more than 150 Japanese companies have rapidly reorganized their R&D systems, equipped research institutes, and recruited new staff to evaluate the applications of biotechnology. The breakdown by funding sector of Japan's total expenditures for recombinant DNA (rDNA) related R&D for fiscal year 1981 is illustrated in figure B-1.

Japanese pharmaceutical companies, whose penetration of international markets heretofore has been low, show promise of becoming increasingly competitive with the United States in world pharmaceutical markets. The Japanese pharmaceutical market is currently second only to the U.S. market in size. In addition to the pharmaceutical companies, Japanese companies from the food, chemical, textile, and pulp and paper industries have also begun to further exploit their accumulated experience in bioprocessing by diversifying into newly developing pharmaceutical product

Figure B-l.— Breakdown of Japan's Expenditures for Recombinant DNA Technology R&D, Fiscai Year 1981



Total rDNA expenditure = $38.1 million (Y 9.5 billion)

SOURCE. Off Ice of Technology Assessment, based on data from Science *and Techno/ogy~,In* Japan, April/June 1983

● NBFs, as defined in *Chapter 4: Firms Commercializing Biotechnology*, are firms that have formed specifically to capitalize on developments in biotechnology markets, * The field of specialty chemicals will be another highly competitive area of Japanese involvement. Japan is already the dominant international force in amino acid production, and two of the largest amino acid producers, Ajinomoto and Kyowa Hakko Kogyo, have production plants in the United States. Japanese companies' current emphasis on research in specialty chemicals such as enzymes and amino and organic acids reflects efforts to pull the Japanese petrochemical industry out of its present decline in international markets. The urgency of this task is greater in Japan than in the United States, because Japanese petroleum-based industries such as chemicals and textiles are solely dependent on imported petroleum feedstocks. Although some specialty chemicals have traditionally been made by bioprocesses, opportunities for using bioprocesses to make specialty chemicals previously made from petroleumderived feedstocks have arisen with biotechnology. Producing specialty chemicals using biotechnology offers Japanese companies in these industries an opportunity to reduce their dependence on petroleum and at the same time switch from the production of high-volume, low value-added products to products with higher profit margins.

GOVERNMENT TARGETING POLICIES AND FUNDING OF BASIC AND APPLIED RESEARCH

Within the Japanese Government, a consensus regarding the importance of biotechnology to the future health of the Japanese economy has been achieved. Three Government departments in Japan—the Science and Technology Agency (STA), the Ministry of International Trade and Industry (MITI), and the Ministry of Agriculture, Forestry, and Fisheries (MAFF)—have specifically targeted the development of biotechnology.

STA was the first to demonstrate an interest. As early as April 1971, STA'S advisory group, the Science and Technology Council, composed of government, business, and academic leaders, stressed the importance of promoting life science on a nationwide basis because of its commercial potential (4), and STA responded in 1973 by establishing its Office for Life Science Promotion. This office, which is Japan's highest science and technology policymaking body, also manages and coordinates R&D projects in biotechnology. Until the early 1980's, STA'S basic, generic applied research)* and applied programs in biotechnology were the largest and best funded Government programs in Japan, and even today STA'S programs are comparable in scale to those of MITI (see below). The agency is currently funding corporate generic applied research projects to develop DNA synthesis techniques, bioreactors, immobilized enzyme processes, screening techniques for new micro-organisms, and new medicines.

Mfi did not enter the biotechnology field until 1981. That year, MITI established its "System for Promotion of Research on Next-Generation Industrial Technologies," an overall plan to promote "next-generation" industrial technologies, including biotechnology (11). To focus MITI's overall biotechnology effort and to oversee its three next-generation biotechnology projects, an Office of Biotechnology Promotion was established within MITI's Basic Industries Division.

MITI's three next-generation projects in biotechnology— bioreactors, rDNA technology, and mass cell culture-are a part of a 10-year program that is specifically designed to develop and diffuse new biotechnology among Japanese companies. * * MITI has invited 14 companies to participate in the projects and will provide allocations over 10 years of $43 million each to the rDNA and bioreactor projects and $17 million to $22 million for the mass cell culture project (2). Some 10 percent of the R&D work (by expenditure) for MITI's biotechnology projects is conducted in the national laboratories of MITI's Agency for Industrial Science and Technology. Ninety percent of the work is conducted in industry laboratories.

To facilitate coordination, the 14 companies that MITI has invited to participate in the biotechnology projects have been organized into the Biotechnology Development Research Association. This association has its own central office through which the various companies communicate with MITI, but otherwise maintains no intercompany institutions or laboratories. MITI subsidies to the companies cover 100 percent of all direct expenses (salaries and laboratory expenses) for biotechnology R&D, but no overhead is allowed, and any capital equipment purchased is nominally the property of the Japanese Government. Furthermore, all patents resulting from the work belong to the Japanese Government. MITI has assured both domestic and foreign companies access to the patents (11).

"The first Japanese companies to enter the field of rDNA-produced pharmaceuticals, Green Cross, Hayashibara, and Suntory, were led by pioneering entrepreneurial managers. For example, the Hayashibara venture into producing interferon with hamsters was possible only because the owner owns or controls 12 companies (hotels, gas stations, and candy manufacturing) and does about $150 million (¥37.4 billion) worth of business a year (14). Suntory's (a whiskey company) diversification into rDNA-produced pharmaceuticals is a similar situation.

● Basic, generic applied, and applied research are defined in *Chapter 13: Government Funding of Basic and Applied Research*.

•*The Biotechnology Forum, a group of five major Japanese chemical companies that had organized independently after the announcement of the Cohen-Boyer rDNA process patent, was instrumental in lobbying for the establishment of the biotechnology projects.

The third Japanese Government agency that is taking an active role in biotechnology, MAFF, recently established the Committee on Biological Resources Development and Utilization, which compiled a report recommending actions MAFF could take to promote biotechnology development (7). Currently, MAFF is actively promoting cooperative biotechnology research with private industry at its laboratories and is funding work both with Nippon Shokuhin Kako and Oriental Yeast at the National Food Research Institute and with Kao Soap at the National Institutes of Agricultural Sciences. It is also planning cooperative research with Japanese seed companies in the areas of plant breeding and species improvement. Although achievements from the cooperative research are used jointly by Government and industry, these companies that participate in the research projects receive exclusive licensing rights to the patents resulting from these projects for a 3-year period (9). MAFF funding for biotechnology R&D is comparable to that of MITI and STA (11).

In addition to STA, MITI, and MAFF, three other Japanese Government agencies are funding basic and generic applied research in biotechnology: the Ministry of Health and Welfare, the Ministry of Education, and the Environmental Protection Agency. Total Japanese Government funding for biotechnology R&D in 1983 is $67 million (11). Although the level of Japanese funding may be slightly lower than Government funding in both the Federal Republic of Germany and the United Kingdom and is dwarfed by that of the United States, a far greater proportion of Japanese than U.S. funding goes to applied research.

The importance of the Japanese Government's investment in applied research relevant to biotechnology, however, should not be overstated. Of greater importance than the Government's investment in research per se is the Japanese Government's success in encouraging industry's involvement in and long-term commitment to biotechnology. The strength of Japan's biotechnology policy lies in its emphasis on the sensible development of mutually agreed on research strategies, horizontal organization and coordination within the private sector, and timely funding of the necessary high technologies (known in Japan as the "seed corn" policy).

FINANCING AND TAX INCENTIVES FOR FIRMS

Private sector financing in Japanese biotechnology is still mostly indirect and mediated through the Japanese banking system. At present, most Japanese firms using biotechnology are very thinly capitalized. The ratio of debt to equity is still far higher in Japan than it is in the United States. As far as can be determined, however, the financing of R&D efforts is not a major problem for the large companies in Japanese biotechnology. The Japanese companies involved in biotechnology R&D have either their own internal sources of funds or close relations with the banks (11).

Certain weaknesses in Japan's financial system have been especially evident in biotechnology. Despite many changes in recent years, capital remains heavily concentrated in the Japanese banking system, and stock markets play a relatively small role in allocating capital. Only 111 Japanese companies currently have their securities traded over the counter, and total venture capital investments amount to no more than $84 million (l). * Mostly because of the lack of venture capital and the cultural factors inhibiting risk-taking entrepreneurialism, Japan does not have a large class of startup companies that specialize in biotechnology R&D such as that found in the United States.

Japan's private sector has recently taken some initiative in developing a source of "venture capital" by pooling corporate resources, The Japan Associated Finance Corp. (JAFCO) is a private venture capital fund that was organized by Nomura Securities Co. 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 according to the ratio of the capital contribution to the fund (3). 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 Japanese Government is interested in changing the country's financial system. In 1982, MITI set up a new Office of Venture Enterprise Promotion in parallel with the creation of the Office of Biotechnology Promotion (6). In fiscal year 1981, a Government-related organization called the Center for Promoting R&D Type Corporations guaranteed approximately $3.7 millon (x 750 million) in loans (a total of 24 loans), and beginning in 1982, this center began making its own loans as well as guaranteeing other lender's loans. In an equally significant development, MITI and the Ministry of Finance (MOF) have recently begun discussing an '(automated over-the-counter share transaction system" to make it easier for enterprising small and medium-sized firms that lack business experience to raise funds in the finance market. Currently, MOF'S evaluation standards are so strict from the standpoint of protecting investors that venture businesses find

"Institutions such as Japan Godo Finance, Sogo Finance, and Universal Finance Corp. are viewed as nascent venture capital companies.

it difficult to have their shares sold when they want to go public.

In the past, Government-funded banks like the Japan Development Bank UDB) have played a key role in providing large amounts of low interest loans to heavy industries. Certain funds within the JDB loan portfolio are targeted for "technology promotion," and loans from the fund are made at interest rates between 7.5 and 8.4 percent. Currently, however, these funds are not being channeled into biotechnology (11).

Japan's corporate tax code exhibits a uniformity across industrial sectors that is not evident in the United States. Furthermore, corporate taxes are generally lower in Japan than they are in the United States (13). A number of Japanese tax code provisions are aimed at benefiting R&D activity and technological innovation across the board.

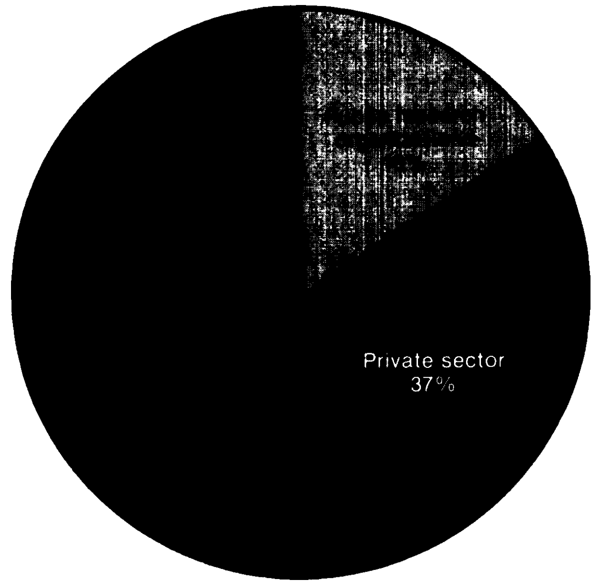
One Japanese tax break of particular relevance to the development of biotechnology is the special depreciation schedule used for companies that are members of a Ml'TI-approved National Research Association (e.g., the Biotechnology Development Research Association). Such companies can take an immediate 100-percent depreciation deduction on all fixed assets used in connection with their research association activities. Because of the decentralized character of most National Research Association R&D—90 percent of it is performed separately in corporate laboratories—the tax writeoffs directly encourage R&D activity within corporate laboratories.

PERSONNEL AVAILABILITY AND TRAINING

Since World War II, the training of industrial microbiologists and bioprocess engineers has been encouraged by both Government and industry funding in Japan, and as a result, a steady supply of these personnel has been maintained. In fact, Japan is considered the world leader in this area. On the other hand, largely because of its weak basic biological science research base, Japan is experiencing a shortage of molecular biologists and immunologists. Some Japanese companies have addressed this problem by sending some of their personnel to the United States for training in molecular biology. Other companies have had success in repatriating Japanese workers already trained overseas. Figure B-2 gives a breakdown of Japanese personnel engaged in rDNA R&D by type of research organization.

Retraining of corporate workers in biotechnology is being pursued actively in Japan. In Japan, more than in any other industrialized country, worker training is the responsibility of the corporation. Japan's ability to adjust rapidly to weaknesses in its labor force, based primarily on the Japanese corporations' funding

F gu e B 2 Breakdown o Japanese Pe sonne Engaged n Recomb nan DNA Techno ogy R&D by Type o Resea ch O gan za on F sca Yea 98



98

of worker retraining, is truly extraordinary. In 1981, for example, no more than 10 private Japanese companies had more than 10 researchers working on rDNA technology; a year later, surveys revealed that 52 out of the 60 leading companies surveyed had obtained 10 or more research workers in that area (11).

UNIVERSITY/INDUSTRY RELATIONSHIPS AND DOMESTIC TECHNOLOGY TRANSFER

In applied research areas such as bioprocessing and microbiology, Japanese university/industry relations and the transfer of information from universities to industry are generally very good. In basic research areas, however, the transfer of information from universities to industry is impeded by the fact that almost all university rDNA and hybridoma research in Japan takes place in '(basic" science departments, and these departments pride themselves on independence from industrial influence. The Japanese Government has launched new programs designed to cross the barriers between university basic science departments and industry, but their future success is questionable (11).

The movement of knowledge across industrial sectors in Japan is facilitated by the unique "keiretsu" structure (a group of companies with historical ties, which usually consists of a company from each industrial sector and a bank or trading company which plays a dominant role by virtue of its contact with other companies within the group). The transfer of information among companies within sectors, however, is inhibited by extreme secrecy and a lack of mobility of personnel from one company to another. MITI's "next generation" projects in biotechnology are designed in part to compensate for this problem and to diffuse knowledge among companies using biotechnology. In part because they suspect they would have to sacrifice proprietary positions in some commercially important research areas, however, some Japanese companies have not joined the MITI projects in the areas in which they have comparative advantages (11). For example, Kyowa Hakko, a leader in work on rDNA, is not participating in the "next generation" project in this area.

OTHER FACTORS

Historically, Japan's guidelines for rDNA research have been among the most restrictive in the world. Although the guidelines have recently been relaxed somewhat, they are still quite restrictive. Japanese companies have mounted intensive lobbying efforts to get the guidelines changed. Although companies have had extreme difficulty in obtaining approval to do work with more than 20 liters of culture, this situation is expected to change soon.

Although estimates are difficult to obtain, the cost of gaining approval for new pharmaceuticals is believed to be lower in Japan than the United States. In Japan, the cost of obtaining approval for a new drug is about $12 million to $20 million (3 billion to # 5 billion), compared to about $87 million in the United States. The time required for drug development and approval is similar (about 10 years) in both the United States and Japan (5).

The basic law governing worker health and safety in Japan is the Industrial Safety and Health Law. This law imposes on employers the obligation of preventing health impairment caused by substances and conditions found in the workplace. Substantial criminal penalties and fines are imposed for violations. At the present time, no regulations are addressed specifically to biotechnology. Furthermore, specific measures governing environmental effects of biotechnology applications have not been prepared by the Japanese Government.

Because the United States is considered a world leader in the commercial applications of biotechnology, Japanese companies have been actively importing technology from the United States and other countries through R&D joint ventures and licensing agreements. NBFs in the United States in need of financial support widely accept research contracts from Japanese companies, often because U.S. partners cannot be found.

An issue brought up in recent U, S.-Japan trade negotiations was U.S. access to the technologies developed by the MITI-sponsored National Research Associations. MITI has promised to abandon its past policy and disclose the patents obtained in National Research Associations to foreign firms. MITI is also promising membership in National Research Associations to U.S. companies that have Japanese subsidiaries or substantial technological expertise.

Japan is engaged in international efforts to secure sources of biomass* in the event that biomass becomes the favored route to meeting energy needs. In cooperation with developing countries (mostly Asian), Japan is organizing biomass centers. This foresight may operate to Japan's advantage in the future.

Nontariff trade barriers in Japan, especially in the area of pharmaceuticals, may hinder U.S. companies' penetration of Japanese markets. The Japanese Ministry of Health and Welfare has not yet begun to accept clinical test data from the United States, although as of April 1983, Japan did begin accepting foreign test data on animals. Foreign stability test data and data on specifications and test methods will be accepted from October 1983 onward (10).

Unlike the United States, Japan has constraints inhibiting foreign acquisition of domestic companies. Foreign acquisitions in Japan require the unanimous approval of the Japanese company's board of directors and also the approval of MOF. Recently, however, the regulation surrounding the establishment of foreign subsidiaries in Japan has noticeably eased; large numbers of European pharmaceutical companies have established wholly owned subsidiaries in Japan during the past year. The ease of foreign acquisition of domestic companies in the United States is an important issue to consider, because Japanese companies very often acquire foreign companies to gain access to their technology, markets, and distribution networks.

CONCLUSIONS

Because of its present competitive strength in biologically produced specialty chemicals, Japan can be expected to be a major competitor in future specialty chemical markets defined by biotechnology. The fu-

* Biomass, discussed further in *Chapter 9: Commodity Chemicals and Energy Production*, is all organic matter that grows by the photosynthetic conversion of solar energy.

ture competitive position of Japanese companies in future pharmaceutical markets is more difficult to assess. Japanese companies traditionally have not had a significant presence in world pharmaceutical markets, but Government promotion of the pharmaceutical industry, rising investments in pharmaceutical R&D (including related biotechnology applications), and increased competition in the domestic pharmaceutical market all portend a greater role for Japanese companies in future international markets. *

Federal Republic of Germany

INTRODUCTION

A powerful private sector, a well-developed administrative infrastructure, an extensive research base, a generous funding program, and an adequate supply of personnel all contribute to the potential of the Federal Republic of Germany to compete with the United States and other industrialized countries in biotechnology. The overall West German effort does have certain deficiencies (e.g., an inflexible research grants system), however, and the ability to correct them will be a factor that influences the country's competitive position.

The ability to correct these deficiencies, however, will not by itself guarantee competitive success. Politics, for example, and its most powerful ally, public perception, could influence the course of biotechnology development more immediately in the Federal Republic of Germany than in any other country. The West German environmentalists, embodied in the political party of the Greens, have yet to focus their attention on risks specifically associated with biotechnology, but the leading German companies using biotechnology have already aroused public protest as major chemical polluters, The Greens, now incorporated in the Federal parliamentary process, represent a potential threat, especially in the event of a mishap, to the progress of biotechnology in the Federal Republic of Germany (24).

INDUSTRY

The Federal Republic of Germany's competitive position in biotechnology will be determined by the ability of large, established West German companies to develop and market biotechnologically produced goods and services, Responsibility for most of the development of the country's industrial capabilities in biotechnology to date rests largely with chemical companies such as Hoechst, Bayer, and BASF, three of the four largest in the world, and with the slightly smaller pharmaceutical companies such as Boehringer and Schering. Small and medium-sized West German companies have played no significant role in biotechnology innovation, despite the West German Government's efforts to encourage this through the provision, for example, of startup funding for high-risk undertakings (24).

To speed the transition to new biotechnological techniques and processes, the large West German companies that are developing biotechnology have sought outside expertise. Hoechst, for example, signed a 10-year, $70 million contract with Massachusetts General Hospital to support work in molecular biology (18). Hoechst, criticized in Germany for a breach of faith with national science and in the United States for the ap~ropriation of U.S. technology, apparently entered into this agreement with the objectives of getting a "window on the technology" and gaining access to a large, state-of-the-art laboratory in which to train its scientists (18).

GOVERNMENT TARGETING POLICIES

A government policy for the commercialization of biotechnology rates as one of the Federal Republic of Germany's strengths. According to a 1979 statement by the Federal Ministry for Research and Technology (BMF'I', Bundesministerium fur Forschung und Technologies), the German Government has an obligation to establish the preconditions for industrial innovation in key areas of technology in order to strengthen the competitive performance and competitive capacity of the German economy in long-range growth areas, and in the process, correct weaknesses revealed through international comparisons (24).

The present biotechnology targeting policy has evolved from the West German Government's historical interest in the life sciences. In 1972, BMFT commissioned a report on old biotechnology from the German Society of Chemical Engineering (Deutsche Gesellschaft fur Chemisches Apparatewesen) (19), and in 1979, BMFT presented its first official policy specifically for biotechnology (16). This "performance plan" (Leistungsplan) outlined biotechnology research programs with specific objectives, such as the development of unconventional feed and foodstuffs, bioinsecticides, and pharmaceuticals from plant cell cultures. BMFT's more recent statements continue to promote the development of specific product areas (e.g., pharmaceuticals, plant agriculture) and particular proc-

• For example, in 1981, Japanese companies ranked first in terms of the largest number of major new drugs introduced into world markets. In 1982, not only did Japanese companies account for over 16 percent of all U.S. patents issued for pharmaceutical and medicinal products, but 38 percent of all U.S. medicinal patents granted to foreign firms went to Japanese originators. See *Chapter 4: Firms Commercializing Biotechnology* for a more detailed description of Japanese pharmaceutical activity.

esses (e.g., cell culture), but they also focus attention on the importance of basic research and the need for greater interdisciplinary cooperation between biologists, chemists, medical experts, and engineers, disciplinary areas which are important to the development of biotechnology (24).

BMFT implements its policy primarily through a strong and varied funding program. Types of BMFT support fall into three broad categories: 1) funds specifically set aside for the development of biotechnology, 2) grants that fall into already existing schemes for industrial development work, and 3) funds distributed by third-party organizations to which BMFT contributes as part of more generalized funding programs for all areas of public research. For its own biotechnology program alone, BMft in 1982 spent $29 million (DM70 million), up $5 million (DM12 million) from 1981. In 1981, BMFI' also contributed to the German Research Society (DFG, Deutsche Forschungsgemeinschaft) (25) and to the Max Planck Society (Max Planck Gesellschaft) (15). It is impossible to calculate the exact proportion of these other funds dedicated to biotechnology research, but a reasonable estimate might range from $20 million to $40 million (DM50 million to DM 100 million). Since data are unavailable to support this estimate, a total BMFT biotechnology funding figure of $5o million to $7o million (DM120 million to DM170 million) for 1982 should be regarded with caution.

GOVERNMENT FUNDING OF BASIC AND APPLIED RESEARCH

The Federal Republic of Germany maintains an extensive public research base. Both basic and generic applied research are generally good. Three different types of nonindustry laboratories conduct basic research in biotechnology: 1) laboratories belonging to the universities, 2) laboratories dependent on BMFT for operating expenses and on DFG for project support, and 3) laboratories supported by the Max Planck Society (which, in turn receives support from BMFT).

The operating costs of the universities are supported by the individual States (Lander). Highly publicized deficiencies in German university research have resulted from budget cuts and university reform laws. With the current shortage of funds, grant allocations go to tenured professors (27) and to replace used equipment, not to the young researchers (29). University reform laws have created excessive administrative duties for university professors, making it difficult for them to dedicate sufficient time to their research (20). Despite such problems, however, universities such as those at Heidelberg, Munich, and Cologne continue to conduct research fundamental to the development of biotechnology (21).

Although laboratories supported jointly by BMFT and DFG, such as the Cancer Research Center at Heidelberg, carry out important biotechnology-related work, laboratories funded by the Max Planck Society are responsible for the bulk of the basic research advances in biotechnology. The Max Planck Institute for Plant Breeding Research in Cologne boasts some of the best plant genetics teams in the world (24). Other leading Max Planck institutes working in basic research related to biotechnology include those in biochemistry at Martinsried, biology and virus research in Tubingen, genetics in Berlin, and cell biology in Ladenburg (21).

Some of the Max Planck institutes conduct generic applied biotechnology research, but the center for such research is the Society for Biotechnological Research (GBF, Gesellschaft fur Biotechnologische Forschung). GBF is a Government-supported though private institution that was originally founded to conduct generic bioprocessing research to meet the needs of industries (26). GBF employs 365 people (249 permanent and 116 temporary), and its 1982 budget was $13 million (DM31.6 million), of which 89 percent came from BMFT, 9 percent from the lander, and 2 percent from its own earnings (Gesellschaft fur Biotechnologische Forschung, 1982). GBF's current activities include the general development of bioprocess technology, the scale-up of laboratory processes, the screening of micro-organisms and plant and animal cell cultures, the support of other research groups in biotechnology, the participation in joint biotechnology projects with industry, and the advanced interdisciplinary training for scientists, engineers, and technicians. GBF suffers from the usual rigidity of a large German research organization—funds, once allocated, cannot be shifted from one area of research to another. Nevertheless this well-equipped and well-staffed Government-supported applied research facility in West Germany is one of Europe's best.

FINANCING AND TAX INCENTIVES FOR FIRMS

There is no parallel in the Federal Republic of Germany to the U.S. venture capital industry. The powerful and rather rigid banking structure in the Federal Republic of Germany virtually inhibits the formation of venture capital, though there is apparently little demand for it (24). Commercial banks provide most of the funds used for industrial expansion, and it is common for such banks to have equity participation in companies in which they invest. The commercial *banking* sector is dominated by three banks, and the linkages between the banking and corporate structures are so close that the Monopoly Commission in 1976 concluded that the banks effectively utilize management functions to the detriment of competition (24).

In 1975, a consortium of 28 banks recognized that the German banking system was not conducive to funding high-risk innovative, startup firms and formed a venture capital concern called the Risk Financing Society (WFG, Deutsche Wagnisfinanzierungs-Gesellschaft) (17). The principal objective of this organization was to aid small and medium-sized firms in commercializing their products. So far, however, this concern has not shown much interest in biotechnology companies, a major reason being that since 1980 it has been looking for innovations that could achieve success within 24 months. If this continues to be the criterion for a firm to receive funds from WFG, it would be surprising if many biotechnology startup firms were established in the Federal Republic of Germany with WFG funds.

Tax incentives are a less important source of financing for private sector innovation in the Federal Republic of Germany than direct Government subsidies. This country maintains the highest nominal corporate tax rate of the six countries analyzed in this report (56 percent on retained earnings and 36 percent on distributed earnings). Measures such as an investment grant provision allowing a company to recover up to 20 percent of the cost of R&D capital expenditures contribute to lower the effective tax rate, although the United Kingdom, Switzerland, and Japan still have the lowest effective tax rates of the competitor countries.

PERSONNEL AVAILABILITY AND TRAINING

The Federal Republic of Germany has sufficient personnel to compete with the United States and other competitor countries in biotechnology. Molecular biologists with expertise in rDNA and hybridoma research are in short supply, but the training of such specialists is now a high priority (24). 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. Thus, the supply of personnel in these areas appears to be adequate.

The Max Planck Society's senate and the present Minister of Research and Technology have indicated that there is a significant drain of German researchers from the Federal Republic of Germany to the United States (21)28). The "brain drain" of scientists from West Germany, however, appears to be less serious than that from the United Kingdom (see below).

UNIVERSITY/INDUSTRY RELATIONSHIPS AND DOMESTIC TECHNOLOGY TRANSFER

The Federal and State Governments and the private sector in the Federal Republic of Germany use several mechanisms to accomplish the transfer of technology developed in public research laboratories into domestic industries, The Max Planck Institute for Plant Breeding Research and GBF both have several contract arrangements with private companies. On a much larger scale, the pharmaceutical company Schering joined with the State of Berlin and its two universities to establish a biotechnology research institute (Biotechnikum). Though the institute will undertake primarily basic research in rDNA technology, it will also support industrial microbiology research and the production of hormones and amino acids (22). Bayer, BASF, and Hoechst have also established cooperative research programs with West German universities and other research institutes.

OTHER FACTORS

In general, the West German regulatory environment is comparable to that in the United States and poses no additional barriers to the commercial development of biotechnology for either domestic or foreign firms. Guidelines for rDNA research, food and drug testing regulations, intellectual property law, and international trade laws in West Germany are approximately equivalent to those in the rest of the competitor countries.

CONCLUSIONS

The Federal Republic of Germany could become one of the principal competitors of the United States in the commercialization of biotechnology. West Germany's extensive research base would be one of the most well-balanced in the world, were it not for the funding and administrative problems in the universities and the resulting effects on the quality of research. Another problem is that the Government bureaucracy for implementing biotechnology policy is somewhat inflexible. Once funding has been granted for specific projects, money cannot be shifted to other potentially more promising studies. One of the Federal Republic of Germany's strengths, however, is the country's private sector. The size and international market penetration of established German chemical and pharmaceutical companies suggests that these companies are likely to be competitive in the commercial use of biotechnology.

United Kingdom

INTRODUCTION

In many respects, the United Kingdom has the capabilities to compete in biotechnology on an equal basis with the United States, Japan, and the Federal

Republic of Germany. Government initiatives, national science and technology resources, both human and material, and efforts by a few individual companies to commercialize biotechnology place the United Kingdom on a par with these other competitor countries. A relative lack of experience in joint government, industry, and public research cooperation compared to the United States and, with some exceptions, a generally risk-averse private sector, however, could become obstacles to the smooth development of biotechnology in the United Kingdom.

INDUSTRY

A number of NBFs have been started to commercialize biotechnology in the United Kingdom. These include Celltech, Agricultural Genetics, Plant Sciences, Imperial Biotechnology, IQ (Bio), and other companies that were founded specifically to exploit results of basic research in biotechnology-related disciplines. Although the United Kingdom has more NBFs than do other European countries or Japan, the importance of NBFs to the commercialization of biotechnology in the United Kingdom does not generally rival that of their U.S. counterparts. The 1983 marketing by Celltech of MAbs to detect and isolate interferon (34) and of two blood-typing kits using MAbs (47), however, demonstrates a certain dynamism within the United Kingdom's NBF sector.

The large established U.K. companies such as ICI, Burroughs-Wellcome, G. D. Searle, Unilever, Glaxo, and others will play the major role in determining the United Kingdom's competitiveness in the commercialization of biotechnology. These companies, like established companies in the other competitor countries, are better equipped than the NBFs to absorb the high costs of large-scale production, health and safety testing, and marketing, in fields such as pharmaceuticals, food, or agriculture. Although they appear to be investing large sums in biotechnology R&D (44), it remains to be seen whether established companies in the United Kingdom can generate the same level of innovation from in-house research and arrangements with universities as the NBFs in the United States.

GOVERNMENT TARGETING POLICIES

Until recently, many analysts in the United Kingdom believed that biotechnology products would reach markets only after 10 to 20 years (36) and that the British Government should maintain its traditional functions with respect to developing technologies, i.e., limit itself to supporting basic R&D, training qualified personnel, and creating a propitious climate for industry to capitalize on discoveries made in public research facilities (35).

In 1980, a Government committee published a report that identified weaknesses in the development of biotechnology and recommended that the Government take specific corrective actions to assist the transfer of the results of public sector research to industry and to expand existing programs supporting training, research, and innovation (3o). The British Government has responded to this report, commonly known as the Spinks' Report, by increasing funds both for the British Technology Group (BTG) for investment in innovative private sector projects in biotechnology and for the Research Councils and Government departments for the support of basic life science research.

In 1981, the British Government, through BTG and in association with four private investors, established Celltech, Ltd., to develop and market products made by some of the new technologies, In 1982, the Department of Industry launched a new 3-year, $3o million program of support for biotechnology in industry (30. The Government has also encouraged the creation of university centers of expertise in biotechnology to bring together experts in different disciplines within a single field and has established a Biotechnology Directorate at the Science and Engineering Research Council (SERC) to coordinate biotechnology R&D in all public sector research laboratories.

GOVERNMENT FUNDING OF BASIC AND APPLIED RESEARCH

The United Kingdom has a strong and well-established basic research base. The Research Councils and the universities possess considerable depth in basic research fields such as immunology and plant genetics. Although the economic recession has forced cuts in both university and Research Council grants (46), the Government has attempted to protect the basic science research budget and to redirect resources within this budget to priority areas such as biotechnology. Research Council funds for biotechnology have actually increased. University funds have been reduced in some areas, but the Government has encouraged universities to protect basic research, and the University Grants Committee has been funding the establishment of new posts at many different universities (37).

Generic applied research in biotechnology has been receiving strong support in the United Kingdom. The British Government sponsors generic applied research at a number of locations, including the Centre for Applied Microbiology Research in Porton Down ('bioprocess engineering); Warren Spring Laboratory in Harwell (downstream processing); and the Biotechnology Institute and Studies Centre Trust (enzymes). These and other programs all contribute to make development a strength of the Government's support for biotechnology.

Definitional problems make it difficult to arrive at a figure for overall Government expenditures for biotechnology R&D. Though the British Government uses the Spinks' Report definition, * research institutes tend to classify work in scientific terms such as rDNA technology, hybridoma technology, and others. A conservative estimate of biotechnology funding for all phases of R&D would fall between $56 million and $60 million for 1982 (46), though the Government expects to increase this level substantially during 1983. The 1982 figure roughly equals spending in Japan, the Federal Republic of Germany, and France.

FINANCING AND TAX INCENTIVES FOR FIRMS

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.

Funds for the industrial development of biotechnology, especially for NBFs, are available from both public and private sources. The major public source of venture capital is BTG (see above). Private venture capital groups with either investments or plans to invest include Biotechnology Investments, Prutec, Advent Eurofund, Cogent, Technical Development Capital, and others. Of these, Biotechnology Investments, a branch of N. M. Rothschild Asset Management, is the largest, with an initial capital pool of $55 million (39). Most of the fund's investments to date have been in U.S. NBFs and in primarily foreign quoted companies (39), although the company recently purchased equity in Celltech (33) and is now considering more project proposals from British firms than from U.S. companies (43). Other sources of capital for NBFs include banks and other financial institutions, whose project loans are guaranteed by the Government, and the Unlisted Securities Market, for companies with profits of less than $1 million.

Tax law in the United Kingdom tends to favor established companies with programs in or plans to implement biotechnology R&D rather than NBFs. Most of the Government's tax incentives apply to companies earning taxable income (i.e., the large established companies) and are used primarily to encourage additional expenditures on R&D or on plants and equipment required for research or scale-up. The tax code allows the largest and most rapid depreciation allowance of capital expenditures for scientific research of all the competitor countries (100 percent in the first year of use). This provision contributes to making the effective corporate tax rate in the United Kingdom among the lowest of the countries analyzed by this report.

Few of the tax incentives in the United Kingdom, on the other hand, encourage the formation of capital, a necessary precondition for starting an NBF. Both the taxation of long-term capital gains (30 percent) and of income resulting from the sale of technology (in the form of patent sales or licensing royalties) are the most unfavorable of the competitor countries. The British Government recently introduced new measures 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 trades, but the effect of this policy remains to be seen.

PERSONNEL AVAILABILITY AND TRAINING

Like the United States, the United Kingdom boasts both qualified personnel and excellent training and education programs for personnel in the basic life sciences. Personnel supported by the Medical Research Council are internationally prominent in the development of rDNA and hybridoma technologies. * Also like the United States, the United Kingdom is experiencing personnel shortages in areas related to scale-up. The shortage in the United Kingdom in part results from the fact that very limited opportunities in British universities have led some scientists to leave their posts in academia for positions in foreign biotechnology companies. Approximately 70 Ph. D.s have left the United Kingdom in the past few years. Slightly less than two-thirds of these scientists have come to the United States, though some of them may not be working exclusively in biotechnology. About 30 of the 70 have joined commercial enterprises (13 now work at Biogen S.A. in Switzerland). This "braindrain" also affects another class of professionals, i.e., individuals skilled in applying the new technologies such as bioprocess and chemical engineers and masters-level microbiologists. 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 (45).

The effects of this outflow on the overall British effort are difficult to determine; no one really knows

*This and other definitions of biotechnology are presented in *Appendix A: Definitions of Biotechnology.*

*British researchers Georges Kohler and Cesar Milstein at the Medical Research Council were the first to develop hybridomas.

whether the United Kingdom may be losing visionaries as well as scientists or whether 100 people represent a significant portion of the available specialized personnel in the United Kingdom (41). In an effort to correct a situation which often obliges some younger researchers and engineers to emigrate, the British Government has recently launched a program to make room for "new blood" in the life sciences in the universities. The creation of these new positions will raise the number of lecturers and create new openings for postdoctoral research and postgraduate courses. In addition, SERC maintains a list of British biotechnologists outside the United Kingdom and may be taking measures to encourage them to return (45).

UNIVERSITY/INDUSTRY RELATIONSHIPS AND DOMESTIC TECHNOLOGY TRANSFER

The universities in the United Kingdom have had very few ties with industry in biotechnology. As a result, the transfer of technology from public research to the industrial sector in the United Kingdom has not always been effectively accomplished. In 1975, for example, the Government failed to patent Kohler and Milstein's technique for making hybridomas, the specialized cells which produce MAbs, and the Americans were the first to recognize the commercial potential of MAbs (40).

With the growth of biotechnology and of public support for these technologies, however, the British Government has taken steps to encourage the process of domestic technology transfer. BTG, which encourages cooperative projects between industry and public sector research and serves as a public source of venture capital, has committed $21 million in support for biotechnology projects so far, with $6.5 million annual increases expected for the next few years (44). In addition, the Department of Industry launched in 1982 a new, 3-year, $30 million "Biotechnology in Industry" program, independent of BTG's activities. Directed by the Laboratory of the Government Chemist, this program sets aside funds for consultancies and project feasibility studies, supports demonstration plant construction, and sponsors joint industry-research centers (31). SERC has initiated several collaborative research programs and promoted, for example, the Leicester Biocentre. The British Government's establishment of NBFs such as Celltech and Agricultural Genetics Co. in association with private investors and BTG's loss of the rights of first refusal* on inventions in public research (32) may help stimulate direct relationships between researchers and industrialists,

*This is the right to choose whether or not to produce and market any good or service, without having to bid competitively with other firms,

OTHER FACTORS

The regulatory environment in the United Kingdom poses little threat to the development of biotechnology in that country. Approval for the marketing of a new drug in the United Kingdom, for example, occurs twice as quickly as in the United States (46). *

The public body that has been responsible for setting and enforcing the United Kingdom's guidelines for rDNA research is the Genetic Manipulation Advisory Group (GMAG). GMAG's status was recently reviewed by the Health and Safety Executive, and the subsequent report recommended the relocation of the group from the Department of Education and Science to the Department of Health and Social Security (42). GMAG, now called the Health and Safety Commission Advisory Committee on Genetic Manipulation, has been moved to the Department of Health and Social Security and will advise the Health and Safety Commission and Executive on general questions, giving advice, when requested, to Government departments. This change in status of the old GMAG reflects a belief by the Government that those responsible for agriculture, environment, and industry need the committee's advice now more than those in charge of education and science (44). Only in exceptional instances will the Advisory Committee on Genetic Manipulation actually review project proposals. The burden of this task has been passed on to Government officials (42).

British patent law in general conforms to European standards. The lack of case law specific to biotechnology inventions, however, precludes an assessment of whether certain patents that are issued in the United States would receive the same treatment in the United Kingdom. Antitrust laws are approximately equivalent to U.S. statutes.

CONCLUSIONS

The United Kingdom could be a major competitor of the United States in specific product markets in biotechnology. The country's strong basic and generic applied research base, the British Government's strong interest in direct measures to stimulate the commercial development of biotechnology, the excellent university system, and the relatively positive regulatory environment all contribute to allow domestic industries a competitive foothold in biotechnology. The future of commercial biotechnology will be decided in part by the speed, content, and scale both of political decisionmaking with respect to biotechnology and of industrial commitment to developing the technologies.

Although the number of NBFs has grown in the United Kingdom because of an increasingly positive

*For further discussion, see (38).

public attitude toward high technology in general, the development of high-technology fields in the United Kingdom may lack some of the dynamism of similar enterprises in the United States. The causes of what appears to be a lack of entrepreneurialism fall outside the scope of conventional modes of analysis and may be due in part to cultural factors which defy measurement.

The ability of all interested parties to adopt recent Government measures to encourage technology transfer from public institutions to industry and to solve other problems will, to a large extent, determine whether the country can challenge the United States, Japan, and West Germany in this new set of technologies. The United Kingdom's affinity with the United States and longstanding commercial ties to the Pacific Basin could very well be assets.

Switzerland

INTRODUCTION

Switzerland reveals an impressive national commercial potential in the area of biotechnology. It has a good university system and several renowned research institutions. A strong financial sector and a technology-based, export-oriented economy also contribute to Switzerland's potential competitiveness in biotechnology. Swiss companies produce 10 percent of the world's pharmaceuticals (53), and, by reinvesting large proportions of sales revenues in R&D, they achieve high rates of imnovation essential to competitive success.

Switzerland is organized as a federation of 26 relatively autonomous regions (cantons), and a liberal economic tradition constrains the Federal Government's role in industrial policymaking. Consequently, the Swiss Federal Government has not developed a central policy for biotechnology. A number of steps have been taken to promote innovation through Government loans to highly focused, small-scale projects, but these have not been focused on biotechnology (53). In fact, in 1982, a proposal to establish a national research program specifcally for biotechnology under the auspices of the Swiss National Science Foundation (Schweizerischer Nationalfund zur Forderung der Wissenschaftlichen Forschung) was voted down by this organization.

INDUSTRY

Private sector biotechnology R&D in Switzerland is concentrated among three large pharmaceutical companies (Ciba-Geigy, Hoffmam-La Roche, and Sandoz), an NBF (Biogen S.A. *), and, to a lesser extent, several companies involved with bioprocess engineering and biomass conversion for producing chemicals and for energy production (Bioengineering AG, Chemap AG (now owned by Alfa Laval), Petrotec Holding Co. AG, and Batelle Geneva Research Center (U.S. owned).

All of the three large Swiss pharmaceutical companies spend a substantial portion of their R&D expenditures abroad. Ciba-Geigy has made the greatest in-house commitment to biotechnology R&D by improving current production lines such as antibiotics with genetic manipulation. Ciba&eigy's commitment to the development of biotechnology can be seen in its new $19.s million biotechnology research center employing 150 people and in its extensive program of support for research in local universities and its own institute laboratories (53). Ciba-Geigy, spent about 8 percent of its 1981 total sales of $1.8 billion (SFr 3.8 billion), on overall R&D. Of this amount, almost 60 percent was spent within Switzerland, while expenditures in U.S. facilities comprised 23 percent and those in the rest of Europe and Asia accounted for 20 percent of the total outlays (49).

In comparison with Ciba-Geigy, Hoffmann-La Roche and Sandoz look more toward the United States for developing biotechnology expertise through contracts and R&D subsidiaries. Hoffmann-La Roche, in conducting biotechnology R&D in its research institutes throughout the world (especially New Jersey) and forming partnerships with NBFs in the United States, spent $59 million on biotechnology R&D in 1981 (50). Approximately one-third of Hoffmann-La Roche's biotechnology R&D budget goes to rDNA experiments (48). Similarly, Sandoz pursues biotechnology through a half-million dollar contract with the Wistar Institute (Philadelphia), a contract with NPI (Salt Lake City), a $5 million investment in the Genetics Institute (Boston), and the purchase of Zoecon (Palo Alto), in addition to research conducted in its Austrian institutes. Though only $5 million of the $226 million Sandoz R&D budget has been spent on biotechnology since 1977, biotechnology will account for an increasing share in the future (48). For example, a biotechnology research institute recently established by Sandoz at University College, London, a center of neurobiology and neuro-

● Biogen, S.A., a Swiss company, is one of the four principal operating subsidiaries of Biogen N. V., which is the parent company of the Biogen group and is registered in the Netherlands Antilles. Biogen N.V. is about 80 percent U.S. owned. The other three subsidiaries include: Biogen Research Corp. (a Massachusetts corporation) which conducts R&D under contract with Biogen N.V. and Biogen B.V. (a Dutch corporation) and Biogen, Inc. (a Delaware corporation) both of which perform marketing and licensing operations. Biogen's principal executive offices are located in Geneva, Switzerland. Biogen N.V. is largely U.S. owned.

chemistry, will receive $7.6 million over the next 3 years.

While the established pharmaceutical companies are beginning to explore new applications of biotechnology in the area of pharmaceuticals, the NBF Biogen S.A. is applying biotechnology to several industrial sectors with a diverse R&D program. Biogen was established in 1978, largely at the initiative of venture capitalists from the United States, with funds from International Nickel Co. Biogen currently has three other principal shareholders: Monsanto (U.S.), Schering-Plough (U.S.), and Grand Metropolitan Limited (U.K.). Biogen S.A. has yet to sell any products made from biotechnology, but it was the first firm to obtain expression of hepatitis B surface antigens, leukocyte interferon, and the viral antigen of foot-and-mouth disease from rDNA technology. The diverse background of its scientific board suggests a flexible R&D policy with widespread applications of biotechnology to mining and metals refining, pharmaceuticals, chemicals, energy, agriculture, and food and beverage production (54). In 1982, through $20.5 million generated from contract research (primarily with Schering F.R.G.], Shionogi [Japan], and Fujisawa [Japan]), Biogen S.A. supported an $18.4 million R&D program (48).

GOVERNMENT FUNDING OF BASIC AND APPLIED RESEARCH

Though the Swiss Federal Government has no specific biotechnology policy, its funding for biotechnology-related research is increasing (48). The Swiss National Science Foundation serves as a clearinghouse for Federal funds for the support of basic research related to biotechnology at specific universities and other institutions. Much of the fundamental research in the life sciences, however, is carried out in the largely canton-supported universities (52). Out of Switzerland's total biological and biomedical research budget of about $73 million (SF150 million), about 4 percent or $980,000 (SF2 million) goes to biotechnology.

The major Government source of applied research funds is the Commission for the Encouragement of Scientific Research (Commission zur Forderung der Wissenschaftlichen Forschung). This commission provides grants for applied research projects of proven interest to industry, normally contributing 50 percent of the costs. The Department of Biotechnology (Institut fur Biotechnologie) at the Swiss Federal Institute of Technology at Zurich (ETH-Zurich, Eidgenossische Technische Hochschule) receives strong support from the commission. ETH-Zurich, with an additional complex at Honggerberg, conducts research in the areas of basic biological research, bioprocess engineering, and water and sludge treatment. In addition to funding these activities, the Commission for the Encouragement of Scientific Research itself plays an active role in identifying potential industrial partners and interesting them in particular research projects (53). Given the proprietary nature of much of the work, funding figures are unavailable (52).

TAX INCENTIVES FOR FIRMS

Beause of low corporate tax rates, Switzerland provides a favorable environment for established companies in biotechnology. Though corporations conducting business in Switzerland are subject to both Federal and cantonal taxes, the Swiss effective corporate tax rate is the lowest in Europe (51).

PERSONNEL AVAILABILITY AND TRAINING

The access to distinctive universities and the high standard of living in Switzerland, attract highly qualified persomel from around the world to participate in Swiss biotechnology. Although the availability of personnel may not be important 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.

OTHER FACTORS

Swiss antitrust laws preventing monopolies present no serious problems for R&D joint ventures. In Government-industry joint projects, Swiss law assigns patents to industry, though holders of inventions whose R&D was supported by a Federal grant must repay the Federal contribution from license fees generated by the patent.

Health and safety laws in Switzerland do not generally impose barriers to biotechnology development. Although Switzerland is following a previous, and more restrictive version of the U.S. guidelines for rDNA research, there are no requirements covering large-scale work. The licensing of pharmaceuticals is more streamlined in Switzerland than in other countries. There is no requirement for Government approval before initiation of clinical trials, and the drug approval process generally takes from 6 to 10 months. *

*The Swiss pharmaceutical industry exports roughly 90 percent of its products. Thus, the drug and other product regulations of importing countries cause more concern to these companies than Switzerland's relatively relaxed regulatory framework (s3).

CONCLUSIONS

The factors cited above and a growing commitment to biotechnology by the private sector suggest that biotechnology is advancing in Swiss industries. Both the Federal Government and most companies have been slow to initiate R&D programs in biotechnology, although the Swiss pharmaceutical industry and especially four companies have boosted their activities in these fields. For several reasons, Switzerland has only recently begun to dedicate its collective efforts to biotechnology (53):

- financial experts and bankers have lacked the technical expertise to evaluate high risk technologies;
- manufacturers have been averse to incorporating biotechnology into some Swiss industries because of the high financial risks and uncertainties caused by public and professional concern about the safety of rDNA research;
- Swiss industrial scientists have trailed Swiss and non-Swiss academic scientists in recognizing the widespread potential of biotechnology; and
- Swiss industries are highly oriented toward chemical synthesis and thus have underestimated the commercial implications of new biological processes.

In conclusion, the majority of Swiss biotechnological expertise rests in the large pharmaceutical companies and in Biogen S.A. and a few other small firms. The large companies generally conduct their R&D in foreign subsidiaries or in the form of proprietary research at in-house facilities and make no concerted effort to support domestic basic research outside industry (48). Thus, technology transfer between large Swiss firms and the universities is limited. Nevertheless, given the quality of Swiss educational institutions teaching the knowledge needed for the development of biotechnology, the attraction of foreign talent to Switzerland, and a new Government focus toward biotechnology development, the industrial use of biotechnology by Swiss companies is likely to become more widespread in the near future.

France

INTRODUCTION

France is currently in a less favorable position to compete with the United States than Japan and the other European countries analyzed in this report. The country's research system and industries generally lack a critical mass of qualified personnel in many disciplines important to the development of biotechnology, In addition, attempts by the socialist government to increase R&D expenditures have met with frustration because of an adverse macroeconomic situation in France during the last 2 years, However, the existence of isolated centers of excellence in scientific disciplines such as immunology, molecular biology, and bioprocessing, and of a few companies with bioprocessing expertise and a strong commitment to developing biotechnology, such as Elf Aquitaine and Rhone Poulenc, may help France to compete with other industrialized companies in selected product markets.

INDUSTRY

Three large French companies have R&D programs in biotechnology-Elf Aquitaine (67-percent Government owned), Rhone Poulenc (100-percent Government owned), and Roussel Uclaf (40-percent Government owned and a Hoechst subsidiary). Of these three, Elf Aquitaine has committed the most effort and money to biotechnology. It owns Sanofi, a pharmaceutical company that has the right of first refusal on all development research at Institut Pasteur Production (the scale-up branch of the Institut Pasteur), and has established Elf Bioindustries and Elf Bioresearch to develop biotechnology in the foodstuff and agricultural sectors. Medium-sized French companies, especially in the foodstuff sector, spend very little in overall R&D (about 0.1 to 0.2 percent of revenues) and have hesitated to devote their energies to biotechnology (62). Furthermore, France has only a few NBFs (e.g., Genetica, Transgene, Hybridolab, and Immunotech), and most of them are subsidiaries of large companies or commercializing arms of research institutes. Thus, the ability of large companies to commercialize biotechnology products will determine France's competitiveness in certain product markets.

GOVERNMENT TARGETING POLICIES

Official interest in the commercialization of biotechnology in France emerged only recently, with the appearance of the Pelissolo report in December 1980 (59). Since the election of the socialists, the French Government has resolved to push the development of several new technologies in its national industries and has accorded a privileged position to biotechnology within this scheme.

The French socialist government has established the most highly coordinated policy for the development of biotechnology of any of the six major competitor countries identified in this assessment. This policy rests on two cornerstones:

- a *general* research law (Loi de Programmation et d'Orientation) adopted by the French National Assembly in the first week of July 1982, and

- a program specifically for biotechnology ("Programmed Mobilisateur: L'Essor des Biotechnologies") presented toward the end of the same month (58).

The general research law sets two objectives: l)to stimulate French effort in new technologies by "guaranteeing" real increases in the overall civilian R&D budget of 17.8 percent per year, economic conditions permitting, and setting up seven technological "programmed," including one for biotechnology, on which a major portion of research funds are now to be directed; and 2) to open up French science to industry and education by encouraging scientists in research institutes to work in collaboration with private sector colleagues and to teach in universities (65). The Programme Mobilisateur, presented in July 1982 by the Biotechnology Mission of the newly organized Ministry of Research and Industry (now the Ministry of Industry and Research), outlines in detail the steps the Government should take to strengthen French biotechnology. This document calls for intervention from Paris through a myriad of organizations and committees in all aspects of research, education, technology transfer, and industrial development.

Both the research law and the Programme Mobilisateur demonstrate the French Government's determination to promote the necessary multidisciplinary approach to the various technologies and to establish vertical chains (filires) that incorporate all the relevant expertise in basic research, generic applied research, and large-scale production necessary to bring a product to market (60). The effectiveness of the French policy, however, will depend in part on the extent of voluntary cooperation among the various Government groups implementing the policy and the sectors the plans affect (i.e., public research centers, universities, and private industry).

GOVERNMENT FUNDING OF BASIC AND APPLIED RESEARCH

Most basic research in France is conducted in public research centers ("grands organisms"), similar in principle to the British Research Councils, or in a few university laboratories associated with these centers. * One of the three major "grands organisms," the National Center for Scientific Research (CNRS, Centre National de le Recherche Scientifique), conducts basic research related to biotechnology in three different divisions, and some of the projects CNRS sponsors overlap with similar work both at the center itself and at other centers and universities (62).

Little public sector generic applied research takes place in France. There are no national applied research laboratories, and with the exception of isolated programs at the universities at Compiegne (enzymology and bioprocess engineering) and Toulouse (biotechnology), the Government of France supports almost no generic applied research of benefit to its domestic industries.

Until recently, Government funding of both public and industrial R&D counted as a French strength. Although it should be noted that definitions of biotechnology differ from one organization to the next, funding estimates vary according to referred sources, and many research projects receiving biotechnology money have nothing to do with biotechnology (62), the French Government probably spent between $35 million and $60 million on biotechnology R&D in 1982. * Notwithstanding the Government strong initial effort to fund biotechnology, increases planned for 1983 were effectively reduced. The National Assembly reduced the scheduled 17.8-percent real increase in the 1983 civil research budget to about 10 percent (66), and the reduction for researchers in biotechnology related fields was even greater. CNRS saw its original 1983 budget cut by 12.5 percent, and the Programme Mobilisateur research has lost a quarter of its allocation. These austerity measures allow research funding to keep pace with inflation, but little more. In spite of the reductions, the overall research budget still represents a 7.5-percent real increase over 1980 levels, and the Ministry of Industry and Research continues to support its policy of increasing allocations for science (56).

FINANCING AND TAX INCENTIVES FOR FIRMS

A new law enacted in February 1983 created a legal structure allowing the formation and investment of venture capital (67), but the venture capital market in France is poorly developed. Banks are the major source of financing in France, and have always hesitated to take major equity positions in industry. The financing that French banks provide, however, is designed for long-term projects, thus eliminating the problem, encountered by companies in the United States, of finding sources for second- and third-round financing.

With the exception of one provision, tax law in France generally conforms to European and American standards. A generous depreciation allowance in the tax code permits a company in France to write off So

*For a more detailed description of the research infrastructure in France, see R. Walgate, "Great Schools, Great Contradictions" (63) and "CNRS—The Core of Research (64).

*This estimate is based on a 3-year (1983-85) projected total of $175 million, with a guaranteed (by law) 17.8-percent annual increase in the civil research budget, plus increased support for industry through existing schemes.

percent of its expenditures on R&D capital assets during the first year following the acquisition of these assets.

PERSONNEL AVAILABILITY AND TRAINING

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 (55). 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 (62), these are isolated clusters of expertise and 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 called for the active involvement in the educational process of public sector researchers outside universities (65), 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 (58). 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 (58).

UNIVERSITY/INDUSTRY RELATIONSHIPS AND DOMESTIC TECHNOLOGY TRANSFER

Universities in France have had very few ties with industry in biotechnology. Large firms in France actively seek out developments in basic research, either by locating plants near research centers or through an office that monitors current developments in biotechnology research in France and other countries.

The French Government encourages domestic technology transfer through the National Agency for the Evaluation of Research (ANVAR, L'Agence National de la Valorisation de la Recherche). ANVAR, which has no right of first refusal on the results of research in public laboratories, acts as a catalyst for the direct interaction between these institutes and private firms (e.g., through publications on the status of innovation with applications in different industrial sectors). *

OTHER FACTORS

The French legal and regulatory environment, with one exception, poses no real barriers to the commercial development of biotechnology. France maintains the most rigid investment control laws in Europe (61). These regulations allow the French Government to prevent strategic companies from being acquired by foreign concerns and may well hinder foreign firms' ability to penetrate French markets.

Health and safety regulations, as well as patent and antitrust laws in France, however, are approximately equivalent to those in other European countries.

CONCLUSIONS

At present, France lags somewhat behind the United States, Japan, the Federal Republic of Germany, the United Kingdom, and Switzerland in the commercial development of biotechnology. If the country can solve its personnel problems, however, French industries could well gain a competitive footing in selected product markets. The Government's well-coordinated formal policy and adequate but precarious funding program represent a strong commitment to the development of biotechnology that needs to be completed with the necessary qualified personnel. Although the French private sector until rather recently has hesitated to develop its biotechnology capabilities, large companies do have the money and the means of uncovering the latest technological developments. Therefore, the ability of both the public and private sector to recruit and train scientists and technicians and the maintenance of sufficient Government allocations for R&D in the face of adverse macroeconomic conditions may ultimately determine the competitiveness of French biotechnology in the international marketplace.

Sweden

Sweden is a technologically progressive country, but adverse public opinion toward rDNA technology has resulted in the imposition of Government restrictions on the use of rDNA in research and industry. Furthermore, a lack of trained personnel in basic sciences has restrained the commercialization of biotechnology.

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*For a general review of ANVAR'S functions and activities, see "Commentary on the National Agency for the Evaluation of Research," *Le Monde* (57).

Swedish public opinion and Government policies may be changing to encourage biotechnology in Sweden. If this proves to be the case, Sweden may market products in areas such as the following:

- *Support sector.* Swedish scientific instrumentation, filtration, and industrial separation systems are used around the world and are important in the commercialization of biotechnology.
- *Bioprocess engineering.* A large portion of Sweden's combined public and private sector R&D efforts is devoted to heterogeneous bioprocessing systems, stabilization of immobilized cell systems, membrane technology, and downstream purification and regeneration (76).
- *Pharmaceutical industry.* Swedish pharmaceutical companies maintain aggressive export policies and are active in innovation. The five largest Swedish companies have a gross annual income of about $1 billion, with 70 percent derived from exports (76). It is not known to what extent Swedish pharmaceutical companies will use biotechnology, given Sweden's shortage of trained personnel in rDNA technology and other areas. In the near term, most Swedish companies will probably rely on licensing arrangements with NBFs in the United States to gain access to biotechnology (76).

Among the Swedish companies that appear to have the potential to use biotechnology for producing goods and services are Pharmacia AB, KabiGen/KabiVitrum, and Alfa-Laval.

Pharmacia AB concentrates on pharmaceuticals, separation products, diagnostics, and cosmetic products, and derives 90 percent of its revenues from exports; the U.S. subsidiary, Pharmacia, accounts for 25 percent of these sales. With demonstrated abilities to serve specialty markets, this company is a leader in separation science and is working to establish rDNA capabilities.

KabiGen/KabiVitrum, operated by the Swedish Government, is currently the world's largest supplier of pituitary derived human growth hormone (hGH). In order to protect its hGH market from foreign competition, Kabi has entered into a licensing arrangement with Genentech (U. S.) to market rDNA-produced hGH outside of the United States. KabiGen is also moving to establish its own rDNA capabilities, intending to pursue projects on human insulin, methanol production, bacterial metal enrichment from ores, interferon, and anticoagulant pharmaceuticals (71,72). Furthermore, Kabi is involved with the development of support equipment, including a polynucleotide synthesizer (69).

Alfa-Laval has large-scale fermentation capabilities and is currently working to establish rDNA capabilities through its subsidiary AC Biotechnics, in which it shares ownership with Cardo Co. Biotechnics has a budget of $8 million to $10 million for an unspecified length of time to produce specialty chemicals and ethanol using rDNA technology.

Other Swedish companies interested in biotechnology include Sorigona AB, which produces chemicals and foods; Astra, which is working in collaboration with U.S. researchers to develop long-acting anesthetics (74); and approximately a dozen additional firms.

Funding for high technology in Sweden is available from several Government sources. Since each department of the Swedish Government establishes its own R&D budget, however, overall R&D funding estimates are difficult to obtain. Some degree of R&D coordination is maintained by the National Swedish Industrial Board (Statens Industri Verk), which is responsible for promoting technological development, organizing training, and orchestrating Government actions, and the National Swedish Board for Technical Development (STU, Styrelsen for Teknisk Utveckling). STU, which is the main source of Government funds for biotechnology, granted an estimated $4 million for biotechnology in 1982, and Swedish industry probably spent an additional $15 million (72).

The manner in which STU distributes R&D funds reflects a Swedish Government policy of directly promoting strategic industries. STU works through joint Government/private ventures with foundations established by Swedish and foreign companies interested in a particular field of development. STU provides half the R&D funding as provisional grants and the foundation provides the other half. If the venture is successful, the funding is treated as an interest-free loan; otherwise, it is considered a grant. Research grants/loans are limited to $100,000, and those for product development to $600,000. In 1973, 20 Swedish, 2 Danish, 2 Finnish, and 1 Norwegian company established a specific foundation to promote biotechnology called the Biotechnology Research Foundation (SBF, Stiftelsen Bioteknisk Forskning) (72). SBF, in conjunction with STU, is currently conducting research on heterogeneous bioprocessing systems, immobilized cell systems, membrane biotechnology, and regeneration of coenzymes (76).

Private industry R&D in Sweden is encouraged by corporate tax incentives, which include a 10-percent deduction for R&D and a 20-percent deduction for any increase in R&D from the previous year.

Sweden's Central Investment Bank and commercial banks provide risk capital in promising technological areas. Information about the banks' views toward new biotechnology is not available, but in 1982, $300 million for all R&D loans in Sweden were tendered. Capital for risk ventures from other sources is limited

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in Sweden, and the larger Swedish companies, such as Fortia, rely primarily on internal funds and Biotechnology Research Foundation loans (73).

The Swedish Government has encouraged high-technology, export-directed growth for many years and has promoted relations among the Government, industry, and the universities. Seven Swedish universities have liaison officers with industry whose salaries are paid by STU. A 6-year, $7 million agreement has been established between the University of Uppsala, the University of Agriculture, the Swedish Veterinary Institute, and Fortia AB, that is intended to develop expertise in rDNA technology and to create the (most intensive programme of biotechnology in the "world" (68).

Although extensive interaction between the sectors is encouraged and funded, Swedish efforts to commercialize biotechnology suffer most from a shortage of certain types of trained personnel. Estimates of the number of Swedes working in biotechnology vary from 30 to 40 people (72) to as many as 200 workers at Uppsala alone (68), but shortages of personnel in key areas such as rDNA technology hamper wider commercial applications (75).

Personnel training for biotechnology has been largely inhibited by negative Swedish public attitudes toward rDNA experimentation. As a result of the restrictive rDNA guidelines, which required the Swedish National Recombinant DNA Advisory Committee's permission to conduct any rDNA research, there was little need for trained personnel, and Sweden's private sector relied on foreign companies for developing products requiring rDNA processes (70). In a joint project between KabiVitrum and Genentech (U. S.) to develop and produce hGH, for example, the first actual cloning of the hGH gene was performed in the United States by Genentech. Since the relaxation of the guidelines, however, the need for qualified engineers and scientists has increased, and some Swedish universities have instituted training programs in biotechnology.

The Swedish Government's identification of biotechnology as an industrially strategic area, as exemplified by the establishment of joint programs with SBF and other promotional activities for research, indicates that Swedish views may be changing. With Sweden's demonstrated ability to successfully exploit new technologies, Swedish companies may prove to be competitive in the future in the support and bioprocess sectors, as well as in pharmaceutical markets.

Netherlands *

The Dutch Innovation Programme on Biotechnology, started in May 1981, is aimed at filling the gap between basic research and applied development work in Dutch universities. Funds supplied by the Government of the Netherlands will be used to develop research in areas where current national effort is insufficient. The program will be coordinated by the Dutch Programme Committee on Biotechnology. The program will last until the end of the 1980's, after which the existing research budgets of universities and institutes will furnish Dutch industry with the needed basic research.

The Programme Committee on Biotechnology (Programma Commissie Biotechnologie) requested $11.2 million (NLG30 million) to be spent on basic biotechnology research from 1983 until 1988. This amount is in addition to the $11.2 million to $15 million (NLG30 million to NLG40 million) which the Government spends yearly on research projects in the fields of molecular and classical genetics, microbiology, cell biology, biochemistry, enzymology, and bioprocess and bioreactor engineering.

In addition to the aforementioned sums, $2,6 million (NLG7 million) will be used by university/institute and industry groups in the Netherlands for multidisciplinary biotechnological research projects. According to the Programme Committee, these projects should be in the following areas:

- host vector systems for industrial and agricultural applications,
- somatic cell hybridization,
- second generation of biotechnological reactors and processes, and
- downstream processing.

Established Dutch companies that are setting up inhouse R&D efforts in biotechnology include the following:

- Gist-Brocades N.V.
- Akzo-Pharma N.V.
- Unilever H.V.
- N.V. DSM
- Heineken N.V.
- Dupher N.V.

* This summary is based on a personal communication with Dr. Ir. R. R. Van der Meer, Secretary-Coordinator, Programme Committee on Biotechnology, Gravenhague, April 1983 (78).

Gist-Brocades N. V., one of the two companies in the world that supply more than 60 percent of the world's enzymes for industrial use, is devoting almost all of its $20.6 million (NLG55 million) budget for R&D to biotechnology. Intervet International, a subsidiary of Akzo-Pharma, was the first company to market vaccines produced through rDNA technology, Intervet's vaccines, introduced in March 1982, prevent scours (infectious diarrhea) in calves and piglets (77).

The Programme Committee on Biotechnology forecasts no personnel shortages. In fact, there is an excess of biochemical and microbiology students for the available Dutch jobs in industry. There are no tax policies aimed at encouraging biotechnology in Dutch industries. The Dutch have eased their regulatory guidelines for working with rDNA technologies to conform to U.S. guidelines.

Australia *

The Australian Government supports a highly respected basic research system, especially in plant breeding and molecular biology, but it regards the development of biotechnological applications, including scale-up development and bioprocess engineering, as the responsibility of the private sector. Owing to a historic dearth of capital for high-risk ventures and a lack of trained personnel in applied technology, commercial biotechnology in Australia is not well developed. Australia's problems are exacerbated by the emigration of some of its top scientists to other countries where attractive jobs exist, although there is some indication that this situation might change in the future. The Australian Government is taking steps to implement incentives to help retain scientists and encourage venture capital formation to help foster promising applications of biotechnology.

Australian efforts are not expected to have an immediate impact on the markets discussed in this report. Nevertheless there is a strong possibility that, by using biotechnology to help solve local problems, Australia will find new markets for biotechnology products. Areas of biotechnology application in Australia being pursued include the following:

- plant improvement programs to develop agricultural species that are adapted for higher yields in Australian conditions;
- animal health products, particularly veterinary and nutritional products that improve the marketability of Australia's animals and animal products (especially wool) for export;*
- microbiological mineral recovery to reduce extraction and separation costs for certain minerals that Australia exports in great quantities;
- biomass conversion to ethanol and chemicals, based on Australia's large resources of grain crops and sugar cane residues.

Other applications of biotechnology in Australia include animal breed improvements through embryonic gene transfer, MAb-based diagnostic reagents for a number of human diseases, and, on a small scale, interferon and other rDNA projects to develop pharmaceutical products.

Government funding for biotechnology in Australia is administered through several Government agencies, including the Australian Science and Technology Council, which emphasizes expanded manufacturing and agricultural production with biotechnology, and the Commonwealth Scientific and Industrial Research Organization (CSIRO), the main research agency in Australia, which provided $4.6 million ($A4.5 million) for biotechnology research in 1981. Other sources are the National Health and Medical Research Council, which distributed $19.0 million ($A18.7 million) in research funds in 1980/81 (some of which benefited Australian biotechnology); the Energy Research, Development, and Demonstration Program which distributed $3.9 million ($A3.8 million) in 1980/81, partly for biotechnology project development; the Department of Health, which gave $1.88 million ($A1.85 million) to the Commonwealth Serum Laboratories to conduct research on interferon from 1980/81 to 1983/84; and the Australian Research Grants Scheme, which awarded $18.3 million ($A18 million) in 1982 to individual research scientists, some of whom use biotechnology in their work. In addition, financial assistance for general industry R&D projects is provided under the Australian Industrial Research and Development Incentives Scheme which in 1980/81, distributed $9.8 million ($A9.7 million) in commencement grants and $36.6 million (A$36.1 million) in project grants.

Other Australian incentives include tax policies that give minor benefits to firms undertaking R&D activities. Buildings used solely for scientific research purposes are depreciable over a 3-year period, compared to general industry's 40-year depreciation schedule. New equipment used for scientific research is also depreciable over a 3-year period, as opposed to a 5-year period for general industry equipment.

* This summary is based on information presented in "Biotechnology Research and Development, the Application of Recombinant DNA Techniques in Research and Opportunities for Biotechnology in Australia" (79) and "Genetic Engineering--Commercial Opportunities in Australia" (80).

* To date, most rDNA efforts have centered on cloning the genes that encode sheep wool keratin and other wool constituents in an effort to improve wool quality and lessen treatment costs of wool.

In addition to basic research funding and tax incentives to businesses, liaisons between Australian universities and industry are encouraged. In some cases, academic researchers have financial equity in biotechnology firms. In other cases, the relationship is through contracts with the universities. One example is an agreement under which Agrigenetics Research Association, Ltd. provided $2 million for biotechnology research at Australian National University. * Although Australia has the infrastructure to support healthy biotechnology development, lack of capital for high-technology firms retards growth. The Government and Australian banks make loans available to small businesses at low interest rates, but these loans are not generally available to high-risk enterprises such as NBFs. High-risk ventures are hampered by a smaller capital base in Australia than in the six major competitor countries. With increased Government interest in commercial biotechnology, more capital may become available. This increase in capital might in turn encourage increased efforts by existing NBFs to find applications for new biotechnology, as well as the formation of more NBFs. It should be noted, however, that Australia has some of the most restrictive drug licensing laws in the world, and these regulations may impede Australian applications of biotechnology to the pharmaceutical industry.

Biotechnology companies in Australia include the following:

- Biotechnology Australia Pty., Ltd. (a subsidiary of CRA Ltd.). Projects include animal feed additives and health care products, specialty chemicals, biomass conversion, and mineral extraction schemes.
- Austgen Pty., Ltd. (includes Biojet International [Australia] Pty. Ltd.). projects include nutritional additives and waste treatment systems. Much of Biojet International's R&D is oriented towards products that can be exported.
- Australian Genetic Engineering Pty., Ltd. Projects focus on MAbs for diagnosis (a $5 million per year market for MAbs for diagnosis currently exists in Australia; a $15 million market is expected by 1986).
- Bioclone Australia Pty., Ltd. This firm markets MAbs made by the Garvan Institute and CSIRO on a worldwide basis. Its best known product is an antiprolactin MAb. Eleven additional MAb products have been or will soon be marketed.
- Australian Monoclinal Development Pty., Ltd. This company supplies MAbs primarily for research purposes.
- Fielder Gillespie, Ltd. This milling company funds MAb and biomass conversion projects.

In conclusion, Australia has the potential to develop and commercialize several applications of biotechnology successfully. A good Australian research base exists, but increased infusions of capital are necessary for new commercial startups if the potentials of biotechnology in Australia are to be realized. Australian Government policies have targeted the development of biotechnology, but the effect of the policies remains to be seen. Some Australian products, such as MAb diagnostic products, may prove to be competitive in world markets, but overall, major competition in the pharmaceutical and specialty chemical industries is unlikely.

Israel

For several reasons, Israel may be unique among developed nations in fostering a strong basic and applied research capability in biotechnology without having a large industrial infrastructure to exploit the successes of research endeavors. Israeli scientists train in U.S. institutions prominent in biotechnology and have become well-versed in molecular biology and immunology. Except for small brewery plants and one bioprocess plant (Gadot, which manufactures about 7,000 tons of citric acid per year), however, Israel does not have companies using old biotechnological techniques. Furthermore, Israel's tax and financial structures do not encourage financial risk-taking or the formation of new firms. Therefore, there are few industrial positions available for scientists trained in biotechnology.

As a result of the lack of depth in industrial expertise in Israel, Israeli universities, through their University-Connected Research and Development Organizations (UCRDOs),* turn to foreign companies that have the expertise to evaluate Israeli research and the resources needed to commercialize the results of this research. The number of joint ventures between Israeli UCRDOS and foreign firms is fairly large.

Noteworthy basic research in biotechnology is taking place at several Israeli universities and institutes, among them Hebrew University, Technion Institute at the Israel Institute of Technology, the Center for Biotechnology at Tel-Aviv University, and the Weizmann Institute of Science.

At Hebrew University, 12 departments in the medical school are conducting biotechnology-related research projects, ranging from cellular biology to can-

*The goal of this research is to incorporate the nitrogen-fixing genes of bacteria into plants adapted to Australian conditions.

* UCRDOS are set up by Israeli universities to promote commercialization and applied research. These organizations may enter into joint ventures or own equity in spinoff firms.

cer research. The agriculture department has initiated several projects and has received over $410,000 (more than DM1 million) from the Minerva Fund in the Federal Republic of Germany for cooperative projects on improving plant tissue culture techniques, rDNA and protoplasm fusion in plant breeding, nitrogen fixation and control of soil-borne plant pathogens by microorganisms, and new uses of algae *(84).* Hebrew University's UCRDO Yissum signed a $5 million agreement on nitrogen-fixation research with Biotechnology General (Israel), Ltd. (82), an Israeli NBF, and another $3 million agreement has been signed with International Genetic Sciences Partnership (U. S.) (85),

Technion Institute, at the Israel Institute of Technology, is doing research on biotechnology instrumentation and on blood and blood plasma substitutes (82). Tel-Aviv University, Center for Biotechnology, conducts research on MAbs, enzyme systems of anaerobic bacteria, and immobilized enzymes (82).

The Weizmann Institute of Science is Israel's main center for rDNA research and is especially noted for its work with interferon. Additionally, research is proceeding with MAbs, antiviral vaccines, synthetic antigens, and new genetic forms of wheat, within seven departments.

Applied research using new biotechnology began in Israel in 1978. As of 1981, 17 universities, institutes, and venture firms in Israel had been identified as performing or funding applied research in biotechnology. Of the 17, perhaps 10 use the new technologies in their work (87). The four universities and institutes cited above, in addition to conducting basic research, also do applied work.

Israeli companies noted for their applied R&D include Biotechnology General, Interpharm, Inter-Yeda, Kibbutz Beit Ha'Emek. Biotechnology General develops research findings from the Weizmann Institute and Hebrew University. Its main emphasis is on foot-and-mouth disease vaccine, bovine growth hormone, biological disease control agents, and nitrogen fixation (82).

Interpharm, a subsidiary of Applied Research Systems (ARES), a Dutch multinational firm based in Geneva, sold over 1.15 million shares of common stock on the United States over-the-counter market in 1981. At the time of offering, Interpharm had a contract to supply ARES with hGH. Further, Interpharm may soon market human fibroblast interferon for labial and genital herpes, depending on results of clinical trials, produced by its R&D susidiary Inter-Yeda (83). Other projects with commercial possibilities include an immunoassay separation technology, extraction technologies for follicle-stimulating hormone and luteinizing hormone, and research on hybridomas (81).

Inter-Yeda, a joint venture firm owned 60 percent by Interpharm and 40 percent by Yeda, will concentrate on four areas: production of interferon using rDNA techniques, identification and isolation of interferon-associated proteins, artificial production of interferon, and MAb research (82). Inter-Yeda is shipping human fibroblast interferon to the Serono Corporation in the United States (81).

Kibbutz Beit Ha'Emek hired researchers in order to use advanced tissue culture techniques to "develop plant varieties resistant to herbicides, diseases and other environmental hazards" (86). The kibbutz claims a $1 million income from "tissue-cuhurederived products," of which 65 percent are exported, mainly to the Netherlands and the Federal Republic of Germany.

At present, there is no central planning of any R&D by the Israeli Government, and thus the Government has no national targeting policy for biotechnology. Each Ministry within the Israeli Government determines and funds the R&D it deems necessary. The major source of Government funds for biotechnology R&D is the Office of the Chief Scientist in the Ministry of Industry and Trade. The Israeli Ministry of Industry and Trade plans to invest $25 million in biotechnology R&D over the next 5 years (85).

Canada

Canada's economy relies greatly on its natural resources such as agriculture, livestock, mining, and forestry. In the past 3 years, Canada's Federal and Provincial governments, as well as a few Canadian companies, have worked to incorporate biotechnology specifically as it relates to the development and exploitation of the country's natural resources. A focus on improving domestic capabilities in the necessary technologies and avoiding dependence on imported products and processes, however, represents an attempt by both the public and private sectors in Canada to compete in selected world markets. Whether Canada becomes internationally competitive in areas of biotechnology such as agricultural plant strain development, mineral leaching, or lignocellulose conversion, for example, will depend to a large extent on the rapidity with which it can exploit national expertise before other countries with extensive R&D programs in these fields.

Interest in the commercial development of biotechnology has evolved slowly in Canada. In June 1980, the Canadian Federal Government commissioned a Task Force on Biotechnology to evaluate the opportunities available to Canada in this area. This task force, in its report to the Minister of State for Science and Technology, identified specific weaknesses in

Canada's research base, Federal Government programs, regulations, and industry, and made specific recommendations to help correct these deficiencies (96). The Canadian Federal Government took more than 2 years to act on these recommendations, In early May 1983, it announced two separate yet complementary initiatives to help promote biotechnology in Canada,

First, as part of a broader plan to support the development of emerging technologies in general, the Ministry of State for Science and Technology designated biotechnology as one of the priority technologies targeted for development (94). The plan to support emerging technologies consisted of five basic components. The first was identification of strategic areas of development most important to Canada. Adopting the recommendations of the Task Force on Biotechnology, the Federal Government will concentrate efforts on research in nitrogen fixation, plant strain development, cellulose utilization, mineral leaching and metal recovery, and animal and human health care products. The second component was creation of research networks. Individual Federal departments will establish and promote networks of research projects in biotechnology and researchers in areas relevant to their mandates. The third component of the plan was establishment of a cost-sharing program. Under the program, and with $7.7 million per year, the Federal Government will match funds invested by industry in universities or Provincial research organizations. The funds could be used for purposes such as specific biotechnology research projects, the replacement of equipment, and the establishment of research chairs. The fourth component of the plan was strengthening of overall Federal research capacity in biological sciences ($3.1 million). The funds will be used to establish and promote networks, to promote interactions between Federal departments and universities and industry, and to strengthen existing programs within Government research organizations. Finally, the fifth component of the plan was the creation of advisory and coordinating committees. A National Biotechnology Advisory Committee, chaired by a member from the private sector with 25 representatives from industry, academia, and Federal Government departments, will monitor the course of the biotechnology policy and advise the Minister of State for Science and Technology on the program's progress. An Interdepartmental Committee on Biotechnology, which functions at the Deputy Ministry level, will control the allocation of funds to departments participating in the Federal plan and will deal with a wide range of issues such as patenting and regulation in biotechnology (92).

Parallel to and coordinated with the five-pronged program outlined above, the Ministry of State for Science and Technology has charged the National Research Council (NRC)* with responsibility for the promotion of centers of expertise in biotechnology. Under this program, NRC will undertake three separate projects:

- construction in Montreal of a $61 million biotech. nology institute which will probably conduct generic applied research on bioprocessing and enzyme technology (95);
- refurbishment and reorientation of the Prairie Regional Laboratory in Saskatoon (95); and
- strengthening of the NRC Biological Sciences Division in Ottawa.

In addition to the Canadian Federal Government, many Canadian Provinces have begun to promote the development of biotechnology. Quebec, Ontario, Saskatchewan, Alberta, and British Columbia have shown an increasing interest in the commercial opportunities offered by biotechnology. Quebec, for example, has developed an explicit policy which gives high priority to biotechnology. Saskatchewan is also in the process of developing such a policy. Quebec and Ontario have invested in commercial ventures in biotechnology (Bio-Endo and Allelix, respectively).

Several problems may limit the commercial development of biotechnology in Canada. First, there is a generalized shortage of personnel trained in the relevant technologies (only 200 to 300 Ph. D. s), and many of those who do graduate with degrees, for example, in molecular biology or biochemical engineering are lured to the United States to work in the private sector (97). Furthermore, very few private firms have directed their efforts to developing an expertise in new biotechnology; most rely instead on more traditional techniques in research, development, and production. **Canada also has very little experience in joint university, industry, and Government cooperation (93), though current Federal initiatives are addressing this problem.

*NRC is an independent Crown Corp. with considerable influence on Federal science and technology policy. Though not a Government Department, the Council is funded primarily by the Federal Government. Because of the scientific expertise NRC possesses, it will administer $120 million for the technology support program (of which biotechnology forms a part). NRC currently employs a total of over 600 persons (including support staff) in biotechnology alone when their program is in full operation.

**Allelix Corp. appears to be one of the few companies devoted entirely to developing new biotechnology. Started by the Provincial Government of Ontario, the Canadian Development Corporation, and John Labatt Ltd. with a total initial capitalization of $105 million (89), this company is currently concentrating on the development of new plant strains, using both cell-fusion and rDNA techniques (88). For further information on private sector activities in biotechnology in Canada, see "Biotechnology Research and Development in Canada" (90).

The current Canadian patent law requires compulsory licensing of all human therapeutic drugs developed by one company to other general generic pharmaceutical companies (92). As a result of the implementation of this law in 1969, all multinational pharmaceutical companies in Canada closed their research operations (91). There is no equivalent in Canada to the U.S. Plant Variety Protection Act, even though certain mechanisms do exist in Canada to protect the ownership of new plant strains (88).

Canadian tax law favors the development of biotechnology. One provision allows for a 100-percent, first year deduction on all current and capital expenditures for R&D. Additionally, corporations in Canada may deduct a further 50 percent for incremental R&D expenditures (calculated from a moving 3-year average). R&D expenditures are also eligible for a 10 percent investment tax credit (small businesses and investments in some provinces receive a higher percentage rate) up to a limit of $12,200 ($C 15,000). R&D limited partnerships are also permitted in Canada (94).

U.S.S.R.

It is extremely difficult to obtain information on development plans for biotechnology in the U.S.S.R. Although it is known that biotechnology R&D is carried out in the Soviet Union, information about the extent of these activities is unavailable to the general public. The following summary formed part of the report on competitive and technology transfer aspects of biotechnology by a working group for the White House Office of Science and Technology Policy (98):

> The Soviet Union is actively supporting biotechnology R&D and has established an Interagency Technical Council to organize and stimulate its progress across a broad spectrum of disciplines, There is no information regarding the budget for biotechnology R&D. However, the rate of growth of the Soviet research establishment mirrors that which occurred in the United States 3 to 5 years ago. Their stated interests are directed toward domestic concerns such as the development of medical/pharmaceutical preparations and agricultural applications. Soviet establishment of U.S. patents covering an amino acid producing organism and the enabling technology suggests an interest in international commercial competition as well.
>
> Although Soviet research is often hampered by difficulties in obtaining equipment and reagents, the Soviet system offers one major advantage over the free enterprise system of the United States; i.e., R&D is supported from inception through production and distribution, The financing gap between completion of basic research which has potential for application, and actual development, the costs of which in the United States must be borne by industry, receives full support of the Government in the Soviet Union. The advantages of this system are:
>
> - risks are taken by the Government;
> - costs of development are borne by the Government;
> - the Government's financial base can support an extended period of development; and
> - the Government can support long-term price control to facilitate international market entry.

It is too early to project potential Soviet success in the international biotechnology market. Much depends on successful completion of research programs now underway, and, most importantly, continued support by the Soviet Government.

Brazil *

Brazil is the only developing country that has a formal government policy for biotechnology. This policy was developed because relations among the university, industry, and government sectors in Brazil tend to be adversarial, inhibiting communication among the sectors, Brazilian industry tends not to fund risky projects, concentrating its efforts instead on already existing products and processes. Historically, Brazilian industry has relied on the purchase of foreign technology and on joint ventures with foreign companies. Brazil's universities have little contact with either industry or the Government and conduct little multidisciplinary research. These historical relationships suggest that the government (both Federal and State) will have to play a strong role in Brazil to develop the R&D infrastructure necessary to develop biotechnology and to aid the commercialization of biotechnological applications.

In general, the major weaknesses for biotechnology development in Brazil are as follows:

- Brazil's human resource base trained in advanced biotechnology techniques is limited. In 1982, six qualified and experienced researchers in the field of rDNA and MAbs were identified.
- Brazil's national industrial sector is fairly underdeveloped and has little in-house R&D capability and little inclination to pursue high-risk, new product operation.
- There is uncertainty about the interpretation of Brazilian patent statutes with respect to biotechnological products and processes.
- Import and bureaucratic delays make it difficult for both public and private laboratories to obtain the necessary R&D equipment and supplies not available on the Brazilian market.

* This summary is based on "An Analysis of Current and Projected Biotechnological Activity in Brazil," a contract report prepared for the Office of Technology Assessment, U.S. Congress, by Robert Goodrich, July 21, 1982

- Adequate analyses of market needs and opportunities are lacking, leading to inadequate orientation of research activities.

Three major Federal agencies in Brazil are involved in the funding of biotechnology: 1) the National Research Council, now known as the Council for the Development of Science and Technology (CNPq, Conselho Nacional de Desenvolvimento Ciendfico e Tecnolojico); 2) the National Funding Agency for Studies and Projects (FINEP, Financiadora de Projetos); and 3) the Secretariat of Industrial Technology of the Ministry of Industry and Commerce. CNPq will devote about 5 percent of its annual budget to biotechnology or $1.12 million (BCr200 million) during 1982-83. FINEP will spend approximately $1.5 million to $2 million (BCr270 million to BCr360 million) during 2 years to aid the commercializing of R&D in biotechnology by supporting economic analyses, commercialization ventures, and marketing studies. The Secretariat of Industrial Technology of the Ministry of Industry and Commerce is responsible for the National Alcohol Program and is already funding extensive R&Din bioprocesses and enzymology.

The Brazilian Federal Government plans to fund the development of two biotechnology research centers. The first, in Sao Paulo, will be an educational facility for multidisciplinary training. Its research program will focus on bioprocesses and enzyme research. The second center, the Biotechnology Center in Porto Alegre, will receive $0.97 million (BCr175 million) in funding and will concentrate on microbiology and applied genetics with little or no concern for product development. It will have an initial staff of four Ph. D. and four M.S. researchers and trainees.

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