Appendix B
Comparative Analysis: Japan

Introduction

This appendix, which accompanies appendix A, is a summary of information regarding biotechnology in Japan that is found in chapters 2 through 12 of this report.

The commercialization of biotechnology in Japan, as in the United States, has matured and developed over abroad range of industries. In 1984, the Office of Technology Assessment (OTA) identified Japan as the major potential competitor to the United States in biotechnology commercialization. In the view of some, Japan continues to be the United States' main competitor in the early 1990s. Others, however, assert that Japan, in the immediate past and for the near term is not a threat. However, the diffusion of biotechnology into several industrial sectors, the changing financial markets, the emergence of the European Community (EC) as a single economic and political force, and the increasing internationalization of business (e.g., communications, strategic alliances, and technology transfers) blur geographical lines and make simple comparison of the competitiveness of various countries more difficult than in the past (see table B-l).

In Japan, industry dominates biotechnology research and development (R&D). Industrial researchers working in the field of natural sciences outnumber their government and university counterparts nearly two to one, and the majority of biotechnology research facilities are corporate-led. In addition, government strategies for advancement of biotechnology in Japan consistently target commercial development. Most government funding for R&D is channeled toward applied research, and government-led initiatives invariably enjoy wide industry participation.

These circumstances contrast sharply with the United States, where government and academia represent the driving forces behind advancement in biotechnology, and basic research claims a larger share of public R&D funds. Additionally, U.S. Government policy tends not to provide direct industry leadership.

Table B-l-Strengths and Weaknesses, Biotechnology in Japan

Strengths
Fermentation and bioprocess industry.
Strong domestic market for pharmaceuticals.
Strong applied research base.
Strong government support.
Weaknesses
Insufficient basic research science base.
Lack of innovative basic research personnel.
Lack of venture capital.
Rivalry between ministries inhibits cooperation.

SOURCE: Office of Technology Assessment, 1991.

There are notable differences between R&D expenditures in Japan and in the United States. Japan directs a relatively small amount of government funding to R&D and very little of those funds go to defense. The government's share of total R&D spending in Japan has continued to fall over the last decade. Industrial sponsorship is four times greater than government sponsorship and continues to grow as a percentage of the Gross National Product (GNP). As a percentage of GNP, Japan's investment in R&D has already reached an international high of 2.8 percent. Still, Japan's research expenditure in absolute numbers is only 38 percent of that spent by the United States.

Research relevant to economic growth is sponsored more frequently in Japan than in the United States. Japan gives less emphasis to basic research compared to applied research, a not surprising situation given the dominance of industry funding. Trends in Japan have actually been toward relatively more spending by industry on basic research (up from 5 percent of total industrial R&D in 1978, to 6.6 percent in 1988) but less spending by the government (down from 14.5 percent of total R&D in 1980, to less than 13 percent in 1988).

Japanese universities and staff are more oriented toward teaching than research. Japanese Government funding goes primarily to institutions and senior researchers, who control funding, rather than to individual researchers thus, perpetuating what many feel is a rigid, hierarchical system that stifles innovation. Despite strong formal and informal ties existing between senior faculty and industry, barriers to cooperation remain between the universities and industry. Until 1990, national university professors were considered to be government employees and were prohibited from receiving industry funds. However, many professors have acted and continue to act as industrial consultants. Industry funding of university research is only 2.6 percent of total university research in Japan, as compared to 6.2 percent in the United States.

Government Funding

The Japanese Government funds approximately 20 percent of biotechnology-related R&D-a much smaller portion than the U.S. Federal Government's stake (which is approximately 50 percent). Japanese Government spending for biotechnology was Y82.5 billion in 1989, an increase of Y12 billion (US$900 million) from the previous year (see table B-2). This total includes expenditures by seven ministries. The Japanese Government's

Table B-2—Biotechnology Budgets for 1985-89 (In billions of Yen)

	1986	1987	1988	1989
Ministry of International Trade and Industry	5.4	5.8	5.7	7.6
Ministry of Agriculture, Forestry, and Fisheries	3.1	3.2	6.6	7.4
Ministry of Health and Welfare	3.4	12.1	31.1	34.5
Science and Technology Agency	10.3	12.0	13.8	18.2
Ministry of Education	13.6	13.6	14.0	14.4
Environmental Protection Agency	0.1	0.1	0.3	0.3
Ministry of Construction	0.1	0.1	0.1	0.1

SOURCE: Nikkei Biotechnology, Mar. 13, 19S9; *JPRS Report*, Nov. 1, 1990.

current pattern of investment in biotechnology R&D is to provide limited seed money, as a catalyst to encourage companies to explore new R&D options.

The Ministry of International Trade and Industry (MITI) sponsors two important collaborative applied research programs.

- the Japan BioIndustry Association (JBA), a nonprofit organization dedicated to the promotion of biotechnology and bioindustry, involving 320 companies from many industrial areas; and
- the Research Association for Biotechnology which includes large Japanese firms, such as Ajinomoto, Mitsui, and Mitsubishi Chemicals.

MITI also provides core funding in diverse areas, such as chemicals, pharmaceuticals, food, marine biotechnology, and alcohol fuel production.

Other ministries funding biotechnology-related programs include the Science and Technology Agency (promotion activities); the Ministry of Health and Welfare (research in dementia, acquired immunodeficiency syndrome, circulatory diseases, cancer, maternal and child health, food safety, and drugs); the Ministry of Agriculture, Forestry, and Fisheries (development of leading-edge biotechnology in agricultural, forestry, fishery, and food industries); and the Environment Agency (to cope with environmental problems associated with biotechnology).

The government supports biotechnology indirectly through tax incentives with R&D tax credits and attractive depreciation schedules on equipment, loans, and education, as well as training for personnel. Often, however, incentives for R&D are more attractive overseas than in Japan. These incentives have driven several firms, such as Otsuka Pharmaceuticals and Hitachi Chemicals, to establish R&D branches in the United States. Another important factor is lower prices on higher quality research abroad.

In contrast to Japan, the Federal Government is the driving force behind R&D funding for biotechnology in the United States. In fiscal year 1990, the U.S. Government provided $3.4 billion to support R&Din biotechnology-related areas (see app. C). As in Japan, funding supports a diverse portfolio of potential commercial applications; unlike Japan's focus on applied research, the bulk of U.S. Federal R&D is targeted toward basic research. Several other factors differentiate the U.S. and Japanese approach to funding:

- The U.S. system of authorization and appropriation of Federal programs is inherently driven by pluralism in the political process. The U.S. Congress plays afar stronger role in funding and oversight than does the Japanese Diet, and executive agencies have markedly less discretion than their counterparts in Japan.
- The structure of the U.S. research and technology base is also vastly different. The U.S. Federal Government provides significantly more funding than does the government of Japan, in both relative and absolute amounts. The United States has a decentralized research system, and several cabinet-level departments have internal research divisions responsible for the research needs of their particular missions (e.g., enhancing health).
- The system for setting research budgets in the United States is inherently political. Each Federal agency has its own culture. These cultures contribute to their success, perhaps simply by embodying the "way things are done." However, the culture is a powerful determinant of future directions, and specific goals may only be reflected in the collective knowledge of agency personnel.

Targeting of Technology and Financing

In 1981, MITI designated biotechnology to be a strategic area of science research, marking the first official pronouncement encouraging the industrial development of biotechnology in Japan. Over the next few years, several ministries undertook programs to fund and support biotechnology.

Of particular interest, today, is governmental activity in the pharmaceutical industry. The Ministry of Health and Welfare (MHW) annually lowers prices on existing drugs,

while allowing premium prices for innovative or important new drugs, thus forcing companies to be innovative and to seek larger markets. This trend is reinforced by the emergence of new foreign and domestic competitors. The push toward innovation is part of the government's overall effort to provide care for its aging population—without bankrupting the national health insurance program.

Despite well-coordinated efforts on the part of government to stimulate biotechnology R&D, several weaknesses persist. For example, overall funding levels remain comparatively low, and competition among ministries and agencies has developed. This state of affairs has resulted in some duplication of research and also has created a situation in which companies wishing to test various processes may need authorization from more than one ministry. Furthermore, this rivalry among governmental bodies tends to inhibit coordination between universities (performing basic research) and firms (focusing on applied research).

Approximately 300 Japanese firms report some type of activity related to biotechnology. A 1985 survey, placed this number at 268; of these, 19 used recombinant DNA (rDNA) techniques commercially. Large, traditional firms dominate the commercial sector. The few startup companies that do exist usually show some link to traditional firms.

Current figures on Japanese private spending for biotechnology are hard to obtain from Japanese sources. Estimates for 1987, place industrial biotechnology R&D at US$l billion, roughly half the amount of U.S. industrial spending.

The Japanese stock market has played only a small role in allocating capital. Most capital is heavily concentrated in the banking system. Venture capital plays a limited role in high-technology and biotechnology financing. However, most Japanese venture capital fund managers lack entrepreneurial management skills and usually operate out of their parent headquarters (e.g., banks, security houses, or giant corporations), and these managers invest conservatively. Most American venture capitalists would hold that Japanese venture capital really isn't venture capital in the U.S. sense. Indeed, Japanese venture capitalists are willing to accept returns at two-fifths or even less than the level that U.S. venture capitalists typically expect. Several other reasons exist for the **conservative nature of Japanese venture capitalists. These** include the stigma of failure and the emphasis on personal relationships rather than depersonalized sales of equity, resulting in equity sales primarily occurring between cooperating firms-a condition hardly conducive to U.S. style venture capital.

Although MITI in 1981 announced its goal of matching U.S. biotechnology within ***5 years,*** its catch-up, get-ahead motto has fallen flat in recent months. The initial positive public perception of biotechnology-demonstrated by sales of products such as bio-lipsticks, genetically modified eels, BeWell bread, and other everyday items whose sales were bolstered by advertising their biotech origins--is changing. According to a recent survey, 90 percent of respondents were dubious about biotechnologists' claims of environmental safety, and 77 percent felt that biotechnology would eventually develop into a major social problem. This development combined with the Illustrations of young scientists over not getting enough support, led one writer to note that: Japan may not be the "land of tPA milk and recombinant honey. "

Recent disenchantment with biotechnology at a commercial level goes back to a failure by several companies to rapidly commercialize products. Although biotechnology is losing its luster among Japanese investors, one analyst projects that funding will not decline, but instead will be spent in a more focused fashion on fewer projects.

With one exception, the purchase of Gen-Probe by Chugai Pharmaceuticals of Japan, international biotechnology-related mergers and acquisitions have not involved the purchase of a U.S. company by a Japanese company or vice versa. By comparison, 33 **biotechnology-related** acquisitions between 1982 and 1988 involved a firm from the United States and a firm from Europe.

North Carolina Biotechnology Center (NCBC) databases reveal 12 cases of U.S.-Japanese equity arrangements. Of these, six explicitly mention marketing or research funding. This seems to indicate that most foreign biotechnology companies believe that the only route to the Japanese market is by teaming up with a large Japanese corporation. As biotechnology companies grow to have product sales and their own sales forces, some of the marketing agreements can even switch direction. Genentech is the leader in what may become a more commonplace occurrence by the early to mid-1990s: in 1987 the Japanese chemical firm Mitsubishi Kasei selected Genentech to develop and market some of its Pharmaceutical products in the United States.

Japanese companies are investing in U.S. dedicated biotechnology companies (DBCs). Examples include:

- **Chugai Ph**armacautical's arrangements with Genetics Institute and Upjohn, and Chugai's acquisition of Gen-Probe for$110 million;
- Tokyo's Institute for Immunology's $20 million investment in IDEC pharmaceuticals; and
- the collaboration between Genetics Institute and Japan's Yamanouchi Pharmaceutical Co., and Cal-Bio's deal with Daiichi Pharmaceutical Co.

Industrial Sector: Health

The United States is the largest pharmaceutical market in the world, with an estimated value of $29 billion in 1987. It is followed, closely, by Japan at $25 billion. It is important to remember, however, that the population of the United States is 2.5 times larger than the population of Japan. Three of the top five brand name pharmaceuticals in Japan are produced by U.S. companies. Of the top 50 brand names, U.S. companies produce 23; Japan produces only 5. The United States is very competitive and has maintained a positive trade balance in this high-technology sector. Japan is increasing the strength of its pharmaceutical industry and placed second in the number of new drugs introduced between the years 1981 and 1985.

Historically, the Japanese market has been difficult to enter without a Japanese partner. Just 20 years ago, foreign companies were prohibited from operating independently in Japan. It was not until 1984, that foreign drug companies could go directly to the ***Konseisho, the*** Japanese equivalent of the U.S. Food and Drug Administration, for drug approval. To ensure market presence, U.S. and European companies have collaborated with the Japanese companies that dominate the Japanese market. For many years, U.S. and European companies have been increasing their presence in Japan by establishing their own marketing forces and, in a few cases, building research facilities or acquiring a Japanese company. Very recently, efforts have begun to establish joint R&D programs between U.S. companies and their Japanese counterparts.

At the same time, Japanese companies faced with sharply rising health care costs that have involved drastically reduced reimbursement levels for drugs, are feeling the push to increase their export markets and are slowly beginning to globalize their operations. In the last 2 years, Japanese firms have acquired four smaller U.S. pharmaceutical concerns.

Despite these developments, the main competitors for the world market in pharmaceuticals are U.S. and European companies. These organizations are large multinationals with research, manufacturing, and marketing operations worldwide, particularly in the United States, Europe, and Japan, the three major markets. Focus on leadership in world markets, not only domestic markets, is key to success in the pharmaceutical industry. Although the Japanese share of foreign markets is currently behind the United States and Europe, considerable time, effort, and money could increase the Japanese share of the U.S. pharmaceutical market. It is unlikely, however, that serious inroads will be made by the Japanese into the U.S. market during the 1990s.

Industrial Sector: Agriculture

Because biotechnology products for agricultural use are still in development, it is not possible to compare the numbers of products manufactured in different countries. Field tests of many products, however, are regulated by national agricultural or environmental authorities. There is no official census of such tests, but the U.S. Department of Agriculture (USDA) keeps an unofficial tally.

Through the summer of 1990, 93 field tests of transgenic plants with potential commercial value had been approved in the United States-far more than in any other country. In contrast, there is little activity in Japan. In general, transgenic plants are being developed in nations that are major exporters of agricultural products, with the greatest activity in the United States. However, the Japanese have made important advances in the area of ornamental plants and flowers, and serious work is underway with vegetables and rice.

Industrial Sector: Chemicals

In both the United States and Japan, biotechnology's **greatest** impact in the chemical industry is likely to have little to do with the production per se of industrial chemicals. Instead, its greatest impact will be the result of the industry's expanding investment in pharmaceuticals and agriculture. Recent trends in the chemical industry have forced restructuring worldwide. In response, chemical firms are emphasizing the development and production of high-value-added products, such as specialty chemicals, advanced materials, pharmaceuticals, pesticides, and related agricultural products (e.g., seeds).

The use of biological means for producing chemicals has, historically, received a great of deal of attention in Japan. Unlike the United States, Japan lacks large deposits of coal or oil, the raw materials on which the chemical industry in the rest of the world is based. Thus, Japanese firms have always had a financial incentive to explore alternatives. When Japan's MITI targeted biotechnology in 1980, three research areas were specifically named: rDNA, mass cell culture, and bioreactors. Although in the United States, the word "bioreactor" usually refers to large chambers used for mass cell culture, MITI defines bioreactors, more generally, as fermentation vessels. The more advanced research in bioreactor development funded by MITI emphasizes the use of microorganisms or immobilized enzymes for the production of fine chemicals. Six Japanese chemical firms have taken part in a government-sponsored joint research effort in this area.

Biosensors combine biotechnology with materials science and electronics to produce sophisticated monitoring devices, an area of active R&D, especially in Japan. Potential applications of biosensors include: human diagnostics, agricultural and veterinary diagnostics, food

testing, environmental monitoring, and industrial process control.

Industrial Sector: Environmental Applications

In the nascent bioremediation field, microbial products packaged for sale are available in both the United States and Japan; these, however, have developed only small markets to date. Both nations have been pursuing biotechnology R&D in improved waste treatment. Still, research efforts are generally minimal, and the diffusion of research results into commercial applications has been slow for a variety of reasons, including lax regulations that encourage the payment of fines by industry for waste emission rather than the use of systems to reduce pollution.

In the United States, several Federal agencies support biological research related to waste management. In 1987, eight Federal agencies spent $11 million on environmental biotechnology-related research. In Japan, the Ministry of Construction launched a 5-year, ¥5 billion (US$40 million) project on waste water treatment through biotechnological processes during the 1980s.

Regulation

In Japan, relevant policymaking is dominated by tension between competing bureaucracies and powerful industries. In the United States, policymaking is driven by the dynamics of interest-group politics. Although Japan is far from monolithic, the sheer number of actors in the United States makes achieving consensus and continuity much more difficult.

As elsewhere, responsibility for regulating biotechnology in Japan is divided among several ministries.

- University research is regulated by the Ministry of Education, Science, and Culture's (MESC) "Guidelines to Experiments in DNA Recombination in relation to University Research," first introduced in 1979.
- Research organizations other than universities rely on the Science and Technology Agency's (STA's) "Guidelines to Experiments in DNA Recombination," also introduced in 1979.
- The MITI oversees the "Guidelines for Industrial Application of Recombinant DNA Technology," introduced in 1986.
- The MHW applies "Guidelines to the Technical Application of DNA Recombination in the Production of Pharmaceuticals," introduced in 1986.
- The Ministry of Agriculture, Forestry, and Fisheries (MAFF) employs "Guidelines to the Usage of Recombined Substances in the Fields of Agriculture, Forestry, and Fisheries," proposed in 1986, and published in 1989.

Both the United States and Japan allow the use of biotechnology with some restrictions and oversight. In both countries, regulations based on existing legislation governing drugs, worker health and safety, agriculture, and environmental protection are being developed to cover the use of biotechnology.

Intellectual Property

Japan is a party to the major international treaties designed to protect intellectual property. Still, Japanese patent practice presents several problems.

- Dozens of firms in Japan file well over 5,000 patent applications annually. The top three filers in the United States in 1987 were Japanese firms. As a result, a U.S. filer often finds that Japanese patent rights are closely circumscribed by applications already filed for a similar invention or process.
- On average, the Japanese Patent Office (JPO) takes 3 years to examine a patent application, compared to 21 months in the United States. Anecdotal evidence indicates that the slow pace of patent examination is even worse for biotechnology-related patent applications.
- The permissible scope of claims in a Japanese patent application is narrower than that permitted in U.S. applications. Delays in resolving scope problems can keep applications in limbo for years.
- Adjudication of patent infringement is also slow. Direct evidence cannot be obtained through the discovery process, and infringement can be difficult to prove.

Although there have been some negotiations between the U. S., Japanese, and European patent offices regarding harmonization of patent practice, major differences remain that hinder inventors in high-technology fields, including biotechnology. In part, to avoid some of the tangles of patent practice in Japan, U.S. firms tend to license their patents to Japanese companies in lieu of exporting a product.

Pharmaceutical and health care patents accounted for greater than half of the biotechnology patents issued in 1988. Over three-quarters of genetic-related patents granted were related to pharmaceuticals and health care. U.S. corporations were the largest source of genetic engineering patents. They garnered twice as many health and pharmaceutical genetic engineering patents as U.S. universities and six times as many as U.S. nonprofit research institutions. Thirty-six percent of biotechnology patents were issued to foreigners in 1988, as compared to 47 percent of all patents. Japan is the United States' leading competitor, followed by Western Europe.

In recent years, legislation was passed in the United States and Japan to extend patent protection to make up for the years lost during clinical development. Similar

draft legislation is being considered by the EC. This extension of effective patent life recognizes the importance of patent protection, the effect of the regulatory process on new product development, and the need for public policies to provide incentives for companies to continue investing in R&D. Unfortunately, there still remains a serious interagency controversy in Japan, which hampers the predictability of plant patent protection. The key issue is whether new plants are to be protected by a Japanese patent or by a registration under the Japanese Seeds and Saplings Act, the latter resembling the U.S. Plant Variety Protection Act.

The interagency dispute, therefore, is between JPO and MAFF. JPO urges that Japanese patent law should not exclude plants per se from patent protection. MAFF, on the other hand, argues that the Seed and Saplings law should protect plants, as well as plant varieties. Similar to what has happened worldwide, Japanese applicants seeking broad protection for a generic agricultural biotechnology invention are critical of the weak protection currently afforded under the Japanese Seeds and Saplings Act.