Title
Why Production Technology is not a Measure of Competitivenessin the Biotechnologies

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In the early 1980s biotechnology was heralded as biology's equivalent to the computer industry. A research intensive field, with applicability in a range of sectors, biotechnology was the darling of financial investors and scientific investigators alike. Hundreds of small companies sprouted up, creating new high-technology clusters, reminiscent of Silicon Valley, and promising fortunes to entrepreneurial biologists and their financial backers. The products they were to create--drugs such as interferon, disease resistant crops, and industrial enzymes--and the methods by which they would be produced, were considered nothing short of revolutionary. Biotechnology captured the imagination of the industrialized world, and immediately comparisons of competitiveness were made among US, Japanese, and European firms. Forecasters predicted that biotechnology, like computers before it, though born in the US would be best exploited by the Japanese because of their deep pockets, production expertise, and penchant for iterative product and process improvements.

Defying initial projections, the United States has for 20 years remained the leader in biotechnology. Two related explanations are offered in this chapter. First, despite Japanese hopes and US fears, production technology has not yet

become the main source of competitiveness in the biotechnology industries. Biotechnology is still very much dependent on the elucidation of disease mechanisms and metabolic functions--the domain of basic scientific research--for the development of commercially useful products. The second explanation of American dominance focuses on the institutional structure undergirding basic science. Not only does the US government heavily support basic biological research in health and agriculture, it encourages researchers to straddle the public and private sector. American academics have been the catalysts transferring technology out of university labs and into the private sector. In Japan, by contrast, the biological sciences are relatively underfunded and the conduits from public to private sector constrained. Japanese industry has suffered from being on the fringes of the major biological research centers, a position exacerbated by the Japanese government's late acknowledgment of the role basic research plays in driving new industries.

The American institutional environment--within which biotechnology firms formulate their technology investment strategies--encourages basic research in the biological sciences, and fosters the creation of firms that focus on the development of novel products. America's peculiar incentive structure, derived from its research and educational system, financial system, and regulatory environment, has driven US labs and firms to the forefront of many biotechnology fields. The Japanese institutional environment, in contrast, supported the strategy of building production expertise. Firms were urged to use the new techniques as a way of leapfrogging into a second generation of bio-products, in that cost and production advantages count. But the strategy did not pan out as expected and Japanese firms have remained competent but not prominent rivals.

After a brief introduction to biotechnology and the industries to which it is applied, the chapter will (1) review why American firms were relatively unconcerned with production problems; (2) why Japanese firms and government agencies pursued production technologies more vigorously; and (3) what the nature of competition is in the biotechnology industries. The chapter will show that while the market imperatives in biotechnology are shifting--as the technologies evolve, as the industries to which they are applied consolidate and globalize, as the regulatory and intellectual property environments adjust to accommodate the new technologies--for the near term the US system of innovation will prove more able to commercialize biotechnology than the Japanese system.

I. Definition of Biotechnology

In its contemporary sense, "biotechnology" refers to a set of molecular biology techniques that employ living organisms, or parts of organisms, to make a range of products useful to humans. The power of biotechnologies such as cell fusion, genetic recombination, and polymerase chain reaction (PCR) lies in their collective ability to manipulate and modify the genes of organisms in a *targeted* fashion. As scientists perfected how to identify, transfer, and express specific

genes over the course of the seventies and eighties, it became possible to genetically "engineer" the entire spectrum of organisms--be they microbes, plants, or animals--to express particularly useful traits.[(1)]The possibilities were exciting, even mind-bending: defective genes could be replaced with healthy ones to cure disease, plants with anti-viral genes from bacteria could resist common blights, and micro-organisms could be tricked into producing human growth hormones as miniature "drug factories."
By the 1970s, the commercial potential of transgenic organisms was apparent and industry observers touted biotechnology as a revolution for both science and industry. Though bio-products are steadily entering the market, the pace is a trot rather than the stampede initially expected. The impediments are scientific and social. First, discovering and developing affordable but commercially useful bioproducts was more difficult than early products would seem to indicate.[(2)]Second, questions of safety and ethics put a brake on biotechnology's quick social acceptance in the non-medical fields.
Since its inception, biotechnology has been bathed in an aura of both awe and suspicion.[(3)]Consumer advocates, environmentalists, religious leaders, and even some scientists are critical of the potential dangers of and the ethical questions surrounding genetic engineering. Initially, the sheer novelty of transgenic organisms made it difficult to determine what effects they would have on ecological stability and public health. The NIH (National Institutes of Health) thus created a regulatory framework for research and development as a precautionary measure to allay public fears. The guidelines for rDNA (recombinant DNA) progressively have relaxed as confidence in safety mounted. Nevertheless, regulations have contributed to the uncertainty surrounding recombinant products, and slowed their development.[(4)]A public distaste for "playing God" also engendered a certain distrust of biotechnology derived products, especially in areas in which non-recombinant products are easily available and considered "more natural." Commercial progress for biotechnology in many fields has, for the above reasons, been slower than initially expected.[(5)]

The reach of biotechnology nevertheless is deep and wide. In 1994 the biotech industry had sales of $7.7 billion in the United States, and world sales are expected to reach $50 billion by the turn of the century.[(6)]While pharmaceuticals and diagnostics account for the bulk of the biotechnology products on the market, agricultural products are now growing fastest, at the rate of 30% per year.[(7)]The fine chemical sector uses biotechnology to produce enzymes that act as detergents, dyes, bleaching agents. Food processing, a sector with more traditional affiliations to the biological sciences, increasingly uses biotechnology for both quality control and as a source of additives for food preparation. The environmental clean up sector, though small, is very interested in organisms that metabolize pollutants. In bio-electronics, the sensitivity of biological components (e.g., cells or monoclonal antibodies) and the information processing ability of micro-processors are combined to create sensors. The greatest promise in bio-

electronics is in the sorting of complex biological information (as done in combinatorial chemistry). Finally, other sectors such as energy and mining have interests in biotechnology but have been slow to bring competitive alternatives to market as of yet.

Biotechnology is thus an umbrella term, gathering under it a impressive range of end products. All applications of biotech are united by the concept of manipulating DNA for human use. In practice, however, the steps necessary for finding, transferring, and expressing useful genes are far from routine. Each organism, or each end product, presents a unique set of challenges. Companies must specialize in niche applications--even within pharmaceuticals[(8)]--simply to master the science and technology essential for new bio-product development. Different diseases, different end markets, and different research techniques become the fault lines that fragment the hundreds of firms in the American biotech "industry" into specialized subgroupings that are not easily interchangeable.

Because it is neither a single industry nor a single technology, biotechnology is best understood as a tool kit that allows humans to change the blueprints of life. Its importance and range of applicability is underscored by the flourishing of research firms. Competition between these companies is unlike the semiconductor or electronic industries, where low cost, high-volume production is the primary source of advantage. So far, biotechnology firms live and die with new product generation, and new products are the fruits of intensive research. So while recombinant products may only gradually be making their impact felt commercially, it is important to remember that rDNA technologies are ubiquitously used in research and development, that eventually lead to new products. The long term impact of commercial biotechnology should, therefore, not be underestimated.

II. The Industrial Organization of Biotechnology in the United States and Japan

The two countries positioned to take the lead in biotechnology in the early 80s appeared to be Japan and the United States. Their approach to recombinant technologies, and their fields of application, were diametrically opposed. Given the mismatch in opponents, industry observers worried about who would "win." In retrospect, characterizing the competition between countries as a race was the wrong metaphor. There could not be a single track along which all the players would run: the industry is too fragmented. So far, however, the all around champion appears to be the Americans.

For over twenty years the center of biotechnology development has centered in the United States. American biotechnology firms far outnumber their Japanese and European counterparts. Laboratories and companies from the United States obtain the largest percentage of biotechnology patents and generate the most genetically engineered products. While the last chapter of biotechnology's history is far from written, so far foreign companies have had more difficulties

incorporating biotechnologies into their commercial activities than their American counterparts. The differences between Japan and the US are illustrated below. The United States is unparalleled in the vast network of small, research-oriented companies spawned by the availability of venture capital and private finance. Ernst and Young estimates that by 1995 at least 1,311 biotechnology companies had been founded.[(9)]Entrepreneurial Europeans created about 400 biotech companies in the same time period, or less than one third as many as the Americans.[(10)]Japan, however, has almost no start-up firms. Interest in biotechnology comes almost entirely in Japan from large, diversified corporations. The disparity in number and size of biotechnology-related firms is most evident in the pharmaceutical industry (see Table 1 below), in which the United States has at least 12 times more firms engaged in bio-pharmaceutical research and 850 times more start-ups.

Table 1 Number of Specialized Biotechnology Firms and Pharmaceutical Firms Engaged in Biopharmaceutical Research and Development

Country	***Biotech Firms***	***Pharmaceutical Corporations***
US	850	175
Japan	1	80

Source: Institute of Biotechnology Information, North Carolina Biotechnology Center, *Foreign Development of Biotechnology in Japan and Western Europe*, Table 1, 1992.

Thus, a major difference between Japan and the United States lies in the size and number of firms willing to gamble on commercial biotechnology. The United States unleashed thousands of its scientists, many of whom were affiliated with universities, to create a new "industry" of biological research firms. Commercial biotechnology in Japan took a far less entrepreneurial turn.
Japanese and American companies also embarked on different research paths. (See Table 2.) For the United States, biotechnology is almost synonymous with pharmaceuticals. Two thirds of all US companies with interests in biotechnology are pursuing therapeutic or diagnostic applications. A minority of American companies apply the tools of biotechnology to other sectors. In Japan, by contrast, there is a more even distribution of interest, with companies pursuing biotechnology in chemical, pharmaceutical, and agri-food sectors. The incentive structure for using biotechnology in the various life-science fields obviously was not identical. Japanese and American firms were simply not pursuing the same goals in applying biotechnologies.

Table 2 National Comparison of R&D Specialization by Market Segment[(11)]

Sector	***US Cos.***	***EC Cos.***	***Japan Cos.****
Therapeutic	38%	20%	26%

Diagnostic	28%	23%	4%
Suppliers	16%	19%	11%
Ag-bio	10%	20%	16%
Chemical & Environmental	8%	17%	40%

Sources: US figures, Ernst and Young, 1992, p. 45. EC figures, Jurgen Drews, SAGB, 1994. Japan figures, adapted from Mark D. Dibner and R. Steven White, *Biotechnology Japan*, North Carolina Biotechnology Center, New York:McGraw Hill Publishing Company, 1989, p. 201.
* Japan figures are compiled from a more detailed list and do not total 100% because biosensors, and other categories from M. Dibner were not included here.

Nor however, did Japanese and American firms achieve the same results in the use of biotechnology. American firms and laboratories forged a clear scientific lead, especially in health. Impressionistic accounts of the quality of basic research in biotechnology usually place the United States as front runner, with the European Community coming in second, and Japan third,[(12)] an impression confirmed by data on publication and impact of scientific papers. In the life sciences, the citation rate for articles written by researchers in the United States is 39.2 percent higher than the world average.[(13)] Japan, on the other hand, was *below* world averages in citation impact, which indicates that, despite efforts at improvement,[(14)] the quality of basic biological research in Japan remains lower than that of the United States.

A measure that better captures the commercial potential of firms is their patent obtention rates. American companies have successfully translated a national excellence in basic science into commercial claims on useful new bio-products and processes. The most prolific biotechnology patent generator is the United States, with American institutions and individuals holding two thirds of the domestic and two fifths of the world's biotech patents (see Table 3).[(15)] Despite Japan's weak research base and late entry into the biological sciences, the country is second only to the United States in patent obtention. The figure may actually not be as surprising as it initially appears. Seventy percent of research is performed by the private sector in Japan and its companies are notorious for their prolific patent applications.[(16)] By outpacing Europe in the obtention of US biotechnology patents, however, Japanese firms have proven that they are capable of becoming strong rivals in biotechnology.

Table 3 Allocation of Worldwide Biotechnology Patents, as of June 1990

Country/Area	*Percentage*
United States	41
Japan	36
Europe	19

Source: The Pharmaceutical Manufacturer's Association, "In Development" and "Europe R&D Falls Behind" as quoted in *An Overview of Commercial Biotechnology in the United States*, Office of Industries, U.S. International Trade Commission, Staff Research Study 17, 1991, p. 61.

The ultimate difference between the United States and Japan lies in the generation of recombinant products.[(17)]Japan's biotechnology patents have not translated into numerous novel Japanese bio-products or production systems. Of the two dozen biotechnology derived pharmaceuticals to date, only one of them is truly a Japanese discovery. Japan has applied fermentation and cell fusion techniques, which are *non-recombinant*, to create very unusual products--such as Sainte Neige Fusion BioA wine, the Shikonin dye, and miniature roses. Recombinant product generation, however, has not been a Japanese forte.

In sum, Japanese and American firms approached biotechnology from distinct industrial bases, and with different success rates for developing new bioproducts. American companies were numerous, small and focused on novel product generation in the pharmaceutical industry. Japanese firms were fewer, but more established and interested less in developing new pharmaceuticals than in pursuing biotechnology's application in fields like fine chemicals, energy, and agriculture. These differences in industry structure between Japan and the United States are critical to understanding why the United States did not concentrate on production problems, and why the Japanese saw production technology as the means by which to overcome their tardy entrance into biotechnology. The rest of this chapter is dedicated to showing why Japanese and American firms behaved differently, why production technologies received varying degrees of attention, and why it mattered.

III. The American System of Innovation in Biotechnology

The American biotechnology "industry" is an object of envy in the world scientific community. It represents some of the greatest qualities of America's system of innovation: strong basic science, mobile researchers, and the availability of funding for new ventures. Yet the very institutions that bolstered the creation of a biotechnology sector in the United States also discouraged a strong emphasis on production technology. Powerful incentives lured researchers and financiers to pursue the gilded promise of new products, and especially of magic-bullet biopharmaceuticals. American biotech firms, and their financial backers, were clearly shooting for scientific breakthroughs, and they succeeded.

Since government funding in the United States is aimed at pushing out the technological frontier, the first stimulus for emphasizing basic research over production comes from the federal government. Although the United States has never had a coordinated industrial policy for biotechnology, its heavy commitment to research in the health sciences implicitly stressed biotechnology's use in medical research. In 1994 the United States spent approximately $4.3 billion on biotechnology, 75 percent of which was money from the Department of Health and Human Services. No other country has dedicated as much to biotechnology research nor been so biased toward health.

American biotechnology companies have without doubt benefited from high federal funding levels. Through government support a steady flow of graduate

students are trained in the biological and chemical sciences; advances in genetics and molecular biology proceed rapidly; and funds are made available to the private sector for basic research projects. Rarely, however, does the US government support research in production engineering. This is consistent with the post-war American understanding of the role government plays in innovation. Subsidizing basic science provides a public good, and creates an infrastructure for innovation that eventually benefits the private sector. With the exception of defense and agriculture, product development is not the responsibility of government.

Commercial biotechnology appears not to have suffered from a lack of federal funding for production engineering. Generous federal support in basic science made for a vibrant academic research community, a resource that turns out to be invaluable for the development of bio- products. The discovery of commercially useful entities continues to be tied to basic research in biotechnology to a much greater extent than in many other high-technology sectors. A recent example illustrates how product ideas cannot be divorced from advances in our understanding of disease mechanisms and metabolic processes.[(18)]A fierce race to identify a gene responsible for hereditary breast cancer, BRCA1, ended successfully in 1995 with a laboratory at the University of Washington being first to cross the finish line. Identifying the gene was only a beginning for oncologists. Within eighteen months the protein for which BRCA1 codes, and its function, were elucidated by researchers at Vanderbilt University. In a stroke of luck unusual in cancer research, the healthy gene turns out to code for a protein that is secreted in the breast tissue and prevents unruly cell division. The news is good for biotech companies: a secreted protein is an easy target for drug developers. A product that could mimic the healthy protein, thus inhibiting cancerous cell growth, would be a gold mine. Indeed, Myriad Genetics already has applied for a patent on the gene. Without the groundwork done by basic researchers on the location and function of BRCA1, such a drug would not even have been imaginable. In biotechnology, science and product development are, for the moment, inseparable.

The research and education system of the United States is also largely responsible for manning the hundreds of small biotechnology firms with researchers, technicians, and scientific advisors.[(19)]Unlike in Japan, scientists in the United States are free to act as consultants on a part time basis, and industry can help fund laboratory expenses, thus creating tight links between the public and private sector. American researchers are much more mobile than their European or Japanese colleagues. During their careers they move frequently from university to university and, to a more limited extent, between the public and the private sectors. The risks involved in interrupting an academic career to pursue an idea for a new business is less daunting for an American than for a Japanese or European because the American is likely to find another job if the venture fails. In fact, in the business world moving from company to company is a sign of experience. The advantage of this flexible system is precisely that it

allows science-based firms to flourish. A biotech firm an academic laboratory share a common culture, and to a certain degree a common set of objectives. How to best produce the end product tends to be a second order problem for scientists at biotechnology firms and it is almost non-existent as an issue in university laboratories.

The costs of running a biotechnology firm mitigates against spending too much on production problems early on. For small companies, biotechnology expenditures tend to be high, averaging about $30 million for a public firm in 1993.[(20)] Only 18 percent of these firms have revenues from products to offset their expenses. As a result, the median survival index for public firms is a short 25 months, and a quarter do not even have enough cash reserves to last one year at current burn rates.[(21)] Financing is, therefore, crucial to the survival of biotechnology firms. More than any other element of the US system of innovation, the financial system, which made available capital for idea-based companies with no revenues, was critical to the explosion of biotechnology firms in the United States. Financial backers did not put a high premium on good production engineering.

In the United States, biotech firms must be resourceful competitors for scarce capital. Using a mixture of venture capital, private equity, public offerings, and strategic alliances, companies can string together capital to fund research and development work over several years. But with over 1,300 biotech firms, the battle for attention from potential investors is fierce. Companies use two sets of signals to indicate to the market their value: (1) patents, and (2) regulatory approval data. The production capability of a company is not often taken into account.

The importance of patents as information sources about biotechnology companies is apparent from the fact that due diligence reviews of patent portfolios are routinely requested by venture capital firms, corporations, and biotechnology companies every time they are considering investing in or collaborating with another group of researchers. As Kate Murashige points out, patents are really the only way to package technology so that it is easily transferable from one group to another. They are the currency of exchange. Though by no means guaranteeing the ability to exclude others from a market, patents call attention to useful products or processes a company has developed, and thereby indicate the commercial value of its research. It is important to note that in the pharmaceutical industry, the correspondence between a patent, a product, and a market is very tight. Patents are issued for new chemical entities or processes for making those entities. Unlike in many other industries, few patents issue for minor improvements, so there is little incentive to cross-license. Competition therefore is based on being first to invent, rather than on producing the better product.

After patents have issued, the status of a regulatory approval is the second signal the investment community follows. Information on the status of a product approval yields far more detail about the quality and safety of a product, and

therefore about the future value of a company, than a patent can. Investors and stock holders follow regulatory approvals of the FDA, EPA, and USDA very closely.[(22)]

Drugs, for example, are the responsibility of the Federal Drug Administration.[(23)]If a product seems to be safe (i.e., having few side effects) and effective in treating a disease in animal studies, a company will file an Investigational New Drug Application (IND) with the FDA to start testing on humans. The company has to complete three phases of tests before it can ask the FDA to review its product. Phase I trials are small scale experiments to establish that the drug is safe in healthy human subjects, and to determine its appropriate dosage. Phase II trials assess the drug's efficacy in actually treating or curing the target disease in sick patients, and Phase III extends the safety and efficacy tests to a much larger population (one to three thousand patients) for better statistical analyses. The assembled data from the three tests is submitted to the FDA as a Product License Application. The FDA then reviews the data and judges whether the product is approvable.

The regulatory approval system can make or break a product, so the disclosure of trial results are critical to the stock value of public companies and to potential strategic alliance partners. Approvals affect not only the individual company, but occasionally pull valuations for the entire biotechnology "industry." In the early 1993 and 1994, disappointing results for antisepsis drugs (which combat acute infections)--the core activity of companies like Synergen, Centocor, and Xoma--made institutional investors bearish about the biotechnology as a whole.[(24)]Wall Street worried about the future of bio-pharmaceuticals if their most promising drugs fail to pass FDA's muster.

For diminutive, cash strapped American biotechnology firms, very few of whom have products already on the market, intellectual property is their most important measure of value. Pursuing patentable new products is the overriding concern of firms, and strong property rights woo the investors who keep research projects afloat. Very little time or money is left to concentrate on downstream production issues, which, in any case, can be relegated to a later stage in the evolution of the business. Production engineering is literally an after-thought for American biotech companies. And though occasionally industry observers fret about the problem, in the end it does not much matter to competitiveness because small biotech firms are not vertically integrating. Production advantages do not matter when companies compete amongst themselves for access to capital, and within their sub-fields to be first to the Patent and Trademark Office with a new compound.

In short, the American system of innovation pushes researchers to think about biotechnology as a set of tools for the creation of *novel* products. Production engineering problems, though important, are secondary. It is not the mandate of university researchers to pursue developmental projects. Small biotechnology firms share in the "basic science" culture of their university colleagues. In

addition, the pressures of continually securing funding from venture capitalists, the stock market, and strategic alliances pushes American biotech firms to concentrate on new product generation because patents, and later New Drug Applications, signal to the market the value of a corporation. Production problems will be solved later, when larger scale production becomes an issue.

IV. The Japanese System of Innovation in Biotechnology

Japanese companies entered the biotechnology industry from a completely different institutional environment, and faced incentives that encouraged a focus on the production problems of biotechnology.[(25)] Where US companies and universities were in the thick of the biological revolution, Japanese firms were on the sidelines watching with some trepidation the American explosion of research companies and biotech patent approvals. Weak generators of traditional chemical products, the Japanese pharmaceutical and chemical companies could not initially hope to compete on a first to market basis, especially in new bio-pharmaceuticals. Nor could they count on exploiting the ideas percolating up from Japanese universities, because the academic community was not geared to provide new products. Japan's early prospects for generating blockbuster recombinant products were not stellar.

Despite these drawbacks, biotechnology's commercial potential was perhaps even more attractive to Japanese firms than to American ones. It offered an entry into the next generation of environmentally friendly, energy saving industries.[(26)] Environmental disasters in the 60s and 70s spurred the government to alter the course of industrialization in the direction of lighter, less environmentally damaging technologies. And ever since the oil embargo of the 1970s, Japan's policy has been to reduce its reliance on foreign energy sources. Part of biotechnology's appeal, therefore, lay in the potential of biomass as an energy alternative; the use of cells and bacteria, rather than petroleum as the starting materials for fermentation; and in the modest energy requirements of most bioprocesses. Biotechnology had the added advantage of potentially revitalizing the floundering chemical industry by creating avenues of diversification. Maintaining jobs in sunset industries has been a critical concern for the post-war Japanese government.[(27)]

The Japanese government, and particularly the Ministry of International Trade and Industry (MITI), deliberately galvanized public interest in the biotechnologies. As usual, MITI was the pace-setter. A report about the industrial future of Japan called "Vision for the 1980s" designated biotechnology, along with new materials and micro-electronics, as one of three "Next Generation Basic Industrial Technologies" (NGBIT). The "Vision" report outlined which high-technology sectors had promising growth potential, and signaled to industry that biotechnology research projects would receive support. Accordingly, the Next Generation program included three biotechnology research associations and represented the first coordinated effort to develop industrial biotechnology. Note

that MITI's main objective was to bring Japanese *companies* up to par in *commercial* applications of biotechnology.
Typical of Japanese industrial policy the level of government funding for research was modest and targeted at the private sector. In 1993, the Japanese government spent on the order of $1 billion for biotechnology, compared to nearly $4 billion by the United States. Low levels of central government funding for R&D is not unusual. Whereas in the United States 47.8 percent of gross expenditures on R&D are by the government, according to the OECD the figure for Japan is a mere 21.5 percent.[(28)] The burden of research and development falls squarely on the shoulders of Japan's private sector, despite the visibility of government projects like NGBIT and the attendant American anxiety of "unfair" subsidies. In biotechnology, it is estimated that companies invest at least two times as much as the government in R&D. As a result, the Japanese system of R&D support is geared to explicitly commercial purposes. Both public and private funds are primarily earmarked for projects with a commercial orientation.[(29)]

Ministries understood their mandate as promoting interest in biotechnology among their constituent companies. MITI as pioneer of biotechnology policy, joined together fourteen chemical companies for the first biotechnology research associations (RAs) in 1981, and the next year established a semi-private industrial organization called BIDEC (the Bioindustry Development Center, later known as the Japan Biotechnology Association) to disseminate information and aggregate industry opinion. Other agencies with oversight in a life-science based industry soon followed suite, including: the Science and Technology Agency (STA), the Ministry of Agriculture Forest and Fisheries (MAFF), the Ministry of Health and Welfare (MHW), and the Ministry of Education. (See Table 4.) No overarching policy harmonized the efforts by each arm of the government. MAFF created research associations and an industry organization for agriculture, seed, and food companies. The MHW, which was predominantly a regulatory agency, has belatedly become an advocate of the pharmaceutical industry and biomedical research. And the STA has pursued research further along the scientific frontier. What MITI, MAFF, and the MHW have in common is a promotional strategy that relies on private sector-public sector cooperation in development and de-emphasizes the role of universities as research sites.

Table 4 A Selection of Japanese Research Associations and Research Companies

Agency	Project Group	Biotechnology Objective
MITI	AIST	
	NEDO	Marine Biotechnology
		R&D Program of Basic Tech for Future Indus.

	JKTC	Protein Engineering, PERI
		Medical Biopolymers
	NRDC	Aqua Renaissance Project
STA		
	JRDC	ERATO projects
	RIKEN	Frontier Research Program
MAFF		1. Bioreactors for the Food Industry
		2. Sensors for the Food Industry
		3. Embryo Transfer in Domestic Animals
	BRAIN	
MHW		Biosensors for medical uses
MPT	JKTC	Protein Engineering, PERI

Based in part on Rolf D. Schmid, "Biotechnology Research Associations in Japan, BFE, Vol. 8 No. 4, April 1991, pp. 166-170.

Research associations are a classic mechanism used by the Japanese government to encourage collaborations in areas of common technical interest between companies. In the best scenario, an RA will raise the level of understanding about a field, distribute information, and provide a stepping stone from which companies can choose to commercialize products. Research associations also act as signals to other companies about the importance of the target technologies. Ministries, by organizing RAs, play a guiding and coordinating role in the diffusion of technology.

MITI, for example, created research associations for applied technologies that it feared would otherwise not be well funded by industry. For example, the three Next Generation for Basic Industrial Technology projects included a bioreactor project, a large scale cell culture project, and a rDNA project, each of which had a significant concern with production issues. The goal of the bioreactor project was to promote the use of fermentation as a cost-effective, low energy production technology for commodity chemicals.[(30)]The large scale cell culture project aimed at improving isolated cells for the production of fine chemicals (e.g., pharmaceuticals). The cell culture project was interested in improving the cultivation of animal and plant cells, whereas the bioreactor project focused on using bacteria as "mini factories." Finally, the recombinant DNA research association was a more amorphous project that tried to perfect recombinant technologies--again, for large scale commercial purposes.

MITI's support of biotechnology illustrates how the government's encouraged a focus on production issues. First, the stated purpose of the RAs was to help companies learn about and commercialize biotechnology, and to do so by making improvements in the production technology. MITI's priority was to help Japanese firms catch up to the United States. Second, success in biotechnology was not seen as intimately tied to advances in basic science. Biotechnology was marketed as a general purpose tool that could be used to improve upon any existing product or process. Third, the government consciously defined biotechnology as

something separate from recombinant DNA technology. In the NGBT project, for example, the rDNA research association specifically explored the use of recombinant organisms, whereas the bioreactor and large scale cell cultivation RAs, were only peripherally involved with recombinant technologies. From the government perspective, improvements in fermentation and cell culture were worthwhile regardless of the provenance of the starting material. Political concerns motivated the Japanese ministries to separate biotechnology more generally from recombinant technology. Clever marketing of "Bio" products, such as Kanebo's Bio-Lipstick, portrayed them as modern, environmentally sound, and fashionable. Since recombinant products were more likely to meet resistance by the public, the Japanese government de-emphasized and regulated the use of rDNA technology while paradoxically promoting "biotechnology" writ large.

MITI's Next Generation for Basic Technology research associations established the ministry a new and important center of funds for the life sciences in Japan , and opened the door for dozens of subsequent biotechnology project.[(31)]The majority of MITI's promotional policies in biotechnology have focused on raising industrial capabilities, and directing research to the chemical, environmental, and energy sectors. Similar efforts by MAFF, and the MHW also channeled industrial research toward production problems.

Although the emphasis in Japanese policy was on industrial technology, it would be wrong to imply that Japan entirely ignored basic research in fostering biotechnology. Recently, Japan has been ratcheting up its support of basic science, primarily through the Science and Technology Agency (STA) and the Ministry of Education (MOE).[(32)]One example of change is ERATO, the STA's flagship program to support Japanese innovation. A type of genius grant, ERATO provides five years of funding to extraordinarily creative young researchers, giving them the luxury of pursuing their ideas unhindered. Half of the ERATO projects have recently been for work in the biological sciences. The average researcher is also benefiting from plans to upgrade basic science by the Ministry of Education. Increased support for R&D in national universities is accompanied by a move away from block grants to a more competitive and merit based allocation of resources among scientists. In order to become an "information society," and biotechnology is heavily information oriented, Japan realizes that it must become a generator of new ideas. Indeed, in some areas of science Japan is the envy of the Western world.[(33)]But for biotechnology the support of basic research has been too little, too late for Japan to be a front runner.[(34)]

Government intentions alone could not dictate how Japanese industries adopted biotechnology. Industrial policy no doubt influenced firm strategies, but it was but one aspect of the larger institutional environment constraining technology strategies. Three other institutional factors pushed Japanese firms to emphasize biotechnology's production strengths. The financial system made the emergence of small research firms difficult; the research and educational system limited the availability and mobility of biological researchers; and finally the regulatory environment favored the use of non-recombinant technologies, making research in rDNA products risky. Combined with easy access to an open and research-intensive American system of innovation, the Japanese focus on licensing new products to learn and improve upon biotechniques was a rational decision.

Japanese companies that became involved in biotechnology, compared to the thousands of American start-ups, were vertically integrated corporations with backgrounds in an impressive variety of industries. Dedicated research firms are rare in Japanese biotechnology for several reasons.[(35)]Although venture capital exists in Japan, it is not invested in embryonic ventures.[(36)]Like most European countries, Japan does not allow companies that have not had five years of profit to post an initial public offering (IPO) on the Tokyo Stock Exchange. With no quick exit strategy, venture capitalists are wary of investing in start-ups. Nor has the banking sector, including the government controlled Japan Development Bank, been a conduit of loans for new biotechnology ventures.[(37)]Finally, very few tax credits are extended to make investment in high technologies less onerous for small companies, as has occurred in the United States. Under tight financial conditions, only established Japanese firms with access loans or internal debt could reasonably hope to invest in biotechnology. No true start-ups have emerged to translate the

basic research discoveries of the public sector into interesting commercial possibilities for the private sector.[38]

The research and education system, and in particular the universities, contributed to the slower and more rigid nature of Japan's response to the birth of biotechnology. At the beginning of the eighties, Japan simply did not have a deep pool of biological and chemical researchers willing to launch new businesses. The life sciences were the poor cousins of the engineering departments at universities, and the number of students reflects their second class status. The United States graduates 35 times as many biology Ph.D.s and 10 times as many chemistry Ph.D.s per year as Japan.[39]And since few Japanese universities even offer courses in molecular biology, it is not surprising that there are only about 2,000 Japanese undergraduates compared to 35,000 American ones in biology and chemistry programs. The university system also restrains the commercial activities of its professors and researchers. As civil servants, strict regulations limit the amount of contract research or consulting work that faculty can accept, thus hindering the transfer of technologies to the private sector.[40]In addition, Japan's rigid employment structure raises to unacceptable levels the risk associated with joining or creating new ventures. If a start-up fails, its scientists will have great difficulty finding employment elsewhere at mid-career. For the above reasons, the larger Japanese firms were best able to field researchers and capital for the development of commercial biotechnology.

The type of corporation that performs research and development in a country shapes the technology trajectory that emerges from its borders. Japanese firms adopted three tactics for biotechnology: (1) they sourced and licensed technology from abroad, (2) they tried to build expertise in their area of comparative advantage--production technology, and (3) they laid the groundwork for stronger R&D capabilities. Technology was easily available from the many cash starved American start-up firms, for whom Japanese partners were ideal because they were willing to forfeit rights to the US market. American universities and hospitals also freely contracted with Japanese firms. From 1985 to 1989 a majority of the biotechnology strategic alliances struck by Japanese companies involved an American partner, and in eighty percent of these alliances, the flow of technology was from the American to the Japanese company.[41]The strategy "has provided direct, quick access to new technologies with decreased risk at relatively low cost."[42]Japanese firms will continue to license from the United States for the near future, as a way of boosting the expertise of their internal research staffs and launching their biotechnology programs.[43]

Japanese companies obviously collaborate with domestic universities.[44]But the university system is simply not brimming over with potential products to be cherry picked by commercial firms. (Japanese firms are the primary locus of biotechnology R&D: all top ten patent generators are companies in Japan, while in the west close to one half are universities and government laboratories.[45]) The dearth of entrepreneur-scientists and the shallowness of the basic science base have hurt Japanese efforts in biotechnology because industrial research teams cannot entirely substitute for the exploratory work that elucidates the disease mechanisms and metabolic functions. Companies, despite their best efforts, often do not have the academic training, inclination, or incentive to pursue basic research as a way of finding new products.[46]It makes far more sense to invest in the developmental work necessary to bring an already promising new product to market.[47]

From the outset, production technology was heralded as Japan's key into the bio-industries for several reasons. The country's reputation as a fierce competitor is built on its genius for parlaying incremental improvements in product and production process into higher quality, lower cost goods.[48]Americans and Japanese alike believed that the same corporate mentality would help Japanese firms bootstrap their way into the biotechnology industries. Robert Swanson, one of the founders of Genentech wrote:

> "In Japan, the biggest share of every research dollar is funneled into bioprocess engineering rather than into basic research. The Japanese have relied on the US and other countries to provide the breakthroughs. Then, by rapidly applying considerable

expertise in process development and scale-up, they can jump well ahead and capture a large share of the world market for biotechnology products."[49]

In fact, during the post-war period Japan became one of the leading producer of amino acids, vitamins, and antibiotics, all of which are based on classic fermentation technologies.[50]If Japan could engineer production advantages in these "old" biotechnologies, it was only logical that the same skills would apply to "new" biotechnology. Because old biotechnologies are produced in larger volume than most of the bio-therapeutics, many believe that Japan's skill will be in "scaling-up" production and in down-stream processing (i.e., the isolation and purification of the end product). Scale-up and downstream processing are often very difficult to achieve when moving from experimental conditions to full-scale production. Building the necessary expertise in production engineering and process technology, therefore, seemed to be the best entry strategy for Japanese firms, since their weak research base prohibited them from rapidly generating new bio-products.

The final aspect of Japan's innovation system contributing to a greater reliance on production technology is the legal/regulatory environment. Although not outrightly hostile to the development of biotechnology, the regulatory system has not provided strong incentives for firms to concentrate on new product development. Regulations in Japan are set, at best, reactively. The regulatory agencies--including MHW, MAFF, and MOE--prefer a slow, cautious approach in order to build a societal consensus. It took the Ministry of Education three years longer than the United States to issue the first regulations covering rDNA research in academic laboratories, even though it essentially copied the US guidelines. In another example, MAFF did not clarify how it would treat recombinant agricultural products, and tightly restricted open-air experiments necessary for testing their safety and efficacy, until 1989. Uncertainty surrounding environmental release of genetically engineered organisms throughout the eighties meant that commercial development of products such as rDNA plants, bacteria for environmental clean-up, and pesticides and herbicides came to a standstill. More recently, the MHW's opaque stance on gene therapy experiments have impeded the progress of this potentially important new class of treatment. The lack of certainty and predictability of regulations increases the risk associated with developing recombinant technologies. If the use of rDNA organisms can be avoided, firms in Japan prefer to use more conventional techniques--bioreactors, cell fusion, and cell culture--to make "bioproducts." The regulatory environment reinforces incentives to focus on scale-up technology and downstream purification because the production engineering end of biotechnology has value irrespective of whether the end-product is recombinant or not.

The strategy had the advantage of channeling company research into products with larger, consumer-oriented markets in which production technology was important. But the government's hesitancy about the safety and acceptability of rDNA technologies is also one of the reasons Japanese firms did not embrace biotechnology as fully as their American counterparts.[51]

With its narrow patent scope and weak enforcement of rights, the Japanese intellectual property system does not often grant strong protection for innovations.[52]According to Japanese Patent Office practices, firms can make only one claim about their innovation per patent application, compelling inventors to file many narrowly defined patents for each innovation. The narrow scope of patents, combined with weak enforcement mechanisms, and the absence of a doctrine of equivalents, means that the monopoly granted to firms when a patent issues is tenuous.[53]Competitors can infringe with more impunity, or simply invent around existing patents. The Japanese IP system is designed to diffuse inventions to society at large by encouraging companies to cross-license.[54]The effect on the biotechnology industry is not easily assessed.[55]One can speculate, however, that companies in Japan are less tempted to pursue the promise of strong protection for new bio-product or processes. In the United States, the goal is to be first to invent a new bio-pharmaceuticals, for example, in order to garner monopoly rents. Frequent and acrimonious patent disputes testify to the importance of defining and protecting one's innovation. In Japan, however, the ease with which patents can be circumvented may

make it more attractive to concentrate on comparative advantage in other areas of production. Being first to invent a new bio-product has smaller rewards than in the United States.

In sum, several aspects of Japan's national innovation system channeled technology strategies away from an over-concentration on novel product generation in bio-pharmaceuticals.[(56)] Instead, Japanese firms attempted to compete as second to market entrants by concentrating on manufacturing and process know-how, incremental product improvements, and to a much more limited extent mass marketing. The strategy was not simply adopted out of habit. It was a rational reaction to the incentives and constraints firms faced from the educational and research system, the financial system, and the legal/regulatory system. The government, and the Japanese firms entering biotechnology in the eighties, saw production technology as their best bet for becoming players.

V. Competition in the Biotechnology Industries--The Present and Future of Production

In one sense, defining biotechnology as either a research tool for new product generation, or as an alternative production process creates a false dichotomy. It is hard to conceive of creating a bio-product without thinking about how it will be produced. Biotechnology must encompasses both product and production. The difference between Japan and the United States is simply in the weight given to these two aspects of research and development. American firms invested in biotechnology with the intention of creating novel drugs, crops, and pesticides. Japanese firms, on the whole, licensed rDNA products, and focused on production technologies while they improved their research capabilities.

Unfortunately for Japan, production engineering has not been a springboard from which to jump into a wide range of biotechnology activities. Unlike most high-technology industries, biotechnology is still heavily reliant on basic scientific research for discovering what products to make, and how to best make them. Inventions, for example, are sprouting from the rapid unraveling of the genetic code for humans, select micro-organisms and plants. The multinational Human Genome Project is proceeding faster than expected: already HGP teams have created a map of the 100,000 human genes, and they expect to identify the function of many of these genes in the near future. Genetic information is flooding the market with possibilities for bio-products. Compared to the vast improvements and innovations that genetic engineering promises, the increases in yield due to production innovations seem minor.

Competition in biotechnology, despite similarities in industrial structure with computers and semiconductors, has little to do with the high-volume production issues that drive consumer industries. First, as mentioned above, access to basic science discoveries is critical to the development of new products. Basic science helps generate novel products--a trait that is especially important in bio-pharmaceuticals--in which success is premised on being first to invent a new drug and to obtain strong, broad patents with which to fend off competitors. Although the situation is changing, the pharmaceutical sector is relatively price insensitive for novel drugs. The Japanese focus on production technology and cost reduction is not ideally suited to competition in the bio-pharmaceuticals. Second, companies in most applications of biotechnology do not compete on a finite set of product quality standards or specifications as in consumer industries. They compete on being first to successfully engineer and produce a new product, often regardless of yield or quality. Production issues become a second-order problem when there are no standard products or technologies to which all companies conform.

Third, biotechnology has no "key technology" that automatically unlocks the door to a range of products, as DRAM production did for computers. Biotechnology is far too functionally fragmented. Diversification from one type of genetic engineering to another, from one organism to another, requires jumping to the top of a new learning curve. Mastering the isolation and purification of erythropoietin, for example, does not guarantee the ability to do so with another protein. Areas of expertise are rather narrowly circumscribed, though not totally impermeable, which makes empire building of the Sony or Microsoft variety difficult in biotechnology. The situation is in fact worsening in the United States, where up and down stream activities are being further separated rather than fused.[(57)] This is a great disappointment to the hundreds of small

American biotechnology firms that harbored the hope of becoming fully integrated corporations. New biotechnology firms have been relegated the task of product development. Universities often provide the basic science from which new ideas for products grow. Contract Research Organizations (CROs) perform clinical trials, testing which new drugs conform to the safety and efficacy standards of each country. And pharmaceutical companies manufacture the end products. The American experience seems to indicate that no single activity in biotechnology holds the key to competitiveness.

Finally, the fact that products and processes involving rDNA are regulated inhibits experimentation and incremental improvements in product quality. Most consumer electronics companies, in contrast, are free to experiment with the production process. But in the US and Japan companies receive approval for one product and for one process for making that product. Any changes would require lengthy and expensive re-certification of safety and efficacy. Companies cannot afford to engage in the type of commercial tinkering that has led to Japanese production strength in other industries. In sum, a strength in production engineering in biotechnology is neither easy to build nor the main source of comparative advantage; nor does it open the door to a wide range of applications.

The picture painted so far for Japanese biotechnology is bleak. Indeed, Japan's unreserved enthusiasm for biotechnology has waned over the course of the eighties and American companies now believe their strongest competitors to be domestic.[58] But it is premature to declare the US the unrivaled "winner" in biotechnology. The industries are still evolving and Japan's approach to biotechnology may have important future payoffs. A cost/benefit analysis of biotechnology makes Japan's cautious investment strategy in research appear quite rational. Through its commitment to health research, and its venture capital system, the United States now invests on the order of $11 billion dollars a year in biotechnology, despite the fact that US sales were only $7.7 billion in 1994. Remember that Japan has invested far less in biotechnology than the United States. Limited capital expenditures, do not prevent Japanese firms from accessing basic science discoveries in the United States. By one account, therefore, biotechnology is an expensive and risky venture that Japanese firms are willing to invest in only when the cost benefit ratio increases.

Assuming, however, that Japanese companies want to be players in biotechnology, their focus on production technologies may eventually pay off. The following five conditions would make a production advantage valuable. (1) *An increase in petroleum stock prices*: When the cost of petroleum based raw materials ultimately rises--a situation that many believe will not happen in our lifetimes--then the cost effectiveness of biotechnology as a alternative production process for many chemicals will become more attractive. The Japanese projects in energy and alternatives to petroleum-based products could then pay-off. (2) *Cost-competition in pharmaceuticals*. The second largest pharmaceutical market, the United States, has been relatively price insensitive compared to Europe and Japan, where the governments set drug pricing. But the rising bargaining power of Health Management Organizations, and competition from generic drug makers, is bringing down American drug prices. Cost savings from process improvements is now becoming more important to pharmaceutical firms, which may help Japanese entrants.[59] (3) *Routinization*: As biotechnology product development becomes less wed to basic science, and more routine, the United States will lose its edge vis a vis Japan, and product quality and production price will play a more important role in competition. (4) *Key technologies*: On a more theoretical level, the development of key technologies could transform the competitive dynamics for subsectors of biotechnology. For example, rational drug design, the modeling of how molecules function, will eventually permit the synthetic creation of new bio-products. Combinatorial chemistry, a technique that permits the rapid screening of thousands of potential molecules for a specific "fit," also suggests that some technologies will endow companies with an advantage important to both research and development. Companies that master such key technologies will be best positioned to enter new markets. (5) *Diversification*: As more non-pharmaceutical products are approved for sales, Japanese products will emerge from the diversity of its biotechnology industries. As regulations for rDNA products continue to relax,

Japan's investment in the many non-pharmaceutical applications of biotechnology will pay off. Barring accidents, consumers will eventually accept recombinant products in agriculture, chemistry, and marine industries. Japanese concentration on these applications will then yield interesting new ideas.

Over time production issues will become more salient. Japanese firms, if they continue to be interested in biotechnology will finally be able to exploit their investment in production technologies. It is very difficult, however, to make predictive statements about a set of industries that are in such a state of flux. The most important changes include industrial reorganization due to alliance formation, the blurring of distinctions with conventional producers, and the globalization of research and production. The pharmaceutical industry, for example, is consolidating rapidly in response to increasing financial pressures and decreasing product pipelines. It is now nearly impossible for bio-pharmaceutical companies to envision vertical integration in a market dominated by multinationals. In all biotech sectors, strategic alliances between firms have become a primary source of funding, tying together firms with disparate competencies and national bases, and redefining the bases of competition. Finally, the globalization of research and production is spreading know-how to countries that have until now not been important innovators in biotechnology. All these trends will ultimately reshape the incentives and constraints to which biotechnology firms must react.

For the near future, it is safe to venture that Japan's relatively weak position in the biosciences will hamper its efforts to become a major competitor in biotechnology. Sourcing technology from abroad, a classic "catch-up" strategy, will only partially offset the lack of innovativeness at home. In highly research intensive industries, production issues are not necessarily the central determinants of competitiveness. Despite the similarities in industrial structure with other US high-technology industries, biotechnology's competitive dynamics are quite distinct. Indeed, where Japanese firms were able to forge ahead technologically through a concentration on production technology in many electronic sectors, for the past two decades, the American system of innovation has proven more congenial to the development of biotechnology. The strength of the US system lies in the availability of funding and the close ties forged between universities and start-ups that keep product development close to the scientific frontier. The United States is likely to defend its position as leader of commercial biotechnology for the next few years, but production issues will gain dramatically in importance. US firms should beware. The signs are not presently auspicious. For the moment, the American biotechnology "industry" is truncating research from development and commercialization through the "virtual integration" of companies. The trend tends to obscure the importance of production engineering research, just as more attention needs be paid to it. Japanese firms may, therefore, be more successful at competing with US firms in the future.

Footnotes

[1.] Dating the birth of biotechnology is an impossible task. In 1973, however, Stanley Cohen and Herbert Boyer published a paper in the *Proceedings of the National Academy of Science* that demonstrated that it was possible to transfer and stabley incorporate foreign, functional DNA segments from one bacteria to another. Although many discoveries, from the structure of DNA to the existence of nucleases preceded the Cohen-Boyer experiment, the proof it provided that the genome of organisms can be recombined to express foreign traits marks the beginning of modern biotechnology.

[2.] The two first biotechnology derived drugs were not really discoveries. Human insulin and human growth hormone where two proteins that are not produced by diabetics and children with growth disorders. Knowing the proteins and their therapeutic effects made them logical targets for production. But the function of most other proteins are not known, and scientists must spend months searching for products with therapeutic value.

[3.] Scientists were the first to call attention to the potential danger that the release of transgenic microbes could have on public health and the environment. In 1975 a moratorium on experiments in genetic engineering was voluntarily put into effect in the scientific community. A

meeting in Asilomar, California brought together researchers and laid the groundwork for safety measures and regulations in the US.

[4.] Nowhere is this clearer than in Germany where the stringency of regulations convinced most pharmaceutical and chemical companies to do their research in recombinant technology in a more permissive environment, usually the United States.

[5.] Most polls show that Americans are for the use of biotechnology in order to create drugs that would not otherwise be easily available for serious diseases. The situation is different for the creation of genetically altered crops, where cheap non-recombinant alternatives are exist as substitutes.

[6.] Biotechnology Industry Organization, "The US Biotechnology Industry: Facts and Figures, 1994/1995 Edition," website, January 1996.

[7.] Present sales of ag-bio products are $130 million. The forecast was made by R.E. Shamel and M. Keough, "Non medical Areas Expected to Show the Fastest Growth in Biotechnology," *Genetic Engineering News*, December 1994, p. 11.

[8.] Examples include companies that specialize in neurological problems (a disease type), gene therapy (a therapy category), or combinatorial chemistry (a research tool).

[9.] Ernst and Young, *Biotech 95: Reform, Restructure, Renewal*, 1995.

[10.] Ernst and Young, *European Biotech 94: A New Industry Emerges*, 1994.

[11.] Japanese figures compiled from Mark D. Dibner and R. Steven White, *Biotechnology Japan*, North Carolina Biotechnology Center, New York: McGraw Hill Publishing Company, 1989, p. 201. Ag-bio category includes Dibner's Animal Agriculture, Plant Agriculture, and Food Production categories. Suppliers include: Bioseparations, Biotechnology Equip, and Biotechnology Reagents. Chemical and Environmental includes: Biomass Conversion, Energy, Commodity Chemicals, Specialty Chemicals, and Waste Disposal/Treatment.

[12.] See "Introduction," *Foreign Development of Biotechnology in Japan and Western Europe*, The Institute for Biotechnology Information, North Carolina Biotechnology Center, Nov. 12, 1993.

[13.] In other words, American papers in the biological sciences were cited by world researchers almost two-fifths as many times as the average for all research papers in biology. From "Strongest Exports of US Researchers: Papers in Physical, Computer Sciences," *Science Watch*, Vol. 3 No. 7, Sept. 1992, pp. 1-2. Please note that while biotechnology is an important area of R&D, it is not a scientific discipline in its own right. In comparing national research capabilities, therefore, one is forced to use biology, medical science and their subdisciplines as indicators of research in "biotechnology."

[14.] Some of Japan's most influential papers are now coming from biochemistry, molecular biology, and pharmacology--all areas relevant to biotechnology. See "Targeting Biological Sciences, Japan Begins to Make its Mark," *Science Watch*, Vol. 2 No. 3, April 1991, pp. 1-2.

[15.] The figures for domestic patents are from the USPTO, as quoted in National Research Council, *Intellectual Property Rights and US - Japan Competition in Biotechnology: Report of a Workshop*, Washington, DC, 1991, p. 30. Figures for world wide patents are from the Office of Industries, U.S. Trade Commission, "An Overview of Commercial Biotechnology in the United States" Staff Research Study 18, 1991, p. 61. See also the Pharmaceutical Manufacturer's Association, "In Development" and "Europe R&D Falls Behind" as quoted in *An Overview of Commercial Biotechnology in the United States*, Office of Industries, U.S. International Trade Commission, Staff Research Study 17, 1991, p. 61.

[16.] The Japanese Patent Office allows only a single claim to be filed with each patent application, as opposed to the US system in that each patent application can contain several claims. The result is that Japan issues over twice as many patents as the United States even though its population is half that of the United States.

[17.] There is a difference in the definition of biotechnology in Japan and the United States. Biotechnology is loosely defined as the use of biological organisms in industrial production. In Japan, little distinction is drawn between "old" and "new" biotechnologies. Old biotechnology includes agriculture, breeding, and fermentation technologies that have been around for thousands of years, as well as the fermentation of antibiotics that dates to the middle of this

century. New biotechnology, that is the use of genetically altered organisms (i.e., recombinant organisms) for the production of new entities, dates from the early 70s. The US tends to define "biotechnology" as meaning the latter, Japan loosely includes both old and new technologies.
[18.]Based on Angier, Natalie, "Surprising Role Found for Breast Cancer Gene," *New York Times*, March 5, 1996, pp. C1, C3.
[19.]Lynn Ziegler.
[20.]Ernst and Young, 1993, p. 53.
[21.]ibid.
[22.]The Federal Drug Administration (FDA) overseas the safety and efficacy of drugs, foods, cosmetics, diagnostics, medical devices, and animal and human food additives. The Environmental Protection Agency (EPA) overseas the safety of the environmental release of chemicals, pest control agents, air and water discharges, and hazardous waste disposal. The US Department of Agriculture (USDA), grants approval for animal vaccines, plant pests and derivatives, transgenic plants and animals.
[23.]For a more in depth review see "Biotechnology Drug Products," the Biotechnology Industry Organization, web site, January 1996.
[24.]See Ernst and Young, *Biotech 94: Long Term Value Short Term* Hurdles, p. 29-31, 1994.
[25.]Much of this section is based on material presented in Bénédicte Callan, *Who Gains from Genes? A Study of National Innovation Strategies in the Globalizing Biotechnology Markets*, Dissertation, University of California at Berkeley, 1995.
[26.]For a detailed exploration of why Japan wanted to promote biotechnology see Malcolm Brock, *Biotechnology in Japan*, Routledge: London, 1989, pp. 47-55.
[27.]I am grateful to Bob Uriu for his comment on this point.
[28.]See OECD Science and Technology Indicators, 1994, table 13-16 as presented in the US Congress, Office of Technology Assessment, *Multinationals and the US Technology Base*, OTA-ITE-612, Washington, DC: US Government Printing Office, 1994.
[29.]Recall that in the US the NIH that supports primarily basic research (it is both a research center and a grant making agency) accounts for three quarters of all US expenditures in biotechnology. In Japan the main supporter of basic research is the Ministry of Education, but it accounted for only 20 percent of public biotechnology expenditures in 1993.
[30.]For a discussion of early MITI research associations see Martin Fransman and Shoko Tanaka, "Government, Globalization, and Universities in Japanese Biotechnology," January 1995, Vol. 24 No. 1, pp. 14-49.
[31.]Of special interest is the Protein Engineering Research Institute (PERI), jointly sponsored with the Ministry of Posts and Telecommunications. PERI's work on the three dimensional function and structure of proteins is world class, and has made important contributions to the advancement of rational drug design. MITI's interests also include research projects, administered by the New Energy Development Organization, to study biotechnology's contribution to environmentally friendly energy alternatives and chemical production. Because of the importance of property rights in biotechnology, MITI now sponsors a larger number of research corporations than RAs.
[32.]Science, November 1996. Also Shiro Nagato, "MITI's Role for Japanese Research and Development in Science and Technology," *Bio Europe 1993*, BioEurope: Brussels, 1993, pp. 141-143.
[33.]In particular, Japan has recently has had more success at building new facilities than the US. Examples include the Super Kamiokande, the KEK B-Project, and the Heavy Ion Medical Accelerator in Chiba. See Dennis Normile, "Big Science is Booming in Japan," *Science* Vol. 271, February, 23, 1996, pp. 1046-1048.
[34.]One example of the chronic late entry of Japan is the human genome mapping project. The Japanese did not join the multinational project that was started in 1990. Only in 1995 did the Japanese government decide that deciphering the information found in gene sequences was worthy of a national project. A research corporation has been set up. But many believe that the effort is too small, and undertaken rather late in the game.

[35.]Some smaller companies have been created to supply chemicals and materials for larger firms, and there are a few subsidiaries of larger firms that are called biotechnology companies. But no research-intensive start ups have been created independently.
[36.]For a discussion of Japanese venture capital see James W. Borton, *Venture Japan*, Chicago: Probus Publishing Company, 1992.
[37.]For a very good discussion of Japanese funding and government policy in biotechnology see Gary Saxonhouse, "Industrial Policy and Factor Markets: Biotechnology in Japan and the United States," in Hugh Patrick, ed., *Japan's High Technology Industries*, Seattle: University of Washington, 1986, pp. 97-135.
[38.]Aoki argues, however, that the lack of start-ups is mitigated in Japan by the fact that Japanese corporations allow their employees to pursue innovative ideas, among other mechanisms, by "hiving off fully or partially owned subsidiaries." Aoki is suggesting that there are alternative mechanisms to invest in risky technologies without resorting to venture capital markets. See Masahiko Aoki, "The Macroeconomic Background for High-Tech Industrialization in Japan," in Ralph Landau and Nathan Rosenberg, eds., *The Positive Sum Strategy*, National Academy Press: Washington, DC, 1986, pp. 569-581.
[39.]For a discussion of researchers in Japan see Alfred Schidegger, "Biotechnology in Japan, Toward the Year 2000 and Beyond," TIBTECH, June 1991, Vol. 9, pp. 183-190. See also *Kagaku Gijutsu Youran*(Indicators of Science and Technology), Tokyo: Kagaku Gijutsuchou, Kagaku Gijustsu Seisaku Kyoku, 1993, p. 42.
[40.]See Daniel Okimoto, "The Japanese High Technology Challenge," in Ralph Landau and Nathan Rosenberg, eds., *The Positive Sum Strategy*, National Academy Press: Washington, DC, 1986, pp. 541-567.
[41.]See Mark Dibner, "Is Japan's Strategy of Strategic Alliances Losing Steam," *Venture Japan*, Vol. 3 No. 4, 1992, pp. 51-52.
[42.]From Greis, Dibner, and Bean, "External partnering as a response to innovation barriers and global competition in biotechnology," *Research Policy*, Vol. 24 No. 4, July 1995, pp. 624-625.
[43.]The importance of international licensing may drop as Japan becomes a generator of its own technologies. It is also important to note that an unspecified number of Japanese firms are no longer licensing from abroad because they terminated their biotechnology programs when commercial benefits were slow to materialize and Japan's recession reduced company spending.
[44.]See Martin Fransman and Shoko Tanaka, "Government, globalisation, and universities in Japanese biotechnology," *Research Policy*, Vol. 24 No. 1, January 1995, pp. 13-49.
[45.]See Martin Fransman and Shoko Tanaka for a discussion of the role of Japanese universities in Japanese commercial biotechnology. "Government, globalisation, and universities in Japanese biotechnology," *Research Policy*, Vol. 24 No. 1, January 1995, pp. 13-49.
[46.]Saxonhouse reports that in 1982 1,200 Ph.D.s worked in US biotechnology firms, while only 161 Ph.D.s engaged in biotechnology research worked for Japanese firms. op. cit., p. 126.
[47.]Note that in the US and Europe, established chemical and pharmaceutical companies have also taken this approach. They contract for rights to license innovation from that originate in start-ups and universities. Basic research in an untested fields is not attractive.
[48.]For a discussion of the strengths and weaknesses of Japanese firms in high-technology industries see Okimoto, op. cit.
[49.]Robert Swanson, "Entrepreneurship and Innovation in Biotechnology," in Ralph Landau and Nathan Rosenberg, eds., *The Positive Sum Strategy*, National Academy Press: Washington, DC, 1986, pp. 429-435.
[50.]According to Roberts and Mizouchi, Japanese firms hold over 60% of the world's patents in fermentation process technology. See Edward Roberts and Ryosuke Mizouchi, "Interfirm technological collaboration: the case of Japanese biotechnology," *International Journal of Technology Management*, Vol. 4 No. 1, 1989, pp. 43-61.
[51.]For a more in depth discussion of Japan's policy about rDNA technologies see Bénédicte Callan, *Who Gains from Genes? A Study of National Innovation Strategies in the Globalizing Biotechnology Markets*, Dissertation, U.C. Berkeley, 1995.

[52.] National Research Council, *Intellectual Property Rights and US-Japan Competition in Biotechnology: The Report of a Workshop*, Washington, DC: National Academy of Sciences, January 18, 1991.

[53.] The doctrine of equivalence holds that patents for innovations that perform substantially the same function in substantially the same way infringe even if the patent terminology does not literally infringe. A famous case is the Sumitomo-Genentech battle over a blood clot dissolution factor called t-PA. The only difference between the two products was a single amino acid (in a protein that has hundreds of amino acids) that caused no difference in clinical effects. Nevertheless the difference was enough for the patents not to be found infringing in Japan.

[54.] It is harder to bring an infringement case to court, and in 80 percent of the cases that are decided in Japan, the patents are found not be infringing. Courtesy of Jon Lindsay, Internet Patent News Service, December 4, 1994.

[55.] Generally, it is difficult to gauge the effect on innovativeness of different patent systems among industrialized countries. More specifically, because biotechnology is a relatively new field of technology there is a good deal of disagreement over the nature and extent of protection that should be granted even in the US. Clear doctrines have not yet emerged that would give companies more certainty.

[56.] Japanese firms have not so heavily concentrated on pharmaceutical applications of biotechnology because the plethora of ministry sponsored research groups pushed firms into several different types of mission oriented applications--be it energy, chemicals, environment, marine discovery, or health. In addition, the Japanese health insurance system made pharmaceuticals far less attractive an end product than the in the US. The Ministry of Health and Welfare caps pharmaceutical prices and periodically lowers the price of reimbursement for existing drugs. The idea is to force Japanese pharmaceutical firms to innovate by putting a premium price on new drugs, and at the same time, to keep the price of health care down (that has been done relatively successfully). But where firms in the US market do not have to contend with government mandated prices, firms in Japan can expect that the revenues over the lifetime of a product will gradually decrease. Pharmaceutical biotechnology, therefore, did not have the gold plated glitter in Japan that it had in the US.

[57.] Analysts of the biotechnology industries speak of "virtual integration," meaning that separate companies perform different aspects of research, development, marketing, and manufacturing. The sum total of their activities creates a virtually integrated production process rather than a vertically integrated corporation.

[58.] See Dibner, 1995, op. cit.

[59.] See Gary Pisano and Steven Wheelright, "Product Innovation Requires More Resources and Attention to Process R&D," *Genetic Engineering News*, Vol. 16 No. 1, January 1, 1996, pp. 4-33.

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