Japanese Biotechnology: New Drugs Industrial Organization, Innovation, and Strategic Alliances

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JAPANESE BIOTECHNOLOGY: NEW DRUGS
Industrial Organization, Innovation, and Strategic Alliances

I. INTRODUCTION

This working paper analyzes the dynamics of the Japanese pharmaceutical industry by focusing on the far-reaching impacts of the new biotechnology. More than two-thirds of the companies now investing in pharmaceutical biotechnology in Japan are traditionally non-pharmaceutical manufacturing firms. Massive efforts by outsiders to enter the market have dramatically increased the level of competitive pressure in the Japanese pharmaceutical market and have changed traditional norms of conducting research and development in that industry.

Although Japanese pharmaceutical companies historically enjoyed a high and stable profit under government protection and high barriers to market entry, now they face a growing, and more direct, competition from foreign companies and an increasing pressure to liberalize the domestic market. Structural changes may provide opportunities for foreign firms in the Japanese market. With growing competition from both domestic entrants and foreign companies, established Japanese firms are uneasy about the future. The Japanese pharmaceutical industry is undergoing structural changes that are forcing it to adapt new strategies that will affect both foreign pharmaceutical firms and the world-wide development of biotechnology, especially smaller U.S. companies.

Section II reviews the emergence and potential impacts of biotechnology on the pharmaceutical industry. Section III discusses the competitive status of the U.S. pharmaceutical industry with respect to Japan

and the industrial organization and performance of the Japanese pharmaceutical industry. It describes the current superiority of American firms over Japanese rivals. Section IV provides an update of the Japanese market by focusing on the structural changes caused by the new biotechnology and direct challenges from foreign firms. Such changes will affect performance of both domestic and foreign firms in Japan's pharmaceutical market. The Japanese market will likely be a major battle field for competition between Japanese and American and European drug makers, as well as Japanese new-comers. Japanese pharmaceutical makers are responding to current challenges by adapting a global strategy to cultivate the overseas market. Section V discusses factors affecting competitiveness in the industry, and Section VI analyzes the importance of strategic alliances between U.S. and Japanese companies, and considers these developments from the viewpoint of the opportunities they open for U.S. and European companies.

II. IMPACTS OF BIOTECHNOLOGY ON JAPAN'S PHARMACEUTICAL INDUSTRY

Biotechnology in the Pharmaceutical Industry

The pharmaceutical market is expected to be the first major target for companies investing in biotechnology. Five biotechnology-based pharmaceutical products have been introduced: human growth hormone, human insulin, alpha interferon, hepatitis beta vaccine, and most recently TPA (tissue plasminogen activator).[1] Genentech and Eli Lilly led in the development of human growth hormone (hGH), one of the first commercialized products to utilize biotechnology. In 1987, the U.S. FDA permitted Genentech to commercialize TPA, a heart-attack medicine long hoped to be the first biotechnology block-buster. Sales of biotechnology drugs are expected to reach $1 billion by the end of the 1990s. Various therapeutic and diagnostic products using monoclonal antibody techniques also have been introduced.

Today many Japanese non-pharmaceutical firms are attempting to enter the market through biotechnology. Non-pharmaceutical companies such as Toray (textiles), Ajinomoto (food), and Asahi Chemical are major players in Japanese biotechnology development. Toray introduced beta interferon, while Asahi Chemical is competing fiercely with Genentech in the development of TPA. Among 170 firms that have joined Japan's biotechnology industry association (BIDEC), more than half are traditionally non-pharmaceutical companies. Major chemical and food-processing firms in the U.S. have also tried to capture this new opportunity, for example Dow, Du Pont, Fluor, W.R. Grace, Martin Marietta, Monsanto, and Eastman Kodak. Kodak, the major photographic company, is one of the most aggressive American companies

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1. Other biotechnology-based drugs likely to be introduced within the next two years are Interleukein-2, an anti-cancer drug, and EPO (Erythropoietin).

trying to diversify through biotechnology. The firm acquired several small biotechnology companies, and in 1986 established its own pharmaceutical division. In January 1988, Kodak made a successful bid for Sterling Drug, Inc. Among 261 biotechnology-related patents in the pharmaceutical/health field issued by the U.S. Patent Office to U.S. companies, 36% were issued to non-pharmaceutical firms.[2] Thus although the extent is greater in Japan, entry of non-pharmaceutical companies to the biotechnology-related pharmaceutical market can be observed in other countries. Therefore, some of the issues we discuss here may also be relevant to the U.S. and Europe.

A Mixed Bag

BRIE's first biotechnology study, "The Japanese Challenge in Biotechnology: Industrial Policy," pointed out that biotechnology can be used in the production of various products in many sectors of the economy.[3] Some applications are genuinely new products, but many are identical to existing products. The same principle applies within the pharmaceutical industry, and today most products duplicate existing products.

By utilizing biotechnology, we can produce naturally available but rare substances, such as interferon and insulin, both less expensively and in larger quantities. Some pharmaceutical products being developed through the monoclonal antibody technique may be characterized as "new."

Because biotechnology is merely one method of manufacturing pharmaceutical products, and because pharmaceutical makers have always tried to develop products and are familiar with the difficulties involved,

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2. Facts at a Glance, Pharmaceutical Manufacturers Association, Washington, D.C. (1987), p. 33.

3. See Akihiro Yoshikawa, Japanese Challenge in Biotechnology: Industrial Policy, University of California, Berkeley, BRIE Working Paper No. 29, September, 1987.

established pharmaceutical companies in general have a conservative attitude toward biotechnology's potential impact on the industry. The following statement, from a senior executive in a pharmaceutical giant, captures this view:

> I simply want to emphasize that recombinant DNA technology...is a mixed bag to the pharmaceutical industry. In some cases, it's revolutionary. In others, it is simply an efficient tool that will have little or no effect on manufacturing, waste disposal, and quality control procedures." (A statement by Theodore Cooper, Executive Vice President, the Upjohn Company.)[4]

A leading executive in the U.S. biotechnology industry remains high-spirited, however. Dr. Ron Cape, Chairman of the Cetus Corporation, stated that we would see "the avalanche" of biotechnology products by the late 1990s.

Schumpeterian Creative Destruction

The emergence of biotechnology may remind one of the notion of Creative Destruction, as described by Joseph Schumpeter:

> The opening up of new markets, foreign or domestic, and the organizational development from the craft shop and factory to such concerns as U.S. Steel illustrate the same process of industrial mutation--if I may use that biological term--that incessantly revolutionizes the economic structure from within, incessantly destroying the old one, incessantly creating a new one. This process of Creative Destruction is the essential fact about capitalism. It is what capitalism consists in and what every capitalist concern has got to live in."[5]

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4. Theodore Cooper, "The Impact of Biotechnology on the Pharmaceutical Industry," in A. Teich, M. Levin, and J. Pace, eds., Biotechnology and the Environment: Risk and Regulation, American Association for the Advancement of Science (1985).

5. Joseph Schumpeter, Capitalism, Socialism, and Democracy, Harper (1942).

Those who successfully and swiftly utilize new technologies may be able to ride the wave of Creative Destruction, and those who fail to do so may disappear.6

Schumpeter mentions that revolutionary innovations and products often are introduced by "new men, new firms."7 The history of innovation provides many examples. Movies were not introduced by people in the theater business; automobiles were introduced by newcomers to the transportation business. Personal computers were first introduced by Apple, not by the industry giant, IBM; semiconductors were developed by small start-up companies, not established vacuum-tube makers; and in biotechnology it was Cetus and Genentech, start-up ventures, that first captured emerging opportunities in biotechnology-based drugs.

However, the pharmaceutical industry traditionally was regarded as rather stable due to its high entry barriers. Syntex Corporation was the last small firm that, in the 1950s, grew to be a major drug maker through its successful birth control pill.8 Investors in biotechnology are hoping that they can create and ride the wave of Creative Destruction to become winners in the pharmaceutical competition.9

Although it was these small start-up companies that contributed to the advancement of biotechnology in the U.S., in Japan it was large diversified

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6. A similar analogy between the emergence of biotechnology and the Schumpeterian Creative Destruction was mentioned by Martin Kenney, "Schumpeterian Innovation and Entrepreneurs in Capitalism: A Case Study of the U.S. Biotechnology Industry," Research Policy 15 (1986), pp. 21-31.

7. Joseph Schumpeter, Business Cycle (1939).

8. Andrew Pollack, "Gene-Splicing Payoff is Near," The New York Times (June 10, 1987).

9. Many of these firms were established by entrepreneurial university scientists. More than 50% of biotechnology companies established between 1971 and 1980 were founded by academic scientists.

firms that aggressively entered the race to develop biotechnology in the early 1980s.

The Year 2000: Strategic Goal

Japanese officials have predicted that during the next 20 years, biotechnology will affect the pharmaceutical market more significantly than other areas.[10] They stated that, although the potential impacts of biotechnology may be greater in energy and agriculture, these applications will take longer to develop. It is estimated that in Japan biotechnology will underlie more than 40% of total pharmaceutical sales by the year 2000.[11] One explanation for Japan's emphasis on pharmaceutical biotechnology is its changing age structure. It is expected that the proportion of people in Japan over the age of 65 will rise from 10.1% in 1985 to more than 20% by the year 2010.

Whether biotechnology will underlie 40% of the market is debatable. There has been a tremendous amount of uncertainty as well as optimistic hype concerning biotechnology. Because of the great fear concerning cancer, many wish to believe biotechnology can provide the ultimate cure. For example, only a few years ago interferon was called the "magic bullet" that could destroy cancer. The potential market was expected to be as great as $1 billion a year. It was later discovered that interferon was less effective than people had hoped. But similar hype has been repeated for other biotechnology-based anti-cancer drugs, such as TNF.

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10. The government of Japan has specified biotechnology as a key technology for future competitiveness for Japan. Yoshikawa, op. cit., p. 8-11.

11. An American analyst maintained that it would contribute to only 5% of total sales in the pharmaceutical market in 1990. Douglas McCormick, "Pharmaceutical Markets for the 1990s," Bio/Technology (January 1987). See also Yoshikawa, op. cit.

However, if biotechnology will underlie 40% of the market in the year 2000, those who can utilize the technology most effectively will likely dominate the market. This possibility alone makes biotechnology an important factor in determining a firm's competitiveness in the pharmaceutical industry.12

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12. Although in the immediate term, biotechnology will affect industries such as pharmaceuticals and food processing, further on it will impact agricultural and electronics. Rather than being an industry in and of itself, biotechnology will affect numerous economic sectors, and may soon become crucial for maintaining a competitive edge in those sectors. See Yoshikawa, op. cit., and Michael Borrus and James Millstein, "Technological Innovation and Industrial Growth: A Comparative Assessment of Biotechnology and Semiconductors," paper prepared for the U.S. Congress, Office of Technology Assessment, March, 1983.

III. STATUS OF COMPETITIVE EDGE -- DRUGS

American pharmaceutical companies' views toward their Japanese rivals can be summarized as follows:

(1) The Japanese are not good enough to invade the U.S. market.

(2) The Japanese pharmaceutical market is, however, very difficult to invade.

In interviewing American pharmaceutical executives, I found them confident of U.S. technological superiority over Japan in this industry. In fact this is one of the few high-technology areas in which the U.S. maintains a favorable balance of trade with Japan. However, one must remember that in the past there was a very limited Japanese effort to cultivate any international markets, but that is changing (see Section IV).

American executives also believe that the Japanese pharmaceutical market has been overly protected and extremely difficult to enter. Since the early 1970s, various foreign countries have criticized the complicated government regulations governing Japan's pharmaceutical market. Although recent trade negotiations produced several positive steps toward opening the Japanese market (as discussed below), it will be several years before we can judge the effect of these liberalization measures.

In this section we focus on the existing pharmaceutical industry. We discuss in detail whether American confidence in its superiority can be justified, whether American firms can compete effectively in the Japanese market, and whether the U.S. can maintain its competitive advantage in this industry.

Pharmaceutical Industry

The total world-wide sales of U.S. pharmaceutical companies was about $32 billion in 1985.[13] The Japanese pharmaceutical market is second only to the U.S, representing about $26 billion (4 trillion yen) in 1985. The pharmaceutical market is relatively small: for instance, in 1985 General Motors had sales revenues of more than $95 billion, and IBM had more than $50 billion.[14]

Although the market is segmented by product, one successful product can generate a great return. In 1986, the top branded pharmaceutical product, Zantac, achieved more than $1 billion in world-wide sales. Tagamet, introduced by SmithKline, also achieved $1 billion in sales world wide.

Among the top five branded products in 1986, three were produced by American companies. Among the top 50 brands, 23 were American. This may support American executives' confidence regarding their Japanese rivals; only five of the top 50 brands were Japanese. Many European companies, such as Hoffman La Roche, Hoechst, Glaxo, ICI, and Sandoz, also enjoy greater market prominence than do Japanese firms.

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13. Facts at a Glance (1986), op. cit., p. 4.

14. Ibid., p. 4.

Table 1. Top Branded Pharmaceutical Products (1986)

Rank	Product	Firm	Country	World-wide Sales ($ million)
1	Zantac	Glaxo	U.K.	1,081.0
2	Tagamet	SmithKline	U.S.A.	1,014.0
3	Tenormin	ICI	U.K.	713.0
4	Capoten	Squibb	U.S.A.	510.0
5	Feldene	Pfizer	U.S.A.	509.0
12	Krestin	Sankyo	Japan	333.8
14	Kefral	Shionogi	Japan	328.1
41	Perdipine	Yamanouchi	Japan	202.3
44	Shiomarin	Shionogi	Japan	197.9
48	Herbesser	Tanabe	Japan	185.2

Source: Pharmaceutical Manufacturers Association (1986).

The pharmaceutical industries in both the U.S. and Japan enjoy much greater profits than do other manufacturing industries. The average return on sales for pharmaceuticals in 1980 was 16.2% in the U.S. and 12.8% in Japan.[15] U.S. industries generally maintain much higher average returns on sales than do Japanese firms, even in sectors where they are losing market share. In 1980, the average return on sales in U.S. manufacturing was 9.1%, while it was 4.6% in Japan.[16] This is partly due to a difference in corporate financial policies. Whereas U.S. firms try to obtain higher profits and dividends to satisfy shareholders, Japanese firms place a

15. There is, however, controversy concerning whether rates of return were really as high as they appeared. Often rates vary widely by choice of profitability measure and depending on assumptions concerning accumulation and depreciation rates for R&D.

16. However, the Japanese pharmaceutical industry is relatively more profitable than its U.S. counterpart when compared with the corresponding manufacturing average.

greater emphasis on debt financing; they "pay less in dividends, borrow more, and grow faster than their U.S. competitors."17

Table 2. Profitability (Return on sales, in percent) for Pharmaceutical/All Manufacturing Industries

Year	U.S.	Japan
1980	16.2/9.1	12.8/4.6
1981	15.7/8.3	12.6/3.9
1982	16.3/6.9	12.7/3.8

Source: Japan Economic Almanac (1985).

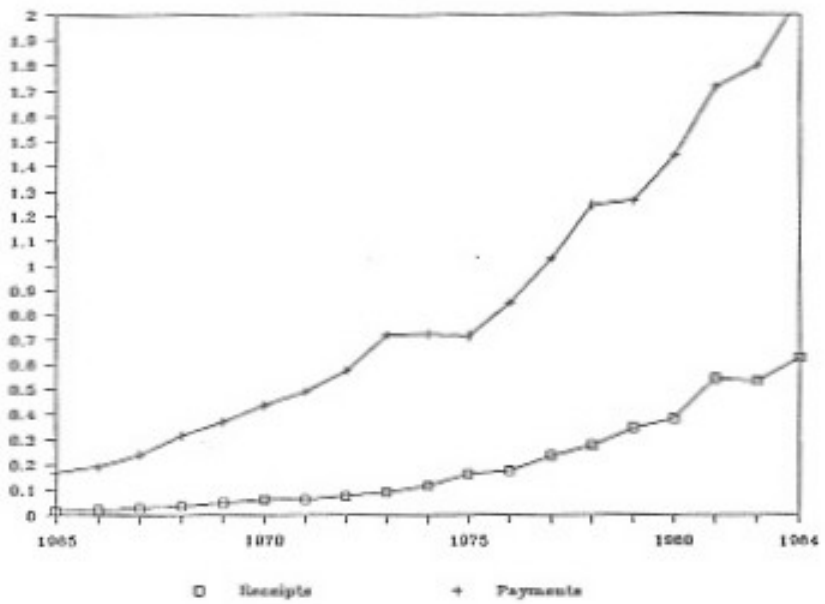
Technology Superiority of the U.S.

In the early years of biotechnology development, Japan depended heavily on technology from abroad. Like other Japanese industries, the pharmaceutical industry imported crucial technologies and perfected them. Figure 1 illustrates Japan's dependence on technology transferred from abroad. Figure 2 illustrates a similar dependence in pharmaceuticals.

17. James C. Abegglen and George Stalk, Jr., Kaisha, the Japanese Corporation, Basic Books, Inc., New York (1985), p. 14.

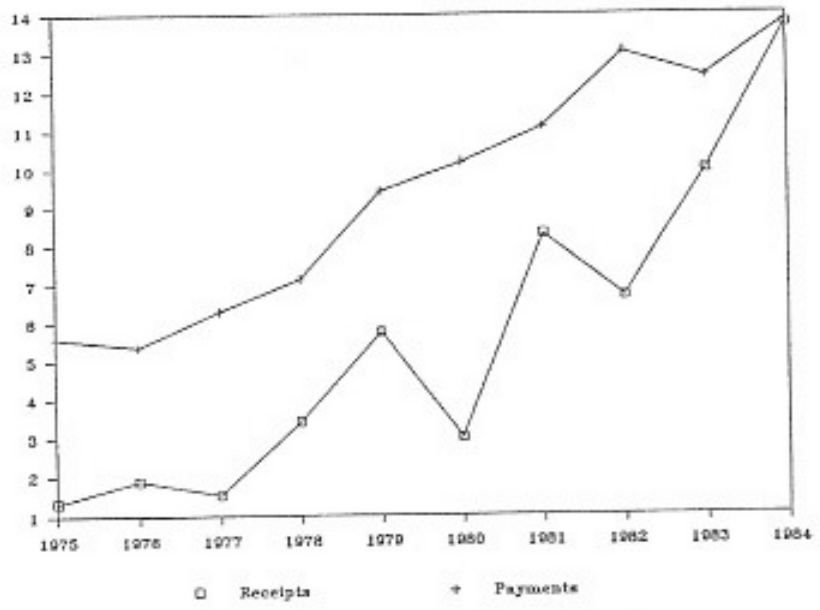
Figure 1. Technology Balance of Payments in Japan

($ billion)



Source: Kagaku Gijutsu Yoran, Kagakugijutsu-cho (1984).

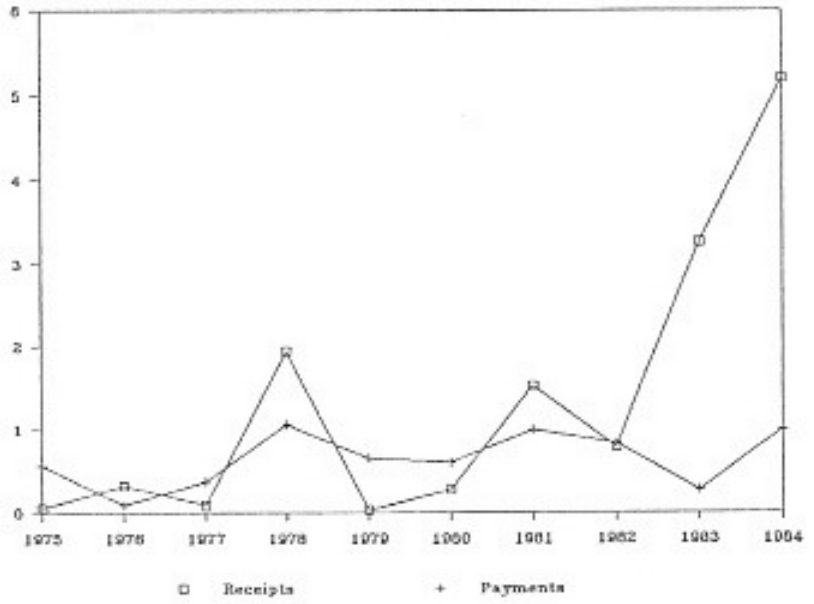
Figure 2. Technology Balance of Payments in Japan's Pharmaceutical Industry
(Billion Yen)



Source: Data Book 1986, p. 38.

In 1984, Japan realized a surplus in technology trade related to pharmaceuticals (see Figure 2). This could indicate the growing technological capability of Japan's drug makers. This trend of increasing pharmaceutical technology export is evident in the balance of payments for new contracts (see Figure 3).

Figure 3. Technology Balance of Payment in Japan's Pharmaceutical Industry--New Contracts
(Billion Yen)



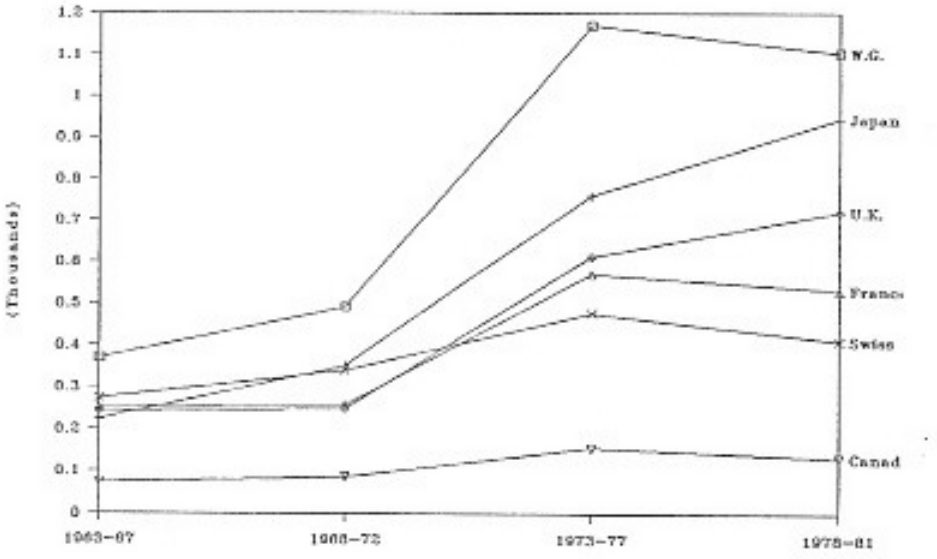
Source: Data Book 1986, p. 38.

Japan's increasing capability in pharmaceutical technology is also shown by the number of U.S. patents registered by Japanese drug makers. Japan is second in number of foreign-origin patents for drugs and medicines in the U.S. The Japanese share of chemical patents registered in the U.S. also doubled in the past decade.[18] Figure 4 shows the increasing Japanese prominence in pharmaceuticals. The Japanese presence in the U.S. market also has grown. For example, the second biggest selling drug to U.S.

18. Japan's share of U.S. patents doubled during the period between 1977 and 1986. Chemical and Engineering News (July 27, 1987), p. 37.

hospitals market is Cefobid, an antibiotic marketed by Pfizer, Inc., which was licensed from Toyama Chemical of Japan.19

Figure 4. Foreign-Origin Patents in the U.S.
Drugs and Medicines



Source: Fact Book, Pharmaceutical Manufacturers Association, p. 3-24.

The competition between American and Japanese firms has intensified. Among the products introduced by Merck, acclaimed America's "miracle company," is an anticholesterol drug called Mevacor.[20] However, the firm was in close competition with Japan's Sankyo in developing this drug. Sankyo independently developed a similar chemical compound and filed its patent in Japan four months before Merck. Sankyo would have been called a

19. John Heins, "Take Two of These and Call Tokyo in the Morning," Forbes (March 24, 1986), pp. 179.

20. John Byrne, "The Miracle Company," Business Week (October 19, 1987).

"miracle company" today if the firm had had better luck. (This race between Merck and Sankyo also illustrate a potential conflict due to different nations' different patent systems.[21])

Between 1961 and 1980, 353 new drugs were introduced in the U.S. market; only 155 new drugs were introduced by Japanese firms.[22] However, Japanese firms introduced 41 new drugs between 1981 and 1983, whereas American firms introduced only 24--another indication that U.S. firms might be losing their competitive edge.[23]

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21. Whereas the U.S. uses a "first to invent" patent system, Japan uses a "first to file" system. Sankyo filed its patent a month prior to Merck in the U.S. Under the "first to file" system, the patent in both the U.S. and Japan would have been granted to Sankyo. However, in the U.S., Merck attained the patent by providing proof under the "first to invent" system. Sankyo had not kept precise records of its research to prove the date of invention, since such records are unnecessary in the "first to file" system. Without such records, the filing date was taken as the date of invention. Some in Japan have argued that the U.S.'s "first to invent" system functions as a non-tariff barrier to foreign firms. Nikkei Business, January 15, 1987, p. 97.

22. Mark Dibner, "Biotechnology in the American Pharmaceutical Industry: The Japanese Challenge," in Daniel Koshland, Jr. ed., Biotechnology: The Renewable Frontier, The American Association for the Advancement of Science (1986), p. 270.

23. Dibner, op. cit., p. 268.

Table 3.
New Pharmaceutical Products (1961-83)
By Country of Origin

country	number of new products by year 1961-80	1981	1982	1983(est.)
Japan	155(10.3%)	15(23.1%)	9(23.1%)	17(35.4%)
West Germany	201(13.4%)	8(12.3%)	1(2.6%)	7(14.6%)
United States	353(26.6%)	9(13.6%)	9(23.1%)	6(12.5%)
France	271(18.1%)	3(4.6%)	5(12.8%)	5(10.4%)
United Kingdom	---(-----)	3(4.6%)	-(-----)	3(6.2%)
Switzerland	109(7.3%)	6(9.2%)	4(10.2%)	-(-----)

Numbers in parentheses indicate shares of total numbers of new pharmaceutical products introduced for the years indicated.

Source: Nomura Research Institute, "Trends of Biotechnology in Japan," Tokyo, July 1983, quoted in Office of Technology Assessment, U.S. Congress, Commercial Biotechnology: An International Analysis (1984), p. 74.

The Japanese Market: Isolation

Unlike the automobile and semiconductor industries, exports represent only a small fraction (about 3%) of Japan's pharmaceutical output (see Table 4). The percentage of imports is even smaller. Thus the Japanese pharmaceutical market is relatively isolated.

In terms of quantity, pharmaceutical imports exceed exports in Japan. In 1985, Japanese imports of pharmaceuticals totaled 310 billion yen, whereas exports amounted to only 93 billion yen. As opposed to Japan's deficit in the pharmaceutical trade, the U.S. has been realizing a surplus, which in 1986 was $764 million. In short, pharmaceuticals are one of the few high-technology products in which the U.S. is experiencing a favorable trade balance and Japan is not.

Table 4.

Imports and Exports in Pharmaceuticals (Japan)
(billion yen, percentage)

year	production (billion yen)	exports	%	imports (billion yen)	%	balance
1970	1025	24	2.3	78	4.0	-54
1975	1792	37	2.1	131	7.3	-94
1980	3482	67	1.9	244	7.0	-177
1985	4027	93	2.3	310	7.7	-217

Source: Boeki Tokei (Foreign Trade Statistics), various years.

The small proportion of imports may suggest that the Japanese pharmaceutical industry is protected. Policies set by the Ministry of Health and Welfare (MHW) concerning new drug approvals and clinical testing have also inhibited entry into the Japanese market.24 (Details of government regulation will be discussed in Section IV.) On the other hand, the small export ratio may imply that Japan's pharmaceutical manufacturers lack the competitive advantage of her other industries. Isolation of the Japanese market is also apparent in comparison with other countries (see Table 5).

24. Clinical testing had to be conducted with Japanese subjects. Faced with growing criticism from foreign governments and businesses, the Japanese government recently modified these policies, as discussed below.

Table 5.

Pharmaceutical Exports by Country

Country	Pharm./ export ratio	Total export/ GNP ratio
France	21	18
Italy	17	21
Japan	2	14
U.K.	55	26
U.S.	11	8
W.G.	24	26

Note: The pharmaceutical-export ratio is the ratio of pharmaceutical exports to total domestic pharmaceutical production. The total export/GNP ratio is the ratio of the value of the total pharmaceutical export to GNP.

Source: The Competitive Status of the U.S. Pharmaceutical Industry, Table 2-17.

Table 6 shows that the U.S. is Japan's largest trade partner in pharmaceuticals. The U.S. is both the leading exporter and importer in the world pharmaceutical trade. Japan is the second leading importer of pharmaceutical products.

Table 6. Pharmaceutical Trade in Japan (1985) (million yen, %)

Exports			Imports		
Country	Value	Share	Country	Value	Share
USA	33,914	25.7	USA	119,729	38.0
W. Germany	10,333	7.8	W. Germany	49,593	15.7
Taiwan	8,093	6.1	Swiss	32,401	10.3
France	7,710	5.8	UK	16,796	5.3
South Korea	7,195	5.5	Italy	14,885	4.7
Others			Others		
Total	131,839	100.0	Total	315,298	100.0

Source: Data Book 1986, Japan Pharmaceutical Manufacturers Association, p.15.

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Domestic Market: Highly Competitive

Although the pharmaceutical market is relatively isolated and protected by the government from foreign competition, the level of competition within the domestic market is high. According to one report, there are approximately 1700 drug manufacturers in Japan.[25] About 70% of them specialize in making drugs, while 30% are diversified companies.[26] Small firms (fewer than 100 employees) represent 90% of these manufacturers, although they account for less than 20% of the value of Japan's pharmaceutical production. Many of these small companies manufacture traditional drugs sold by door-to-door peddlers.[27]

Figure 5 shows the decreasing level of concentration in Japan's pharmaceutical market.[28] It should be noted that the market is less concentrated than the U.S. market. Although the number has been declining since the late 1970s, the eight largest firms in the U.S. accounted for almost 50% of the market in 1982; the top 10 firms in Japan accounted for only about 35% of the market.[29]

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25. Standard and Certification Systems Concerning Drugs in Japan, Yakugyo Jiho Co., Ltd. (1985), p. 17.

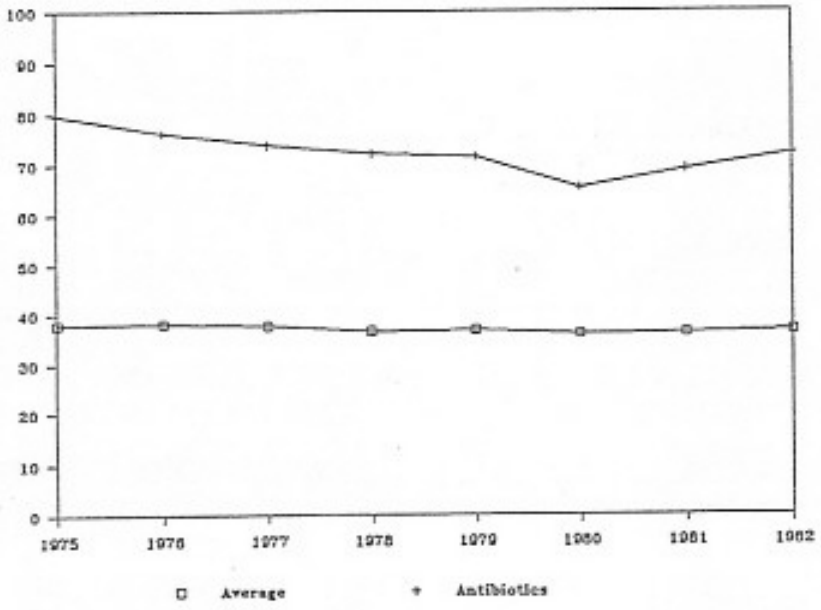
26. Ibid., p. 17.

27. This reflects the historical development of the Japanese pharmaceutical industry. See Pharmaceutical Administration in Japan, 3rd Edition, Yakuji Nippo. Ltd., Tokyo (1986), p. 119.

28. Ibid., p. 123.

29. However, the level of market concentration differs widely among pharmaceutical products in Japan. The antibiotics market exhibits a dramatically higher rate. Although the average level of concentration in pharmaceutical production was only 36.2 in 1982, it was 72.2 for antibiotics. The share of the top three firms, Shiongi, Takeda, and Fujisawa, alone was more than 40%. Ibid., p. 139.

Figure 5. Concentration Ratio (Top 10 Firms)



Source: Pharmaceutical Administration in Japan (1986).

Japanese Companies: Size and R&D

Japanese pharmaceutical firms are smaller than their U.S. counterparts. In 1983 the total sales of the 10 largest U.S. pharmaceutical firms was $16.7 billion; it was $6 billion in Japan.[30] In 1983, while 11 American pharmaceutical firms had sales of more than $1 billion, only one Japanese firm, Takeda, attained the $1 billion mark.[31] Tables 7 and 8 describe the top 10 American and Japanese pharmaceutical firms; Table 9 summarizes the differences between the two groups.

30. Dibner, op. cit., p. 270.

31. Ibid. However, the rapid appreciation of the Japanese yen since 1983 has increased the relative size of Japanese pharmaceutical firms.

Table 7. Top 10 Japanese Pharmaceutical Firms (1985)

Company	Sales (Y= mill)	Sales ($ mill)	R&D ($ mill)	R&D Intensity (%)
1. Takeda	474,852	3,166	202.7	6.4
2. Sankyo	243,136	1,621	106.7	6.6
3. Fujisawa	196,675	1,311	124.7	9.5
4. Shionogi	185,005	1,233	106.7	8.7
5. Tanabe	148,426	990	76.7	7.7
6. Eisai	135,398	903	108.0	12.0
7. Taisho	109,789	732	47.3	6.5
8. Yamanouchi	107,511	717	71.3	9.9
9. Chugai	100,179	668	64.7	9.7
10. Daiichi	88,536	590	66.7	11.3
TOTAL	1,789,507	11,930	975.5	Average 8.2

Source: Diamond's Japan Business Directory (1986). The exchange rate used was $1 equal to 150 yen.

Table 8. Top 10 American Pharmaceutical Firms (1985)

Company	Sales ($ mill)	R&D ($ mill)	R&D intensity (%)
1. Johnson & Johnson	6,421	471	7.3
2. American Home Prod.	4,685	217	4.6
3. Bristol-Myers	4,444	262	5.9
4. Pfizer	4,025	287	7.1
5. Merck	3,548	426	12.0
6. Abbott Laboratories	3,360	241	7.2
7. Eli Lilly	3,271	370	11.3
8. Smith Kline	3,257	310	9.5
9. Warner-Lambert	3,200	208	6.5
10. Baxter Travenol	2,355	128	5.4
Total	38,566	2,920	Avg. 7.6

Source: Moody's Industrial Manual (1986).

Table 9. Summary of U.S. vs Japan (1985)
Top 10 Pharmaceutical Firms

	U.S.	Japan
Total sales ($ million)	38,566	11,930
Total R&D expenditures ($ million)	2,920	976
Average R&D Intensity (%)	7.6	8.2

Source: Diamond's Japan Business Directory (1986), Moody's Industrial Manual (1986).

Although Japanese pharmaceutical firms may seem a little more R&D-intensive than their American counterparts, R&D spending by the top 10 American firms far surpasses that of Japanese firms in terms of absolute value.[32] The total R&D expenditure was $2,920 million for the 10 American firms, but only $976 million for the Japanese.

32. Although the R&D intensity is higher for the top 10 companies in Japan than in the U.S., the industry average is higher for the U.S. companies. In 1986, among more than 100 firms belonging to the American Pharmaceutical Manufacturers Association (PMA), the average R&D intensity was 15% of sales, whereas it was 10.3% for members of the Japanese Pharmaceutical Manufacturers Association (JPMA).

IV. STORM IN A GREENHOUSE

We mentioned above that the concentration ratio is lower in Japan, and that more than 1700 companies compete in the Japanese pharmaceutical market. These facts suggest that the Japanese market is highly competitive. However, there are various non-tariff barriers to foreign firms entering the Japanese market. Thus competition in the Japanese market may be characterized as a "delicately maintained orderly competition" in that there is fierce competition in a domestic market shielded from foreign competition.

The Japanese pharmaceutical industry has been protected from the threat of foreign pharmaceutical giants by various governmental regulations. The industry was in fact contained in a well-maintained greenhouse intended to coddle it. However, direct challenges from foreign companies and massive entries of biotechnology hopefuls have started a storm in this greenhouse.

The First Storm: New Entrants

Pharmaceutical firms entered the biotechnology race relatively late (see Figure 6). Many traditionally non-pharmaceutical companies (textiles, food, and chemicals) decided to enter the pharmaceutical market through biotechnology. Their aggressive attitude may be partly explained by adverse conditions in their primary business.[33] The textile and chemical industries in Japan often are regarded as "structurally depressed." Companies in the textile industry, such as Toray, Teijin, and Asahi Chemical, are some of the

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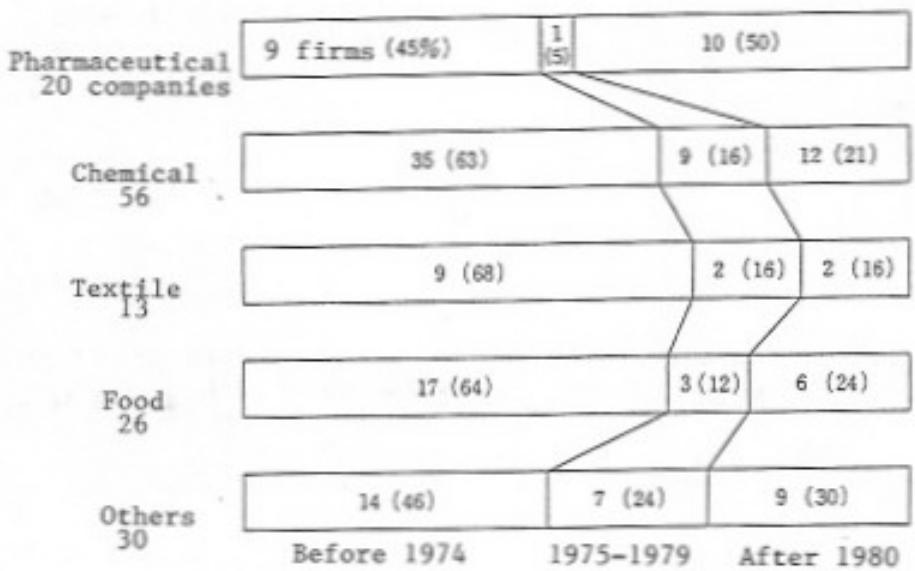
33. Abegglen and Stalk provide insight into Japanese firms' efforts to cultivate new markets. They observed a "strong bias" to grow and a desire to survive. In the West, it is the smaller, less-established firms that exhibit this urge to grow. They conclude that the Japanese are preoccupied with a fear of falling behind their competitors and thus make riskier ventures. See Abegglen and Stalk, op. cit., Chapter 1.

most aggressive entrants to biotechnology (see Figures 6 and 7 and Table 10). They hope to survive Schumpeterian Creative Destruction by integrating their old know-how with newly developed technologies aggressively transferred from American biotechnology start-up companies.34

Figure 6.

Biotechnology R&D in Japan, According to Time Started



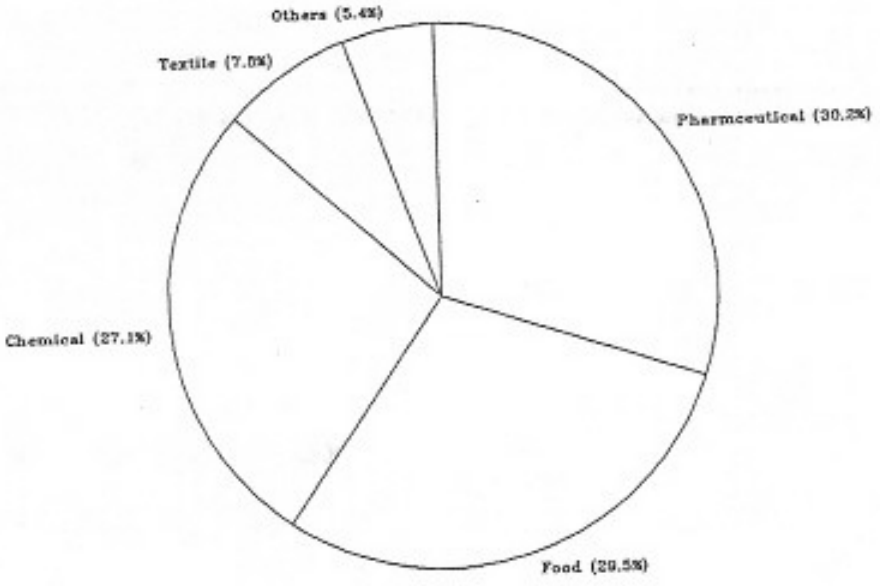
Source: 21 Seiki o Kizuku Baioindasutorii, MITI (1984), p. 221.

34. Yoshikawa, op. cit., pp. 35-41.

Table 10. Three Types of Firms in Pharmaceutical Biotechnology

Specialized pharmaceutical makers	Takeda, Sankyo, Chugai, Fujisawa, Yamanouchi, etc.
Diversified pharmaceutical makers	Kyowa Hakko, Meiji Seika, Toyo Jozo, etc.
New entrants	Kirin Brewery, Suntory, Asahi Chemical, etc.

Figure 7. Pharmaceutical Biotechnology Industrial Background



Source: Trigger (May 1985).

Mitsubishi Chemical established the Mitsubishi Kasei Institute of Life Science in 1971, two years before the invention of recombinant DNA technique and five years before the establishment of Genentech. It is said that the firm spent one-third of its 3.5 billion yen R&D budget for projects related to life science.

Companies in food processing have valuable knowledge and experience in the "old" biotechnology of fermentation. Companies such as Kirin, Ajinomoto, and Suntory are now investing heavily in biotechnology. Some of them have became the world's leading manufacturers of amino acids. Ajinomoto has been the largest integrated food processing firm and leads in advanced amino acid technology, including pharmaceutical applications.

Japanese firms dominate the world amino acid market.[35] Through amino acids manufacturing, many Japanese firms developed processing technologies such as the bioreactor, invented by a Japanese scientist at Tanabe Pharmaceutical. Such processing technology is said to be crucial for the scaled-up production of biotechnology-based products. (This issue will be discussed further in Section V.)

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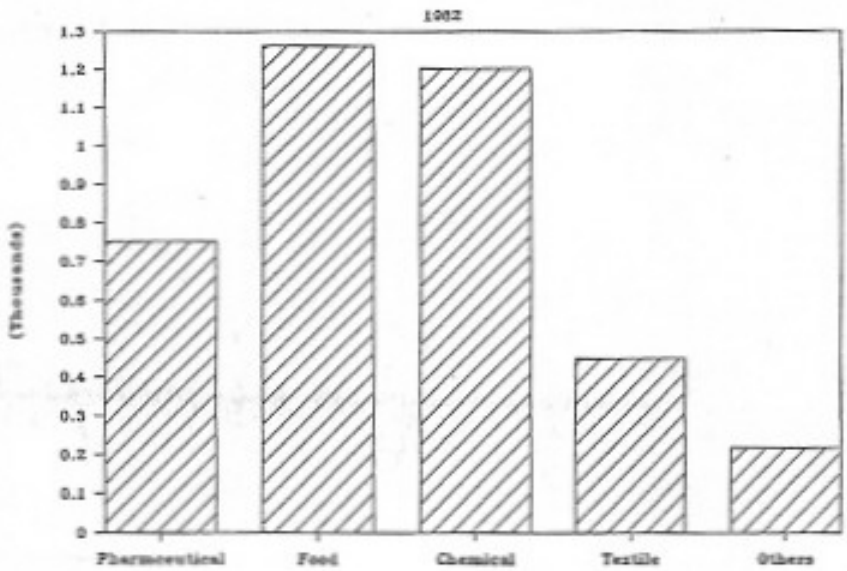
35. Amino acids are used in various industrial applications, such as food/feed additives and medical/nutritional supplements. In terms of quantity, 65% of amino acids are used for food, 31% for feed additives, and 4% for pharmaceutical applications. However, pharmaceutical applications represent as much as 30% of the total monetary value. Today the amino acid market is dominated by the Japanese, although European firms dominate some high value added products. It is hoped that biotechnology will lower production costs and further promote use of amino acids, i.e. as feed additives. More than 70% of glutamic acid has been provided by major Japanese firms: Ajinomoto, Kyowa Hakko, Asahi Chemical, and Takeda Chemical. The Japanese control more than 90% of the market for lysine, for which demand is growing due to its increasing use as a food/feed additive. The OTA Report (1981) stated that the projected market size for amino acids would reach $900 million (at 1980 values) by the year 2000, compared with today's market size of $300 million. (Only four amino acids are included here.)

Through its traditional silk business and silkworm breeding, Gunze has accumulated know-how in anti-growth and anti-cholesterol agents, which can be applied to the commercial development of new health care products.[36] Figure 8 shows the level of accumulated know-how related to biotechnology in various Japanese industries.

Figure 8. Number of Biotechnology Patents



Source: MITI, 21 Seiki o Kizuku Baio Indasutorii (1984).

It should be noted that when penicillin was introduced in the late 1940s, many firms rapidly entered the pharmaceutical market.[37] What happened with penicillin resembles the recent phenomenon of aggressive

36. John Elkington, The Gene Factory: Inside the Genetic and Biotechnology Business Revolution, Carroll & Graf Publishers, Inc., 1985, p. 147.

37. Osamu Inoguchi, Baio Bijinesu no Genba, Diamond, 1986, p. 100.

entries of newcomers into the pharmaceutical market. Companies such as Toray, a textile firm, and Nippon Kayaku, a manufacturer of explosives, entered the pharmaceutical market during this period.[38] These diversified companies are among the most aggressive in biotechnology and are larger than traditional pharmaceutical companies (see Table 11).

Table 11

Sizes of Firms Investing in Pharmaceutical Biotechnology

	Sales	Bio.R&D
*Kirin	1,151,762	2,800
*Mitsubishi Chemical	800,250	NA
*Asahi Chemical	765,292	5,000
*Ajinomoto	447,570	NA
*Suntory	761,500	NA
**Kyowa Hakko	233,000	10,000
**Meiji Seika	202,294	NA
***Takeda	474,852	850
***Sankyo	243,136	NA

Sales: Total sales in 1985 in million yen.
Bio.R&D: Biotechnology-specific R&D expenditure in 1985 in million yen.
Source: BIDEC Kaiin Yoran (1986)

* New entrant to pharmaceutical market
** Diversified pharmaceutical manufacturer
*** Established pharmaceutical firm

New entrants are both larger and more biotechnology-intensive than leading pharmaceutical companies such as Takeda and Sankyo. Kirin and Asahi Chemical spent much more money in their pursuit of biotechnology than did

38. Nikkei Baiotech, Sekai no Biokigyo 500 sha, 1986. DuPont diversified in a similar manner. Pharmaceuticals account for more than 40% of sales for Meiji Seika, the top confectionery firm, which has ties with Merck. Toyo Jozo is an alcoholic beverage manufacturer, but pharmaceuticals account for approximately 50% of its sales. Forty percent of Kyowa Hakko's sales are related to pharmaceutical products.

Takeda, an established drug makers. These powerful entrants are adding tremendous market pressure.

With their financial "deep pockets," the new entrants are rapidly catching up with established drug makers. In terms of pharmaceutical patents filed in Japan in 1985, companies such as Sumitomo Chemical and Ajinomoto were as innovative as pharmaceutical companies such as Yamanouchi and Green Cross (see Table 12). Government policies also encourage chemical and food-processing companies to diversify through biotechnology (section V will discuss this further).

Table 12.

Pharmaceutical Patents Filed in Japan (1985)

	Company	Total	anti-cancer	cardio-vascular
Established Pharmaceutical	Takeda	79	20	14
	Otsuka	64	6	35
	Fujisawa	66	7	15
	Green Cross	49	8	16
	Yamanouchi	43	5	18
Foreign	Hoechst	69	0	23
	Merck	63	0	23
	Bayer	61	0	22
	Pfizer	39	0	10
	Roche	32	10	0
New/Diversified Pharmaceutical	Sumitomo Ch.	41	12	0
	Ajinomoto	42	17	8
	Kyowa	39	11	0
	Asahi Chem.	28	18	8
	Teijin	35	6	14

Source: Toshio Itoh (1987).

Table 12 shows that new entrants are specializing in anti-cancer drugs, rather than more conventional cardiovascular and digestive drugs.[39] In fact, Japanese drug makers today are world leaders in new antibiotic and cardiovascular drugs. Table 13 summarizes Japanese companies' efforts to develop biotechnology-based drugs.

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39. Although many Japanese firms in biotechnology have emphasized development of anti-cancer medications, such as interferons and interleukein-2, as their prime R&D goals. the commercial returns may be greater in less spectacular products, such as human growth hormones. See Bio/Technology, Vol. 5 (February 1987), p. 116, and also Chemical and Engineering News, July 20, 1987, p. 31. Human growth hormones are estimated to have an 80% probability of generating $300 million annually in the U.S. alone. Although development of growth hormones doesn't involve the same amount of uncertainty as does the development of anti-cancer drugs, Japanese firms haven't aggressively pursued it. Almost all the major firms trying to capture the biotechnology-based growth hormone market in Japan are Japan Eli Lilly, Japan Nordisk, and Sumitomo Pharmaceutical. Sumitomo imported technology from Kabi Vitrum (Sweden) and started marketing human growth hormone in Japan in 1986. This lack of interest may be because Japan entered biotechnology relatively late, after growth hormones had been developed. See Baio Bijinesu, Nikkei Sangyo Shinbun (Tokyo, 1987), p. 69.

Table 13. Biotechnology Drug Development in Japan

Product	Japanese Company	R&D Partner
Alfa Interferon	Sumitomo Pharm.	Wellcome
	Takeda	Hoffmann-La Roche
	Yamanouchi	Schering-Plough
	Mochida	Hayashibara
	Otsuka	Hayashibara
Beta Interferon	Toray	Inhouse
	Mochida	Inhouse
	Kyowa Hakko	
Gumma Interferon	Shionogi	Biogen
	Toray	Daiichi/Genentech
	Meiji Seika	G.D. Searle
Interleukein-2	Ajinomoto	Inhouse
	Takeda	Inhouse
	Shionogi	Biogen
	Yoshitomi	Genex
TNF	Asahi Chemical	City of Hope
	Dainippon Seiyaku	Inhouse
	Suntory	Biogen
EGF	Earth/Otsuka	Inhouse
	Wakunaga	Inhouse
	Takeda	Inhouse
EPO	Kirin	Amgen
	Chugai	Genetics Institute
Hepatitis beta vaccine	Banyu	Merck
	Shionogi	Merck
	Green Cross	Biogen
	Takeda	Inhouse
	Mitsubishi Chem.	Genentech
GCSF	Chugai	Inhouse
	Kirin	Amgen
TPA	Kyowa Hakko	Genentech
	Mitsubishi Chem.	Genentech
	Fujisawa	Biogen
	Yamanouch	Damon
	Toyobo/Daiichi	Integrated Genetics
	Asahi Chemical	Kowa

The Second Storm: Foreign Firms

There recently occurred a crucial change in Japan's regulation of the commercial relationship between foreign and domestic firms. Whereas the first storm increased domestic competition, the second is changing the position of foreign firms.

Until the mid-1970s, direct investment by foreign firms in Japan was severely restricted under the Foreign Exchange Control Law. In order to manufacture or import drugs, any foreign or domestic firm must obtain an approval (shonin) and a license (kyoka).[40] Foreign companies were not permitted to apply directly to obtain shonin, but needed the support of a Japanese firm.[41] A firm also had to submit clinical testing data to satisfy both efficacy and safety requirements. Until a recent negotiation between the U.S. and Japan, all clinical testing was to be conducted in Japan on native citizens. This requirement was criticized because it forced foreign firms to repeat costly testing already performed elsewhere.[42] Considering the difficulties involved in export and in direct investment, it was an unavoidable choice for foreign firms to license their technologies and

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40. Whereas an approval is an official recognition that a drug is considered both effective and safe, a license certifies (1) that establishments producing or importing the drug meet appropriate safety and manufacturing standards, and (2) that their board members are legally able to serve in that capacity. Report on Medical Equipment and Pharmaceuticals Market Oriented, Section-Selective (MOSS) Discussion, U.S. Department of the Treasury, 1986, p. 30.

41. Subsidiaries of foreign companies could apply directly. Many foreign firms established their Japanese branches after relaxation of the Foreign Exchange Control Law.

42. In the so-called Market-Oriented Sector-Selective (MOSS) Discussion, it was agreed that foreign clinical test data meet Japan's requirements except for items for which there are believed to be immunological and ethnic differences between Japanese and foreigners. Ibid. p. 4.

establish sales tie-up agreements with established Japanese pharmaceutical firms.

Throughout the years, many U.S. and European pharmaceutical firms established operations in Japan in order to acquire government approval for importing drugs; to gain access to users, such as large hospitals; and to develop contacts with government officials. The Foreign Exchange Control Law was modified in the mid 1970s, and in 1983 the Pharmaceutical Affairs Law (PAL) was revised to make it possible for foreign firms to make direct shonin application.

However, U.S. firms complained that foreign firms that previously had either licensed production in Japan or marketed through Japanese firms holding the shonin (approval) could not benefit from this change, because it applies only to new products.[43] In other words, foreign firms were stuck with Japanese "partners" even when "they held clear and legally demonstrable proprietary rights (e.g., patents) under Japanese business law."[44] Such difficulties were partially resolved by the recent Market-Oriented, Section-Specific (MOSS) Discussion. Today foreign firms can apply more direct, flexible, and aggressive strategies to the Japanese market.

Japanese firms that once enjoyed stable and "captive" business relationships with foreign firms have suffered some set-backs. Fujisawa suffered greatly when Ciba-Geigy decided to discontinue their sales tie-up arrangement, which was worth 12,000 million yen a year to Fujisawa.[45] Takeda's sales also declined when their tie-up with Ciba-Geigy was

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43. MOSS, op. cit., pp. 14-17.

44. Ibid., p. 14.

45. Diamond's Japan Business Directory 1986, p. 351.

suspended.[46] Japanese firms now face a more direct foreign challenge in the domestic market.

Merck & Co. is probably the most aggressive foreign pharmaceutical firm to enter the Japanese market. The firm acquired Banyu Pharmaceutical Co. and hired the ex-head of the Department of Antibiotic Substances at the National Institute of Health to manage its R&D division.[47] It also acquired Torii Pharmaceuticals in 1983.

Table 14 shows the performance of foreign-owned pharmaceutical firms. Although none were in the top 100 in Japan (in terms of declared income) in 1986, foreign firms enjoyed growth rates much higher than foreign-owned firms in other industries and higher than Japanese pharmaceutical firms.[48]

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46. Ibid.

47. Inoguchi, op. cit., p. 165.

48. Only seven foreign-owned firms were in th top 100 in Japan in 1986. They were Toa Nenryo Kogyo (22), IBM Japan (23), Arabian OIl (53), Mobil Sekiiyu (60), Nestle K.K. (85), Esso Sekiyu (87), and Coca Cola Japan (90). Takeda is the highest ranking Japanese pharmaceutical firm and is 59th in the list. Pfizer Taito is the highest ranking foreign-owned pharmaceutical firm in Japan, and it is 335th in Japan.

Table 14. Foreign Pharmaceutical Firms in Japan (1986)

Rank[1]	Company	Declared Income[2] (million yen)	Growth[3] (%)	Foreign Capital Ratio (%)
335	Pfizer Taito	9,484	108.1	100.0
374	Glaxo K.K.	8,611	453.1	100.0
391	Banyu Pharmaceutical	8,219	21.1	51.4
556	Bayer Yakuhin	5,856	125.4	75.0
626	Nihon Schering	5,268	56.5	100.0
737	Sandoz Pharmaceut.	4,425	86.3	100.0
815	3M Health Care	3,928	55.9	75.0
965	Nippon Boehringer Ingelheim	3,248	34.4	100.0
1037	Baxter Travenol	2,978	127.7	100.0
1339	Dainabot	2,262	48.3	60.0
1453	Japan Upjohn	2,090	----	55.0
1501	Int'l Reagents	2,037	53.9	36.5
1561	Bristol-Myers Lion	1,951	41.1	51.0
1589	Funai Pharmaceutical	1,920	35.7	57.6
1635	Miles-Sankyo	1,860	22.6	45.0

Source: Tokyo Business Today, July, 1987, p. 16.
(1) Ranking of firms based on their declared 1986 income in Japan.
(2) Declared income in 1986.
(3) Growth rate between 1985 and 1986.

Efforts by American companies to establish bases in Japan were not limited to large pharmaceutical and chemical firms. Smaller biotechnology firms, such as Genentech and Applied Biosystems, also have established direct subsidiaries (see Table 15). Genentech established its Japanese operation as early as 1982.

Table 15. Foreign Biotechnology Firms in Japan

Firm	Year
Genentech	1982
Amicon	1982
Applied Biosystems	1985
Damon Biotech Japan	1985
Endotronics Far East	1985
Genetics Institute	1985
DRG International Japan	1986
Liposome Japan	1986

Some major foreign pharmaceutical and chemical companies, such as Bayer and Du Pont, also have established facilities to conduct basic R&D in Japan.[49] In 1986 Upjohn announced its plan to establish a full-scale pharmaceutical research laboratory employing 400 researchers. Ciba-Geigy announced a similar plan.

The Storm Continued: Reductions in NHI Prices

Even though in principle firms can market drugs when they earn both approvals and licenses from the Japanese government, their actual sales depend on reimbursement under the National Health Insurance (NHI) scheme, which covers almost all the Japanese population. Reimbursement prices are determined by the Ministry of Health and Welfare (MHW) according to guidelines established by the Central Social Insurance Medical Council (Chuikyo). A prescription drug cannot be marketed unless its price is listed under the NHI system. Foreign firms argued that this situation created uncertainty in introducing new products to the Japanese market.[50]

49. Itoh, "Biotech Trends in the Japanese Pharmaceutical Industry," Bio/Technology, August, 1987, p. 799.

50. The MHW agreed to provide price listings more frequently as a result of the MOSS Discussion. Ibid., p. 8. This NHI reimbursement system has

The difference between the NHI price and the physicians' purchasing price is called the "doctor's margin," and is considered a source of income for medical doctors in Japan. Pharmaceutical makers have strong incentives to cut their prices so that physicians will prescribe their drugs. Competition among Japanese pharmaceutical makers to cut prices below the established NHI prices increases the unpredictability of profits.

Between 1980 and 1986, NHI pricing was cut by 44%, drastically squeezing the profits of pharmaceutical companies. The decision to lower NHI prices reflected the government's efforts to cut the "doctor's margin" because it was essentially a government subsidy to physicians. It also reflected the government's efforts to lower expenses in the face of a tremendous budget deficit.

Some argued that reducing reimbursement prices would hinder firms' incentive to innovate. However, although NHI prices have been cut, MHW pricing has been more favorable for new drugs. Japanese pharmaceutical companies' strategy is, therefore, to innovate products under the assumption that new products receive more favorable reimbursement prices. Thus NHI's policy to cut prices promoted innovative efforts: the firm that can innovate is the one that can survive.[51]

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been criticized by foreign companies primarily because: (1) The regulatory decisions (approval and licensing) are separated from NHI's pricing decision; thus there is a delay in entering the Japanese market. Such delays add costs because of the dynamic nature of the pharmaceutical industry. (2) The listings of NHI reimbursement prices are both irregular and infrequent. (3) The criteria and mechanism for setting the NHI reimbursement price are unclear.

51. Such a strategic emphasis on new drugs, however, might not encourage firms to conduct basic R&D to innovate "genuinely" new drugs. The pressure to rapidly introduce new products may result in greater efforts to create "new" drugs by chemical modification of existing products originally introduced by European or American firms.

After the Storm: Twenty Surviving Companies?

The major factors promoting a reorganization of Japan's pharmaceutical industry are an increased competition due to massive entries of firms investing in biotechnology and decisions by foreign pharmaceutical makers to discontinue their sales tie-up arrangements with Japanese firms and to enter the Japanese market directly. The government policy to cut the NHI price further enhanced competitive pressures. Faced with increasing competition, a pessimistic Japanese pharmaceutical executive stated that only 20 out of 1700 companies currently manufacturing pharmaceutical products would survive the century.[52] The statement was probably designed to encourage bureaucratic interventions to "protect" established pharmaceutical makers from "bullying and disorderly" conduct by newcomers and foreign companies. However, Japan's pharmaceutical market is likely to face major reorganization and internationalization within the next few years.

Globalization of Pharmaceutical Industry

One effect of the competitive pressure on Japan's pharmaceutical companies is their increasing attention to the global market. Although the industry once was largely domestic, many firms have begun to aim at the international pharmaceutical market. Japanese drug makers believe that an offense is the best defense--to cultivate the international market is the key to survival. The cut in NHI prices also promoted a more world-wide perspective.[53]

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52. Nikkei Business, December 9, 1985, p. 9.

53. The foreign pharmaceutical market is not easy to enter due to high entry barriers (e.g., contacts with medical doctors). Thus, the extent of globalization by the Japanese will be less than in the case of semiconductors.

Major Japanese pharmaceutical companies have been quick to establish joint venture partnerships with American companies to produce and market their drugs in the U.S. Fujisawa established a joint sales-tie up with SmithKline to market Fujisawa's antibiotic in the U.S.; Takeda and Abbot are jointly training a U.S. sales force.[54] Forming such partnerships instead of simpler licensing agreements, Japanese companies can gain useful market know-how and access. Whereas the royalty for a licensing is merely 2% to 7% of sales, a joint marketing agreement can entitle a Japanese firm to keep 50% of all profits.[55] However, some express hesitation about such ventures. A senior executive at SmithKline stated that such joint venture partnerships could end up as a Japanese company, as Japan would eventually buy majority control.[56] Needless to say, this scenario is familiar to executives in California's Silicon Valley.

Ad Hoc or Strategic R&D?

The emergence of biotechnology seems to have created a myopic environment in pharmaceutical R&D. Traditionally, companies in the pharmaceutical as well as chemical industries were well aware of the importance of patents and careful that their R&D efforts not infringe on existing patents. In other words, they wanted to be certain that they could commercialize their inventions. Pharmaceutical companies invested a great amount of money and manpower to study other firms' patents before making an

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54. John Heins, op. cit., pp. 178.

55. Ibid., pp. 180.

56. Ibid. John Heins also stated that the most vulnerable American firms toward such Japanese control are companies that "skimp on research spending to boost quarterly earnings or have a poor current record of developing their own new products." Ibid, pp. 180.

R&D commitment. This cautious attitude toward research, however, seems to have changed with the emergence of biotechnology, not only in Japan but in other countries as well.

A U.S. patent attorney criticized recent heated pursuits of new biotechnology-based drugs by asserting that "many biotechnology companies...have plunged into product development without adequate resolution of patent questions."[57] Firms are investing heavily in developing biotechnology-based drugs that ultimately may not be marketable.[58] Whereas such seemingly "ad hoc" behavior is more typical of smaller specialized firms, we can observe similar behavior among large Japanese firms investing in biotechnology. A senior executive at Kyowa Hakko described this simply as "a very strange phenomenon."[59]

Another hint of "irrationality" may be observed in companies that conduct R&D on products for which there is little hope of recovering their investments. For example, today more than 50 companies, many of them Japanese, are trying to develop interferon. Although the market for interferon once was estimated to be as large as $1 billion, today it is estimated to be as little as $50 million world-wide. Walter Gilbert, a Nobel Prize winner who later managed Biogen, stated that the company's criteria for conducting R&D was whether the firm potentially could attain $100 million in sales.[60] Assuming that the firm could capture one-third of the world market, the criterion is $300 million in sales world wide. A simple calculation shows that interferon does not meet this criterion.

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57. A statement by Bertram Rowland, "Biotech Industry Moving Pharmaceutical Products to Market," Chemical & Engineering News, July 20, 1987. p. 18.

58. Ibid.

59. Nikkei Biotechnology, Bio-Intelligence, May 18, 1987.

60. Elkington, op. cit., p. 67.

A senior vice-president at Hoffmann-LaRoche defended their interferon research by calling it a catalyst: "It has facilitated most of what we know about identifying such molecules and producing large amounts that we can study. Down the road, many of the new drugs will be developed the way we're developing interferon."[61] Thus some R&D investments could be regarded as a necessary sunk cost. However, Japanese companies' slowness in retreating from interferon projects may also reflect a certain rigidity in management.[62]

There is some indication that firms may readjust their corporate attitudes toward biotechnology. Nihon Kayaku and Toyo Jozo discontinued R&D on alpha interferon; Green Cross retreated from gamma IFN; and Fujisawa ended its TNF study.[63] Kyowa Hakko also suspended its interleukein-2 study.[64] The next few years may bring a mass exodus, rather than entry, of companies.

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61. Ibid., p. 91.

62. Nippon Kayaku started its interferon program in 1981 but terminated it at the end of 1983. A General Manager who questioned the feasibility of the interferon project spent six months gaining internal consensus to withdraw from the interferon project. In order to avoid internal conflicts and opposition from those involved in the project, such informal consensus gathering, nemawahi, is important within Japanese corporate culture. Nikkei Business, November 12, 1984.

63. Nikkei Bionenkan, p. 20.

64. Bio Bijinesu, p. 192.

V. FACTORS AFFECTING COMPETITIVE POSITIONS AND CORPORATE RESPONSES

This section briefly outlines several factors that affect competitive positions of new biotechnology entrants and foreign firms with respect to established Japanese pharmaceutical companies.

(1) Intangible Good: Advantage of Established Players

In Japan, close contacts with physicians, especially in major medical schools and hospitals, are crucial to the successful introduction of new drugs. Physicians act both as potential prescribers and as partners in developing a product. A reliable relationship with doctors is necessary for collecting data to develop a product and for clinically testing its effectiveness. Close contacts with medical doctors are also important to successfully market a product. The higher ratio of general management and selling expenses to total expenses for drug companies is due partly to drug makers' promotional expenses to impress physicians.

Although the firms currently entering pharmaceuticals through biotechnology, such as Kirin Brewery and Suntory, had no established contacts with medical doctors, they have tried to develop such ties quickly, and have the financial resources to do so. Asahi Chemical formed a study group for TNF by recruiting the head of Nagoya Memorial Hospital and researchers from medical schools.[65]

Some new entrants also have tried to gain access by conducting joint product development with established pharmaceutical companies. Examples are partnerships such as Toyobo-Daiichi Seiyaku, Mitsui Toatsu Chemical-Mitsui Pharmaceutical, and Asahi Chemical-Kowa.

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65. Inoguchi, p. 46.

Because many of the new entrants had difficulty establishing ties with physicians, some decided to concentrate instead on products for which close ties with doctors are less crucial, such as monoclonal self-test kits to determine pregnancy. Others, hoping to build on their expertise in fermentation technology, are trying to capture a niche in industrial biotechnology, as by manufacturing amino acids.

(2) Basic R&D

Although Japan has been praised for its ability to improve and commercialize existing technologies, many believe that Japan lacks innovative ability. America's innovative ability is the basis for drug makers' optimism that the U.S. can maintain its lead over Japanese rivals. We have already noted that U.S. companies spend much more money on R&D than do the Japanese. However, the Japanese difficulty in promoting innovation goes far beyond financial limitations.

In addition to its $530 million-plus R&D budget, Merck, the "miracle company," provides its scientists the maximum level of freedom and flexibility in performing research.[66] Scientists from various backgrounds are encouraged to cooperate and interact. By giving "free rein to its best and brightest," and providing an informal "college-like" environment, Merck generated its "miracle."[67] With its life-long employment and seniority systems, Japanese R&D can be characterized as static and rigid rather than dynamic and open. Such a static R&D environment especially hinders young

66. Byrne, op. cit., pp.86.
67. Ibid.

scientists.[68] Thus the innovative superiority of the U.S. will remain an important factor in maintaining a competitive advantage in pharmaceuticals.

Japanese firms, both established drug makers and newcomers to the market, are aggressively trying to gain access to basic R&D conducted in the U.S. by, among other things, providing financial support to American universities and research institutes.[69] Hitachi Chemical developed ties with the University of California, Irvine, and Suntory has provided financial support to Rockefeller University.[70] Green Cross established ties with the University of California, while Wakunaga tried to develop a relationship with City of Hope Medical Center.[71]

(3) Importance of Financial Stability

Although many firms entered biotechnology R&D competition to make a profit, and although initial entry seemed relatively easy, commercialization has proven difficult. As we observed in the U.S., relatively little capital is required to start a biotechnology operation. However, this doesn't mean that the distance between a basic scientific discovery and its commercialization is shorter in biotechnology than in other industries. In order to introduce a new drug, it takes as much as $100 million and 10 years of commitment.[72] Figure 9 shows the long path from initial research to

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68. This issue has been widely debated in Japan recently after Professor Tonegawa of MIT, a native of Japan, earned a Nobel Prize. He openly maintained that he was able to realize his scientific achievement in the free academic environment abroad, and could have not realized in Japan's rigid research environment.

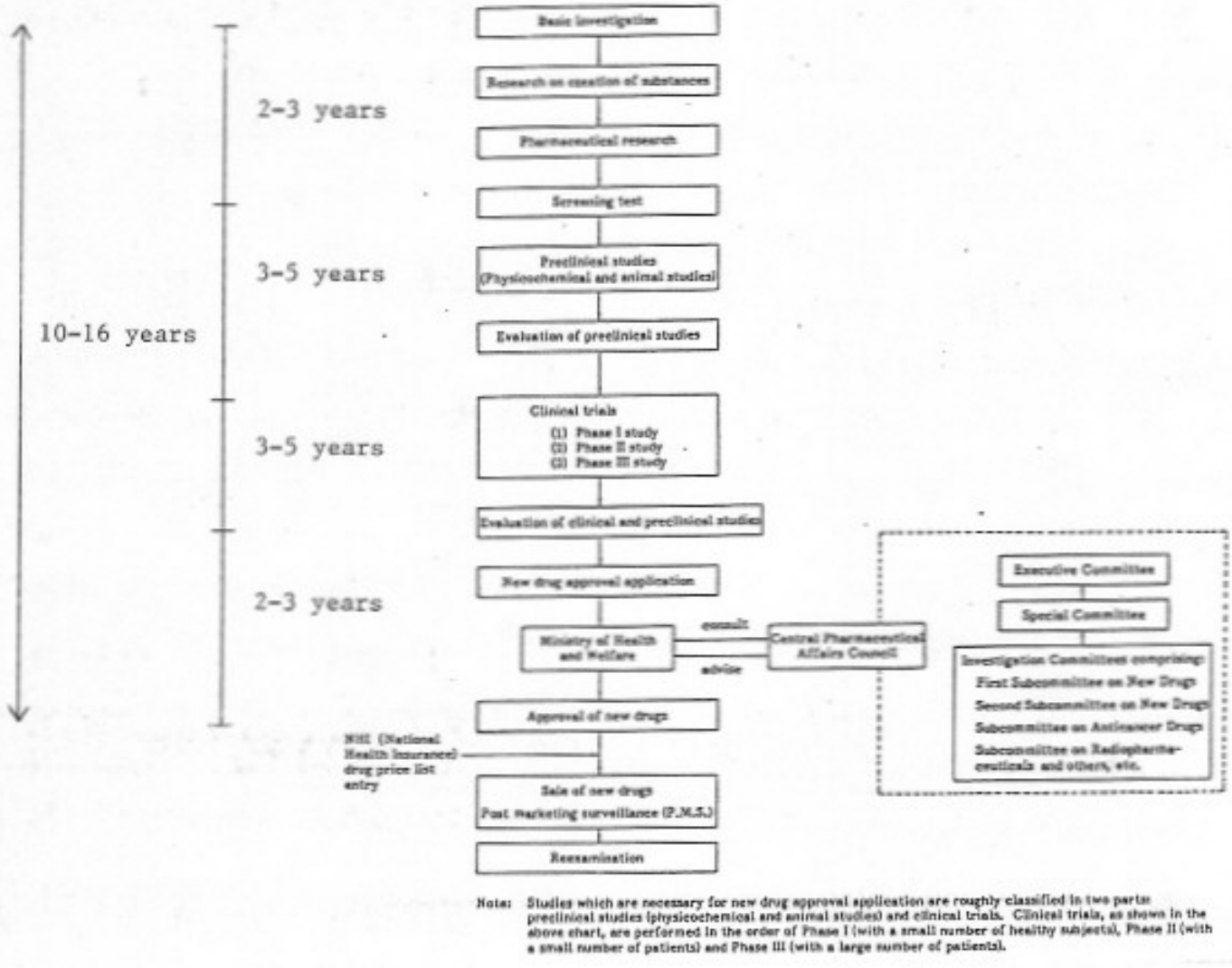
69. Japanese firms are not the only ones establishing such ties: Hoechst, a West German company, gives money to Massachusetts General Hospital.

70. Ibid.

71. Baio Bijinesu, op. cit.

72. Many firms investing in biotechnology-based pharmaceuticals had hoped that approvals of regulatory agencies (FDA in the U.S., and MHW in

Figure 9. Stages in Developing a New Drug



Note: Studies which are necessary for new drug approval application are roughly classified in two parts: preclinical studies (physicochemical and animal studies) and clinical trials. Clinical trials, as shown in the above chart, are performed in the order of Phase I (with a small number of healthy subjects), Phase II (with a small number of patients) and Phase III (with a large number of patients).

Source: Standards & Certification Systems Concerning Drugs in Japan, Yakugyo Jiho, (1985), p.39, and Nikkei Business (December 22, 1986).

Japan) would be easier for biotechnology products than for traditional pharmaceuticals where these new products were essentially identical to natural proteins. However, such an optimistic expectation was appropriate only to a few cases of simple proteins, such as human growth hormone and insulin. For products such as TPN and interleukein-2, obtaining governmental approval would be at least as difficult as for conventional pharmaceutical. Genentech's difficulty in obtaining a government approval illustrates this well. See Baum (1987), p. 13.

final approval.

The development of anti-cancer drugs, such as interferon and TNF, faces the especially great uncertainties involved in cancer research.73 In order to market a product successfully, a firm not only needs to introduce the product at the right time, it must also introduce the right product. One market analyst characterized the uncertainty with a comparison to football: developing a next-generation drug is like throwing a long pass--can you throw the pass? will there be anyone out there to catch it? When making the initial investment, it is difficult to know what will be the most appropriate product in 10 years. Therefore, resources and stability are extremely important.

A quick look at the success rate of new drugs indicates the high risk of pharmaceutical development (see Table 16). Only one in 7167 chemical compounds developed by Japanese firms achieved commercialization and approval for sale. Additional uncertainties involved in gene manipulation may further complicate the development of new biotechnology-based drugs.

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73. Chemical & Engineering News, July 20, 1987, p. 31.

Table 16.

Success Rates for New Pharmaceuticals

	Number of Chemical Compounds	Accumulated Success Rate
Number of Compounds synthesized	494,550	
Number developed	329	1:1503
a) in house	189	
b) licensed	140	
Number Approved	69	1:7167
a) in house	34	
b) licensed	35	

Source: Data Book 1986, p. 33.

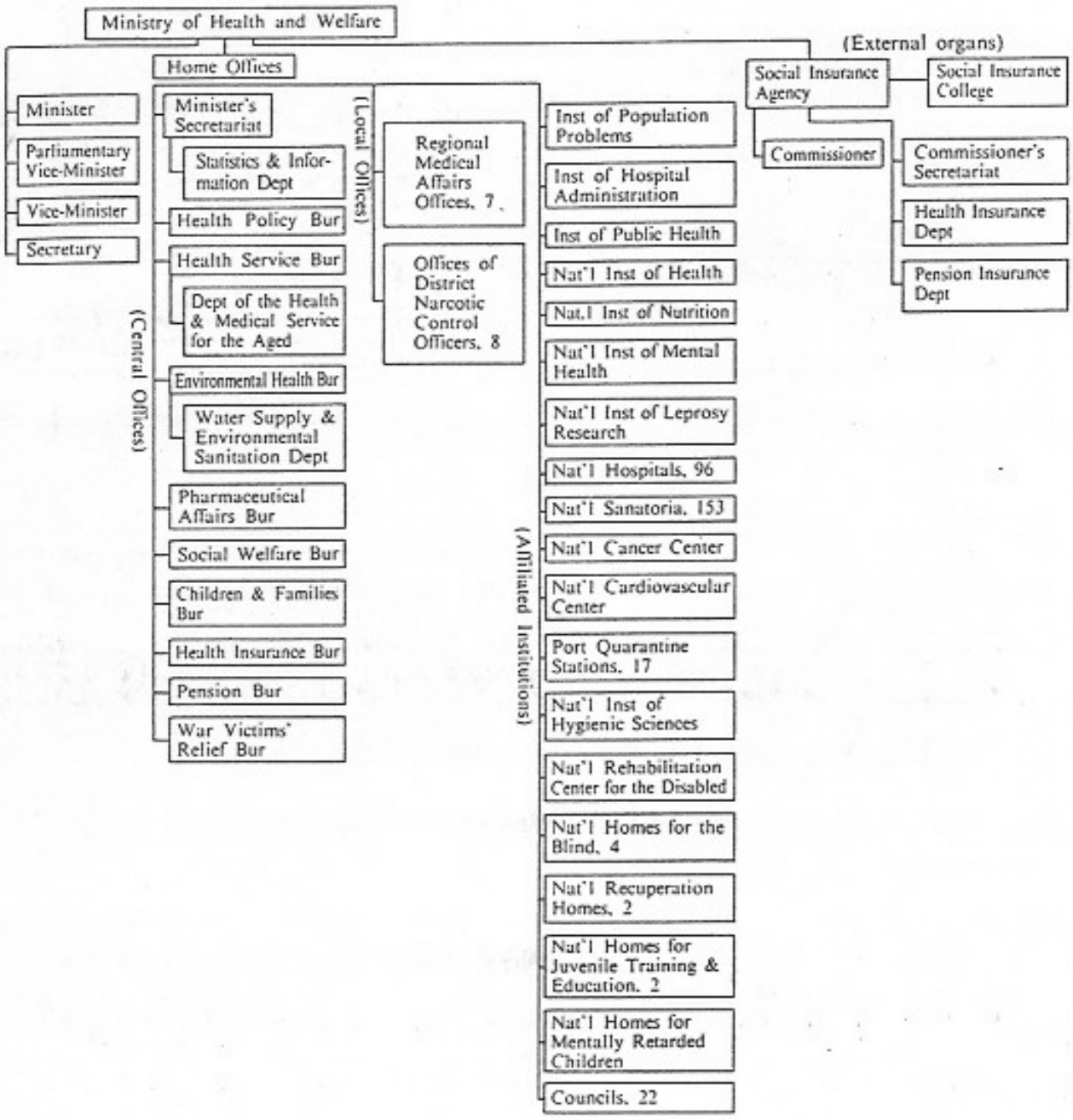
(4) Government Support

In the U.S., more than $10 billion was spent on pharmaceutical R&D in 1984, approximately two-thirds of which was funded by the federal government. Japan spent about $3.7 billion in the same year, and the share of government funding was about 50%.

Japan's Ministry of Health and Welfare (MHW) is the primary regulatory body in public health and welfare. One of its bureaus, the Pharmaceutical Affairs Bureau, provides guidance and regulation of the production, distribution, testing, and research of drugs, cosmetics, and medical devices. The Pharmaceutical Affairs Law (PAL) provides the legal framework for governing pharmaceutical products in Japan (see Figure 10).

Japanese industrial policy also affects the competitiveness of U.S. firms with respect to Japanese. The champion of Japan's industrial policy, the Ministry of International Trade and Industry (MITI), identified

Figure 10. Organization of the Ministry of Health and Welfare



Source: Pharmaceutical Administration in Japan (1986).

biotechnology as one of the key technologies for the future.[74] In order to promote biotechnology R&D, the government of Japan has introduced various policies, both traditional and experimental.[75] In 1986, the Ministry of Health and Welfare (MHW) established the Human Science Foundation to promote cooperative R&D in pharmaceutical biotechnology among private companies, universities, and government research institutes. In 1981 MITI established a similar program, the Next Generation Project, and encouraged cooperative R&D among private companies. In 1985, MITI also introduced the Key Technology Center, based on quasi-venture capital, to finance high-technology R&D. It financed the Protein Engineering Research Center (PERI). The study of protein structure is said to be essential to developing the next generation of pharmaceutical products.

One interesting characteristic of MITI's biotechnology programs should be mentioned. Although pharmaceutical applications are said to be the primary focus of the Japanese effort in biotechnology, only one established pharmaceutical company, Takeda, was involved in MITI's joint research association. Among 14 companies belonging to the association, 10 are chemical companies.[76] This indicates MITI's strong commitment to transform the declining chemical industry into a new biotechnology-based industry.[77] This governmental encouragement will also likely enhance chemical companies and likely affect competitive positions of both domestic and foreign pharmaceutical firms.

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74. Two other technologies targeted are new material and next generation micro-electronics technologies.

75. For a detailed review of Japanese policy to promote biotechnology, see Yoshikawa, op. cit.

76. Ibid., p.21.

77. Ibid.

Finally, in order to encourage fundamental research and to promote a more dynamic research environment, the government of Japan has introduced some experimental research programs. One, the Frontier Research Program, was designed to promote the participation of young scientists. Research projects are designed to be long-range (15 years), and in order to create a dynamic Western-style research environment, some projects are led by American and European scientists.

(5) Fermentation and Bioreactor

One of Japan's strength in biotechnology is its processing technologies, i.e., bioprocess and bioreactor. Bioreactors are vessels in which a bioprocess takes place. These processing technologies, based on traditional fermentation techniques, are important for scaled up production of biotechnology-based products. Previous writings have maintained that the Japanese advantage in biotechnology is due primarily to this superiority in bioprocessing technologies.78

This Japanese "advantage," however, should be considered carefully. Production cost will be a trivial part of the cost of high value added pharmaceutical products, i.e., many anti-cancer medicines. Despite R&D expenditures of perhaps $100 million, production cost may represent only one or two percent of the price. The key for success is an innovative ability to introduce new biotechnology-based pharmaceutical products, rather than producing cheaper. Even though low production costs may help Japanese companies in low value added industrial biotechnology products (amino acids, enzymes), superior process know-how alone will not guarantee Japan's success in developing next-generation pharmaceutical products.

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78. See for example, Commercial Biotechnology: An International Analysis, Office of Technology Assessment, U.S. Congress (1984).

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VI. STRATEGIC ALLIANCES

Mark Dibner's study indicated that the number of commercial relationships between Japanese firms and U.S. biotechnology firms (primarily smaller specializing firms) has declined since the peak year of 1982, although the number of such relationships involving large U.S. corporations increased during the same period.[79]

There seem to be two explanations for this declining number of partnerships between with American biotechnology companies. One is that Japan has graduated from its initial learning stage and is less dependent on technology imported from the U.S. A 1987 survey of Japanese firms investing in biotechnology showed that more than 50% regarded Japan as second to the U.S. in biotechnology.[80] However, the survey also showed Japan's increasing confidence in the race to develop biotechnology, and was markedly different from a similar survey taken two years previously. More than 10% stated that Japan had already surpassed the U.S., although no firm rated Japan number one in 1985.[81] The second explanation is that U.S. firms are more reticent to license technologies to Japanese firms now that they see the threat of future competition.[82]

In summary, it can be said that Japanese firms are becoming more selective in buying biotechnology from U.S. firms. They still wish to

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79. Mark Dibner, "An Analysis of Partnerships," in Bio/Technology, October 1987, p. 1029.

80. "Japan Nearing U.S. in Biotech Research: Poll," The Japan Economic Journal, October 17, 1987, p. 12.

81. Ibid.

82. Although many U.S. biotechnology executives have expressed such cautious views, it is not certain whether such an attitude can prevail in the long run. Since many smaller biotechnology firms lack financial resources, they adopted a strategy to finance their operations by conducting contracted research for larger companies. They functioned essentially as industrial laboratories to larger companies. Yoshikawa, op. cit., p. 42.

import technology, but no longer in an indiscriminate manner. At the same time, biotechnology companies that offer valuable technologies, which Japanese companies may wish to acquire, are becoming more financially secure and also more concerned about future challenges from Japanese firms.

Alliances with Japanese Firms

Executives of foreign biotechnology firms have complained that they have had difficulty establishing long-term strategic alliances with Japanese companies.

Japanese firms sought to acquire the basic know-how of American biotechnology. They expected to learn little about processing technologies from smaller biotechnology-specializing companies. They believed that they could learn the basics and then, by themselves, master and commercialize technologies. Thus most commercial relations between U.S. and Japanese firms were not partnerships, but rather involved technology transfer through licensing. For U.S. firms without the finances to develop their technology into a product, licensing helped provide the cash flow necessary for R&D. Thus even though many foreign firms have accused Japanese firms of stealing their technologies, this was often the result of rational corporate strategies on the part of both firms.

Some foreign firms, however, have complained of "artificial" barriers to finding a reliable partner in Japan. Many Japanese firms are members of various government-sponsored joint research associations in biotechnology.[83] For example, 14 firms, including Takeda, Kyowa Hakko, Ajinomoto, Asahi Chemical, Mitsubishi Chemical, and Sumitomo Chemical, joined the government-

83. See Yoshikawa, op. cit., for a detailed treatment of Japanese policies to promote biotechnology and joint research associations.

led Biotechnology Joint Research Association in 1981.[84] With support from MITI, Toray, Mitsubishi Chemical, Kyowa Hakko, and Takeda jointly established the Protein Engineering Research Institutes (PERI) in 1985 to conduct basic studies of protein structure.[85] Foreign firms hesitate to establish commercial alliances to conduct joint R&D with Japanese firms that are also involved in a similar project organized by the Japanese government. Even though no concrete achievements have been realized by government-led joint R&D efforts, MITI has succeeded in getting credit in advance, thereby frightening foreign firms and policy makers.

Despite concerns, joint venture partnerships between U.S. and Japanese firms can be observed in many biotechnology-based pharmaceuticals. Competition in the tissue-type plasminogen activator (TPA) is the most severe and complicated in biotechnology today, but illustrates the formation of international strategic alliances and the fundamental difficulties involved therein.

TPA is an enzyme many expect to be a major biotechnology-based drug for treating heart attack and stroke. Its market size in Japan alone is expected to be as high as 100 billion yen (approximately $700 million). Although Genentech and Genetics Institute are believed to be leading in the development of TPA, Japanese firms, such as Asahi Chemical and Toyobo, are following closely.

Genentech formed an alliance with Kyowa Hakko and Mitsubishi Chemical and has granted marketing rights to them. Facing the Genentech-Kyowa-Hakko-Mitsubishi Chemical alliance, Asahi Chemical is trying to conduct research with Kowa, and Toyobo and Daiichi Seiyaku are jointly financing Integrated

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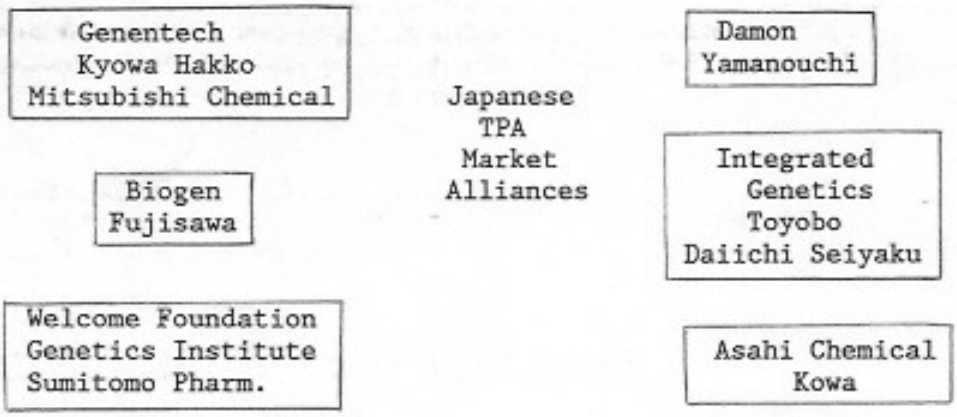
84. Ibid., p. 25.

85. Ibid., p. 29.

Genetics' TPA studies. Yamanouchi is collaborating with Damon Biotech, and Fujisawa is collaborating with yet a different American firm, Biogen, on its own TPA study. Therefore alliances in the TPA race cross national boundaries.

Genentech insisted on its patent priority for TPA; it warned seven Japanese rivals to suspend their R&D on TPA and filed a patent infringement suit against one. However, Japanese rivals, such as Asahi Chemical, Daiichi Seiyaku, Mitsui Toatsu Chemical, Toyobo, and Sumitomo Pharmaceutical, have rebuked Genentech's claim. Contrary to these Japanese firms, Kyowa Hakko and Mitsubishi Chemical welcomed Genentech's tough stance. Figure 11 schematically shows the players in the TPA race.

Figure 11.
Alliances in the TPA War



Similar cross-national alliances can be seen in the development of other biotechnology-based drugs. Erythropoietin (EPO), a hormone that stimulates production of red blood cells and is produced by the kidney, will be used to treat anemia. Amgen is leading its development. Kirin and Amgen

jointly established Kirin-Amgen in 1984.[86] In Japan, Kirin Brewery started clinical testing using technology transferred from Amgen. Japan's Chugai Pharmaceutical is trying to develop EPO jointly with Genetics Institute. Thus in the Japanese market, competition is between two U.S.-Japan joint ventures: the Amgen-Kirin team and the Genetics Institute-Chugai team.[87]

This EPO example demonstrates why American firms are trying to form alliances with Japanese firms. Observers of biotechnology patents predict that few cases of patent infringement will provide clear victory for a single firm.[88] In many cases, two or more companies will have to negotiate to share their narrowly defined patents in order to produce a product.

Genetics Institute, for example, patented a method of purifying EPO from natural tissues, but maintains that its patent covers all pharmaceutical-grade EPO, whether natural or otherwise. Amgen has a patent pending on its rDNA version of EPO, but Genetics Institute is suing for infringement. Unless one or the other is granted an exclusive patent, they may have to agree to cross-license their patents in order to commercialize EPO.

By performing advanced clinical testing, a company can achieve a favorable position in commercial negotiations for the product. Executives I

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86. Kirin-Amgen also established commercial ties with Johnson & Johnson in marketing EPO in 1985.

87. The two firms, Kirin and Chugai, are also competing in the development of granulocyte colony stimulating factor (G-CSF), which could be used in the treatment of leukemia. Chugai developed its own technology with the cooperation of the University of Tokyo Medical School. Kirin, jointly with Amgen, is trying to catch up to Chugai.

88. Recent decisions show the courts' unwillingness to grant broad patent claims. For example, Genentech's patents on TPA were struck down in England in 1987 in litigation with Wellcome Foundation on grounds that the claims were too broad. Some biotechnology companies that cannot afford to undergo lengthy litigation have tried to speed up the patent process by pursuing narrow rather than broad claims. See Scotchmer and Yoshikawa, op. cit., p. 14.

interviewed from both Kirin and Chugai admitted that it is unlikely that either company or its partner (Amgen for Kirin and Genetics Institute for Chugai) can obtain exclusive patent protection. They said that they are competing in its development 1) to achieve a better bargaining position vis a vis their rival and 2) to prepare for immediate commercialization of EPO once governmental approval is obtained. Because it takes so long to conduct the necessary testing, a firm must conduct tests and introduce the product quickly in order to realize any profit.89 Also, it is important for American firms to have a Japanese partner because most of them could not conduct the required tests by themselves in Japan.

Strategic Alliances

Strategic ties with Japanese companies, while potentially beneficial, also often involve conflicting commercial relationships in other products. For example, although Genentech and Fujiwasa are competing in TPA, they are joined in marketing TNF. Genentech also licensed Toray and Daiichi Seiyaku to market gamma interferon in Japan. Thus partnerships tend to be product-specific.

Even if sharing a common objective is not a necessary condition for joint venture partnerships, it is desirable for realizing mutual benefits. The complicated and sometimes contradictory commercial relationships in biotechnology may suggest a lack of strategic planning by smaller U.S. biotechnology-specializing companies, especially in their early stages. It seems that technologies were transferred and licenses granted to various Japanese firms without considering long-term strategic relationships.

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89. The average remaining effective period for a new drug was about six years in Japan.

As a result of recent trade friction between the U.S. and Japan and a Japanese concern over a growing protectionist sentiment in the U.S., Japanese firms today are willing to establish long-term joint-venture partnerships with U.S. firms. Japanese firms expect such relationships to help protect them from U.S. protectionism.

Established Japanese pharmaceutical firms, expecting a massive invasion of their traditionally orderly market, are also concerned about their future. A strategic tie to a U.S. pharmaceutical company can improve their chances of survival.

New entrants to Japanese biotechnology--e.g., Kirin, a food-processing company; Toray, a textile company; and even Kawasaki Steel--can use strategic alliances with foreign pharmaceutical companies to establish credentials in Japan's market. Because they have no established niche to protect in the Japanese pharmaceutical market, they may make more favorable offers to foreign biotechnology companies. Japanese firms, both established and newcomers, now seek alliances with foreign pharmaceutical and biotechnology companies in order to protect themselves from possible trade retaliations.

U.S. firms are also more interested in longer-term relationships than in quick licensing agreements. They are more concerned with Japan's potential threat and less eager to license technologies to Japanese firms in order to realize a short-run profit.

Smaller foreign biotechnology firms may be able to realize mutual goals with a Japanese partner and utilize its financial "deep pocket." Also, the relaxation of Japanese regulations concerning the commercial activities of foreigners leave foreign firms freer to develop strategic relationships with

Japanese firms. Thus today, there are more mutually positive attitudes toward realizing long-term strategic alliances.

If a foreign firm's sole goal is to gain access to the Japanese pharmaceutical market, then a sales tie-up and acquisition of a Japanese pharmaceutical firm are attractive options. Although we expect more than 20 firms to survive the restructuring of the Japanese market, quite a few Japanese firms may be for sale within the next several years. In order to gain access to the Japanese market, it may be more desirable to connect with an established pharmaceutical firms than with a newcomer that has only a small share of the market and may lack close ties with physicians. For example, Kirin (Amgen's partner) began clinically testing EPO in Japan before Chugai, but may have trouble maintaining its lead. Chugai (Genetics Institute's partner), an established pharmaceutical manufacturer with reliable hospital contacts, is confident that it can catch up in clinical testing.[90]

A smaller biotechnology company with a pharmaceutical innovation has reason to develop a joint-venture partnership with a Japanese firm to gain the financial and non-financial resources necessary to turn that innovation into a product. Non-financial resources are, as mentioned above, close working relations with doctors to conduct clinical testing and to successfully market the product, and know-how, especially in processing technologies. Most processing know-how can be obtained only through learning by doing, through experience in drug manufacturing. As stated

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90. A statement by a senior executive at Chugai referred in Baio Bijinesu, p. 57. It should be noted that the two firms, Amgen and Genetics Institute, are also engaging in a patent dispute concerning EPO. The competitive status of their EPO projects will be heavily affected by the legal outcome of the dispute. See Scotchmer and Yoshikawa, op. cit.

above, however, new Japanese entrants may be willing to realize mutual benefits on terms more favorable to a foreign firm. A newcomer may be more willing to share the benefits with a U.S. biotechnology company as they grow together. The alliance between Amgen and Kirin to produce EPO may fit this category.[91]

Genentech's recent ties to Mitsubishi Chemical both in sales and in R&D suggest the firm's efforts to establish a reliable alliance. However, some have expressed doubts about this partnership because Mitsubishi Chemical is not an established pharmaceutical maker and may be unable to provide adequate access to the Japanese market. It is also argued that Mitsubishi Chemical, as a new entrant, doesn't possess a level of technology equal to Genentech's, so that Genentech may derive only limited benefit from joint R&D.[92] On the other hand, a partnership with an industry outsider such as Mitsubishi Chemical can benefit a foreign firm. An established outsider can provide useful technical skills as well as financial resources. Mitsubishi Chemical is also well-established in biotechnology: it created a life science laboratory to conduct R&D in 1971, five years before the establishment of Genentech.

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91. Joel Marcus, an attorney who has represented Kirin-Amgen, stated that the two firms share a common goal: to commercialize EPO throughout the world. See Joel Marcus, "Strategic Alliances," in Bio/Technology, October 1986, p. 861.

92. This is a concern expressed by one industry source. See Arthur Klausner, "Today's Trends," Bio/Technology, October 1987, p. 1023.

VIII. ASSESSMENT OF COMPETITIVENESS

This section summarizes our discussion of Japanese efforts to develop new biotechnology-based pharmaceuticals.

1. Today the U.S. pharmaceutical companies enjoy a competitive edge over Japanese rivals. U.S. drug makers are larger and more innovative than Japanese firms. However, we see evidence of a growing Japanese capability.

2. Although its impact on the pharmaceutical industry is not yet known, biotechnology already has became an integral part of the industry. Biotechnology may underlie up to 40% of pharmaceutical production by the year 2000.

3. The Japanese government identified biotechnology as one of the key technologies for Japan's future competitiveness, and has introduced a number of policies to promote it.

4. Many firms have entered Japan's pharmaceutical market in hopes of profiting through biotechnology. New entrants--chemical, food-processing, textile, and steel companies--are larger but inexperienced in the pharmaceutical business. With their financial deep pockets and commitment to diversify, these large entrants wish to become major drug makers by the year 2000.

5. The Japanese pharmaceutical industry is likely to undergo major structural reorganization due to massive entries of domestic giants and more direct competition from foreigners.

6. In an effort to survive, more Japanese drug makers are focusing their attention on the international market, especially the U.S. This increasing level of globalization will intensify the competition between the U.S. and Japan both domestically and abroad.

7. U.S. companies already have a more than a trivial degree of penetration in the Japanese pharmaceutical market. Compared with the semiconductor case, U.S. pharmaceutical firms have both access to and experience in the Japanese market. With the relaxation of government regulations governing foreign firms in the Japanese market, foreign drug makers can expect increased access to the market.

9. Most U.S. pharmaceutical firms are much bigger and have greater financial sustainability than did semiconductor producers. Most U.S. semiconductor producers were small, fast-growing specialized companies that had less financial leverage than their more diversified Japanese rivals enjoyed. The Japanese "deep pockets" enabled them to compete powerfully with American firms in the late 1970s. American pharmaceutical companies are even larger than their Japanese rivals. However, smaller U.S. biotechnology-specializing firm (from which innovations often emerge) are likely to face problems similar to those of their semiconductor predecessors.

9. Japan leads the U.S. in process technology, such as the bioreactor. Superior process technology is useful, especially in producing industrial biotechnology products such as amino acids, and in producing other relatively price-sensitive (high price-elasticity) pharmaceutical products,

such as antibiotics. For these products, a successful producer is an efficient, low-cost producer. However, production cost may not be crucial in developing and successfully commercializing high value added pharmaceutical products, for instance anti-cancer drugs such as interferon and interleukein-2. Therefore, even though the sophistication of the Japanese bioreactor has been widely discussed and feared in the U.S., superior process technology alone cannot guarantee Japan's success in commercializing high value added pharmaceuticals.

10. Many U.S. biotechnology firms are small start-up companies. They lack both experience in fermentation and process technology and the financial ability to acquire such know-how. Promotion of process technology may be an important element in enabling smaller U.S. biotechnology firms to scale up production and to maintain U.S. competitiveness. It therefore becomes an effective strategy for U.S. public policy. An important question is how to maintain the U.S. advantage from initial innovation through commercialization. Public policy can promote the smooth transformation of a technology into a product.

11. There is a growing interaction between the U.S. and Japan.

A) As a result of recent trade friction between the U.S. and Japan and Japan's fear of a growing protectionist sentiment in the U.S., Japanese firms are willing to establish long-term joint-venture partnerships with U.S. firms. They need to adopt a strategy that enables both partners to realize long-term benefits and avoid possible conflicts. Japanese firms expect that such relationships with American firms can make them partially immune to U.S. protectionism.

B) U.S. firms are also more interested in longer-term relationships with Japanese firms. Their concern about potential competition from Japan has lessened their willingness to license technologies to Japanese firms in order to realize a short-run profit. We are beginning to see international alliances in biotechnology.

12. Industrial reorganization in the Japanese pharmaceutical market will provide opportunities to foreign firms.

A) Many pharmaceutical companies seek foreign partners in order to improve their odds of survival. Small and medium-sized pharmaceutical companies are potential acquisition targets for foreign firms trying to gain quick access to the market.

B) Smaller U.S. biotechnology companies should also try to develop strategic partnerships with Japanese companies. New Japanese entrants to the pharmaceutical market, such as food-processing and chemical companies, can be favorable partners because they may be more willing to share new profits.

14. One must not forget Japan's strategic policies designed to promote biotechnology. Although the extent of their impact is still unknown, the Japanese government has introduced various policies, both old-fashioned and experimental, to promote biotechnology. These strategic policies should be examined carefully.

Epidermal growth factor (EGF) is an enzyme that fosters epidermal cell proliferation. Researchers hope it can be used in treating burns and ulcers as well as in cataract surgery. The leading U.S. firms include Chiron, Amgen, and Genentech. European companies such as G.D. Searle and ICI are also trying to develop EGF products. Japanese firms, such as Earth Chemical and Wakunaga Pharmaceutical, are developing efficient processes to produce EGF.

Erythropoietin (EPO) is a protein molecule that circulates in the bloodstream and is responsible for the regulation and control of red blood cell synthesis. Deficiency of EPO often leads to an anemia associated with chronic kidney disease. Researchers hope that EPO can be used to treat this anemia.

Granulocyte-monocyte colony stimulating factor (GM-CSF) is an immune regulatory protein (lymphokine) produced by cells of the immune system as part of the natural defense against infection. It stimulates the production of white blood cells. It is hoped that GM-CSF can be used to treat blood cell deficiencies.

Interferons (IFNs) are proteins produced as part of the immune response. There are three major types of interferons: alpha, beta, and gamma. Interferons inhibit viral infections and may have anti-cancer properties.

Interleukein 2 (IL-2) is a protein that circulates in the bloodstream and is believed to play an important role in regulating the immune system. Researchers hope it can be developed as a anti-cancer drug.

Superoxide dismutase (SOD) is an enzyme that may be used in treating heart attack and transplant patients. Chiron and Biotechnology General lead in its development. Three Japanese firms: Ube Industries, Toyo Jozo, and Nippon Kayaku, are also developing it aggressively.

Tumor Necrosis Factor (TNF) is a protein of the immune system that appears to destroy some types of tumor cells without affecting healthy cells. Work is being done to develop TNF as a cancer-fighting drug.

Tissue Plasminogen Activator (TPA) is an enzyme that naturally eliminates blood clots, which can cause strokes and heart attacks. Researchers hope that TPA can be used in treatment of these clinical conditions.