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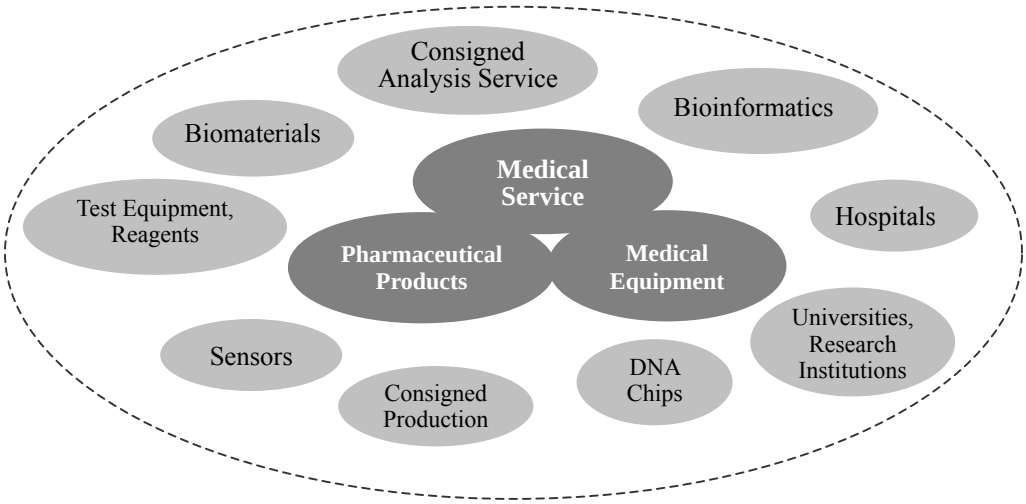
Biomedical

Introduction

Expectations for Biotechnology/Biomedical Industry

The market of the Japanese biotechnology-related industry in 2002 was worth ¥1,433 billion. Some projections indicate that this market will grow to about ¥25 trillion in 2010 and expectations are growing further for this industry to become the driving force for the Japanese economy. Especially, the biomedical industry, an area that applies the principles and technologies of biotechnology and bioengineering to medicine and biology, is a general term for the industry that covers medical, welfare and health-related equipment and products, and has drawn keen attention as a potential prime mover that will widely vitalize the economy.

Biomedical Industry



Biomedical industry is regarded in advanced countries as a key strategic industry and there is fierce competition now going on to fill the position in the post-genome industrial field. In the United States, as many as 2,000 bio ventures are currently conducting business, in attempts to gain competitive advantage in originality and time. Also, in Japan, an enormous budget is being allocated to the biotechnology field with the aim of creating 1,000 biotech-related companies by 2010, and the budget has sharply increased following the launching of the "Millennium Genome Project." As a result, 334 bio venture businesses started up as of February 2003. Against such a background, many regional bureaus of the Ministry of Economy, Trade and Industry and local governments have selected biomedical industry and its related fields as the core of economic revitalization, and formulated industrial cluster plans to help nurture bio ventures. At the same time, quite a few government offices have taken aggressive measures to attract investment from abroad.

Developing Research Results into Business

While the biotechnology/biomedical industry generates great expectations for growth as a future core industry, it is also faced with issues of research results not being smoothly developed into business. There are big obstacles for the business side to clear to enter the market such as the great amount of time and money needed for clinical testing, tendency of large Japanese pharmaceutical companies to avoid taking risks, strict administrative system for permits and licenses, and complex distribution system in the relevant fields of the industry. Due to these obstacles, there are a good number of cases in which many seeds with good business potentials have not developed into real business. Also, despite of growing expectations for venture businesses, the real situation is that they take a very long time to develop into viable business operations. Various attempts and efforts are being made at national and regional levels to close the big gap between seeds found in research and actual business.

Toward Forming Global Partnership

Not only in the biomedical field, but also in many high-technology fields, it has reached the limit of their capacities in terms of speed and cost for one company alone to develop technologies and turn them into business independently. Furthermore, a market is not concluded by one country and global partnership is increasingly needed. Foreign-developed technologies are already playing important roles in various areas of the Japanese biomedical industry, and their needs are expected to grow even further. This survey will identify the current situation and issues of the biomedical industry and market, and discuss concrete measures for foreign companies to enter the Japanese market in this field.

Range Covered by This Survey

Within the broad sense of the biomedical market, this survey will cover the biotech pharmaceutical market and the biomedical support market, including biomedical service, medical equipment, reagents, analysis service, various consigned services, and bioinformatics. Especially, this survey takes a close look at genome-based drug development, cell therapy, and regenerative medicine, which have all been attracting attention as emerging markets, and analyzes business trends by fields.

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Appendix

Yen-US Dollar Exchange Rates

End of Year	Yen/US$
1998	129.2
1999	102.1
2000	114.9
2001	131.5
2002	119.4
2003	107.0

Note : Mean value between offer and bid in the inter-bank foreign exchange market in Tokyo.
Source: Bank of Japan, "Financial and Economic Statistics Monthly"

Summary

This survey examines the current situation of biomedical industry and its market in Japan and after identifying the issues they face, presented specific measures to help foreign companies enter the Japanese market.

The Japanese biomedical market in 2002 was worth an unimpressive ¥818.7 billion (up 7.5 percent from the year before), but according to some projections, it will grow into a huge market worth ¥25 trillion in 2010. Technologies in the fields of genome-based drug discovery and development, cell therapy and regenerative medicine are now in the basic research stage at major pharmaceutical companies and universities' and public research institutions.

On the other hand, the Japanese pharmaceutical market is the world's second largest, with ¥47.5 billion in sales in 2001, but the products actually traded on the market are led by foreign-developed drugs. While foreign companies' subsidiaries and affiliates account for 25 percent of the Japanese market, the Japanese drug makers are trying to strengthen their capabilities through mergers and technical tie-ups with foreign bio ventures.

In the research support fields, DNA sequencers and other analysis systems, bioinformatics and various contract services comprise a stable market. Demand for such contract services for analyses and clinical tests is expected to grow as major pharmaceutical companies are outsourcing more work to make their research and development more cost-efficient.

The number of applications for patents of genome-related technologies in Japan is the fourth largest, following the United States, China and Europe. Of the total core patent applications, 76 percent are those by major companies. According to the Japan Patent Office, the life science fields where Japanese technologies have relative advantage and superiority are the following four: glycoengineering, biochemicals, microbe and enzyme, and bioinformatics. Meanwhile, those fields that are growing fast, although their shares are still small, are those of gene function analysis technologies and protein function and structure analysis technologies.

The main legal regulation governing the biomedical fields is the Pharmaceutical Affairs Law. Part of the law was revised in July 2003 so that clinical tests with medical doctors taking the initiative became possible and safety standards for products derived from biotechnology were newly introduced. Also drastic changes in business models are expected in the future when a switch to a marketing approval system from the current production approval system takes place and lifting of the ban on contract production of drugs will be introduced in the revisions which will go into force in 2007.

Biotechnology clusters are being formed in various parts of the country. Especially, bio venture startups and drug makers are concentrated in the Kanto Region and the Kansai

Region, centering in Osaka and Kobe, and more clusters of a considerable size are found also in Hokkaido and the Tokai area.

For foreign companies wishing to enter the Japanese market, promising fields among basic research and research support fields are the bio research equipment and reagent markets related to genome and protein analyses, or contract services and bioinformatics. In the clinical and pharmaceutical fields, not just drug discovery and development, but also genomics and proteomics, research devices and equipment, and related services are regarded as promising fields for interested foreign companies.

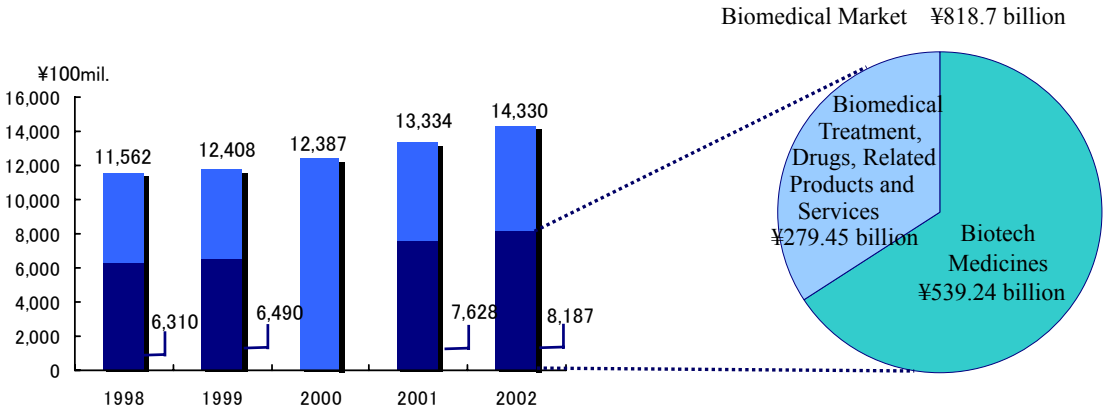
When foreign companies try to enter the Japanese biomedical market, possible modes of entry are, in addition to establishing their own subsidiaries, tie-ups between venture companies, joint ventures with trading firms, and technical tie-ups with major and medium pharmaceutical companies. Those considered to be their likely partners in the Japanese market are major and medium pharmaceutical companies, general trading houses, bio-specialized trading firms, biotech ventures, bio-specialized venture capitals, and universities' and public research institutions. When selecting their partners, they are advised to take into consideration not only the reputation within the industry but also the candidate partners' positions in local clusters. It should, furthermore, be remembered that those candidate companies in Japan are also looking for useful and reliable partners among foreign companies to carry out their long-term business strategy and collaboration, not just in terms of their technical capabilities and products, but also for future possibility of joint research.

I. Market Outlook

1. Market Size

Market for the overall biotechnology industry in 2002 expanded by 7.5 percent from 2001 to ¥1,433 billion. Of the total, the biomedical market[1] accounted for ¥818.7 billion, 7.3 percent larger than the previous year. This biomedical market breaks down into biotech pharmaceuticals worth ¥539.24 billion, and biomedical treatment and drugs-related products and services worth ¥279.45 billion. The market has been growing for the past four years (1998 to 2002) at an average annual rate of 6.7 percent.

Figure 1. Changes in Biotechnology Market



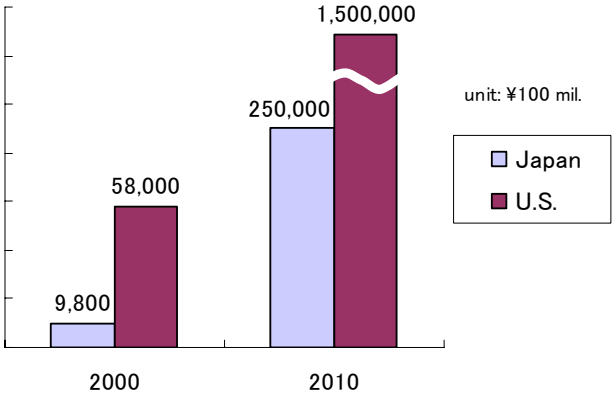
Note : Statistical data for the 2000 market breakdown not available.

Source: Prepared based on the data from Nikkei Business Publications, Inc., *Nikkei Biotechnology Yearbook '99, '00, '03*

The Japan Patent Office predicts that the biotechnology industry market will expand to ¥25 trillion in 2010. However, there is currently a big gap in market size in Japan and the United States, and also a fear that this gap may become even bigger at an accelerating rate.

[1] This includes the biotech pharmaceutical market and biomedical support market, which consists of biomedical treatment and drug-related equipment, reagents, analysis service, various consigned services and bioinformatics.

Figure 2. Projection of Japanese and U.S. Biotech Markets



Source: Japan Patent Office, *"Survey on Trends in Technological Patent Applications Concerning Post-Genome-Related Technologies – Protein-Level Analysis and IT Utilization,"* 2002.

Keenly aware of this situation, the government launched the "Millennium Genome Project" in 2001, the "Pharmaceutical Industry Vision" in 2002, and in collaboration with five governmental departments,[2] the "Biotechnology Strategy Guidelines" in December 2002, and is currently allocating a large budget to various fields of the bioindustry market so as to help develop the biomedical industry into an important industry in Japan during the first quarter of this century.

2. Market Details

2-1 Overview

Main products of biotech pharmaceuticals are those produced by utilizing transgenic technology, cell fusion technology and cell culture technology. Technologies in genome-based drug development, cell therapy and regenerative medicine are now in the basic research-and-development stage at major pharmaceutical companies, universities and public research institutions, with very few of them being produced on a commercial basis.

Of the biotech pharmaceuticals produced in 2002, the highest proceeds of ¥120 billion came from erythropoietin, followed by monoclonal antibody in-vitro diagnostic agents (¥65 billion) and human growth hormone (¥60 billion). Showing particularly strong growth are antibody drugs, with sales growing from ¥900 million in 2001 to ¥13 billion in 2002.

[2] The Cabinet Office, Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare, Ministry of Agriculture, Forestry and Fisheries, and Ministry of Economy, Trade and Industry.

Table 1. Breakdown of the Biotech Pharmaceuticals Market (2002)

Units: 100 million yen

Product	2002	2001	Product	2002	2001
<Gene manipulation>			Recombinant enzyme antibiotics	385	370
Erythropoietin	1200	1160	Recombinant acrylamide	50	50
Human growth hormone	600	600	Nucleic acid (self-cloning)	10	10
Granulocyte colony-stimulating factor	430	440	Cyclodextrin produced through recombinant technology	3	2
Human insulin	490	460	Drugs for animals (IFN, antibodies, ECF etc.)	13.4	12.3
Interferon α	290	120	Swine; Aujeszky disease vaccine	6.7	6.7
Interferon β	26	10	Recombinant vaccines for animals	0.8	0.4
Blood coagulation factor VIII (recombinant)	85	98	Animals for gene manipulation testing	2.5	1.8
Blood coagulation factor VII (recombinant)	15	15			
Glucagon (recombinant)	60	60	＜Cell fusion＞		
TPA (recombinant)	29	25	Monoclonal antibody in vitro diagnostic drugs	650	630
Interleukin 2	105	85	BSE testing kit	37	-
Natriuretic peptide	50	40	Antibiotics (Fortimicin)	1	1
Hepatitis B vaccine (recombinant)	15	15	Monoclonal antibody drug (Orthoclone OKT3)	1	1
Interferon γ	6	6			
Insulin growth factor I	3	3	＜Cell cultures＞		
Recombinant glucocerebrosidase	37	32	Animal testing alternatives systems	3	3
Fibroblast growth factor	27	6	TPA (using non-recombinant cell cultures)	3	5
Antibodies for therapeutic use	130	9	Prourokinase	2	2
Fibronectin for gene transfer	1	1	Interferon α	170	270
Diagnostic products made from recombinant antigens	260	240	Interferon β	135	210
Diagnostic enzymes	40	30	Hepatitis B vaccine (using non-recombinant cell cultures)	2	2
Restricted enzymes (Modification enzymes, kit)	18	18	Biotech pharmaceuticals market total	5392.4	5050.2

Source: Nikkei Business Publications, Inc., *Nikkei Biotechnology Yearbook 2003*

Meanwhile, the actual businesses of the biomedical support market are gradually being developed into venture businesses. In the research support fields such as equipment and reagents, analysis systems like the DNA sequencer, bioinformatics, and various consigned services, in addition to the conventional liquid chromatography, have formed stable markets.

Table 2. Breakdown of the Biomedical Support Market (2002)

Units: 100 million yen

Product	2002	2001	Product	2002	2001
<Equipment and reagents>			<Bioinformatics>		
Preparative liquid chromatography	70	65	Package software	45	40
Analytical liquid chromatography	400	400	Servers	220	200
PCR automation equipment	20	20	System integration	80	50
PCR automation reagents	45	45			
Real-time PCR measurement equipment	45	40	<Other>		
Real-time PCR measurement reagents	10	5	Bovine embryos (domestic)	15	20
DNA synthesis equipment	2	2	Bovine embryos (imported)	3	6
DNA synthesis reagents	30	28			
DNA sequencer	90	100	<Services>		
DNA reagents	50	53	DNA synthesis service	60	60
Peptide synthesis equipment	5	5	Peptide synthesis service	25	20
Peptide synthesis reagents	4	4	Gene analysis service	60	50
Peptide sequencer	13	13	DNA paternity testing	2	2
Peptide reagents	5	5	Protein-related analysis service	12	10
Gene transfer equipment	6	7	Genetically modified animals creation service	4.5	4
Gene transfer reagents	20	15	Schools specializing in Bio (school fees)	15	15
Glyco chain analysis equipment (including reagents)	4	4	Protein production	20	15
DNAchip-related equipment	20	25			
DNAchips and related reagents	40	50	<Healthcare, fine chemicals>		
Lab chip	10	6	Hyaluronic acid drugs	500	500
Mass spectrograph	50	45	Molecule target drugs (excluding antibodies)	80	0
Analytical equipment for interaction between materials	32	25	Diltiazem	225	229
Monoclonal antibody-utilizing cell separation equipment	2	0	DNA probing drugs	125	95
			<Sensors>		
			Medical biosensors	330	300
			Biomedical support market total	2794.5	2578

Source: Nikkei Business Publications, Inc., *Nikkei Biotechnology Yearbook 2003*

3. Market Trends

3-1 Domestic Pharmaceutical Companies

The Japanese pharmaceutical market, worth $47.5 billion in 2001, is the second largest in the world after the United States market, worth $132.1 billion. (Germany comes third with $15.3 billion and France fourth with $13.8 billion.)[3] On the other hand, the Japanese pharmaceutical market is led by overseas products, with drug imports in 2001 increasing by 15.8 percent over the previous year to more than ¥713 billion. Also, the percentage of shipments by foreign capital-affiliated companies within the Japanese pharmaceutical market has been increasing every year, accounting for about 25 percent of total.[4]

In order to secure an enormous amount of research and development funds needed for commercialization, as symbolized in genome-based drug development, the world's major pharmaceutical companies have been forming alliances and partnerships, mergers and acquisitions across borders since the 1990s. Domestic pharmaceutical companies were caught up by this international realignment movement, as seen in the mergers between foreign and Japanese corporations (as in Pfizer Inc.'s acquisition of Pharmacia & Upjohn) and by foreign companies taking over Japanese drug makers (as in Switzerland's Roche takeover of Chugai Pharmaceutical Co. in 2002). This realignment movement did not stop at major pharmaceutical companies but spread to medium drug makers in the form of M&As and joint ventures, such as the merged Mitsubishi Pharma Corp. in 2001 and the joint venture firm, Taisho Toyama Pharmaceutical Co. in 2002.

Amid intensifying competition in developing new drugs, domestic pharmaceutical companies are now stepping up efforts to strengthen their research and development capacity by linking with universities and public research institutions and by cooperating with foreign firms with specific technologies in the form of bio ventures and licences. By doing so, these domestic companies are trying to shorten the time needed for new drug development and spread risks.

3-2 Biotechnology Ventures

The current driving force in the biotechnology industry is venture businesses. According to the Japan Bioindustry Association, there are 334 venture firms in the

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[3] IMS Health, *"World Drug Purchase-Retail Pharmacies,"* 2003. The figures only include drug sales at prescription pharmacies for the United States and Europe. The figure for Japan also includes sales at hospitals. All figures are on a wholesale basis.

[4] Ministry of The Health, Labour and Welfare, *"Survey of Pharmaceutical Industry Production."*

biotech-related industry as of February 2003, and the estimate of their total sales (biotech-related sales only) is 105 billion yen. 334 Of those venture companies, 153 are in the medical service and health business sector, engaging in drug development and regenerative medical care. Also, 154 venture firms are in the research support sector, engaging in bioinfomatics and consigned R&D services, etc.

Table 3. Business Lines of Bio Ventures in Medical Service and Health Business Sector
(As of February 2003)

Categories	Number of companies
Medical service and health business	153
Pharmaceutical products development	94
Medical equipment (treatment and diagnostic equipment)	15
Artificial internal organs, artificial tissues and regenerative medicine	24
Specific health-care food products development	16
Personal care (preventive medicine, health-care promotive sector, health food products, etc.)	34
Others	17

Note : As one companies' activities include in the plural category, the sum total number of companies is different from 153.
Source: Japan Bioindustry Association, "Statistics concerning Bio ventures," June 2003

114 of these (34 percent) are venture firms developed core technologies from universities. Also, as many as 33.5 percent of the total, 112 companies are concentrated in Tokyo.

When compared with other developed countries, Japan is lagging far behind, with 300 biotechnology venture companies as opposed to about 2,000 companies in the United States and 2,500 companies in Europe.[5] It is pointed out that what Japan is lacking particularly in creating venture businesses are capital and management know-how. Especially, in raising funds, Japanese companies obtain necessary funds in many cases through tie-ups with major companies, while in the U.S. and Europe, venture capital plays a major role in financing startups of venture business.

3-3 Research Support Equipment, Service Industry

In biomedical research and development, research equipment and devices such as

[5] Source: Japan Patent Office, *"Survey Report on Trends in Technological Patent Application concerning Life Science,"* 2003.

stem cell separator devices and DNA and protein analysis apparatuses, play important roles as infrastructure. However, many of those devices are imported foreign products and, as a result, cause research costs in Japan to go up. Of the 2002 total sales results, there was a trend of sales regarding DNA-related analysis apparatuses, reagents and DNA chips to decrease, while those of protein-related analysis apparatuses increased from the previous year.

Demand for support services such as genetic and protein consigned analysis, is expected to increase further in the future. Protein Wave Corp., a venture business based in Seika-cho, Kyoto Prefecture, conducts functional and structural analysis of proteins with the advent of the post-genome science era and is offering equipment and devices as well as services to support pharmaceutical-related companies, universities and public research institutions.

CRO (Contract Research Organizations), or company that conducts clinical tests on commission, is an important avenue for outsourcing clinical tests for bio ventures. Even pharmaceutical companies that have conducted clinical tests on their own are now turning more to outsourcing in order to cut costs. On the other hand, as a result of the implementation in 1998 of the new GCP, or Good Clinical Practice,[6] that allows clinical test results obtained abroad to be used as data at the time of application for approval of drugs, more Japanese drug companies are outsourcing clinical tests abroad as they are faster and less expensive.

Services that link people and organizations are important as well. TLOs, or technology licensing organizations established in various parts of the country, basically offer services to link research seeds owned by researchers at universities and other institutions to corporate needs, and such services are expected to become even more important in the biomedical fields. There are some cases where consortiums are formed to link bio ventures' seeds to major companies. Furthermore, Mitsubishi Corp. is offering systems called Cosmos Alliance (membership only) to link U.S. venture companies to major Japanese companies. B-Bridge Japan provides service to act as a bridge for domestic research seeds to be developed on a global scale.

4. Technology Trends

4-1 Patent Trends

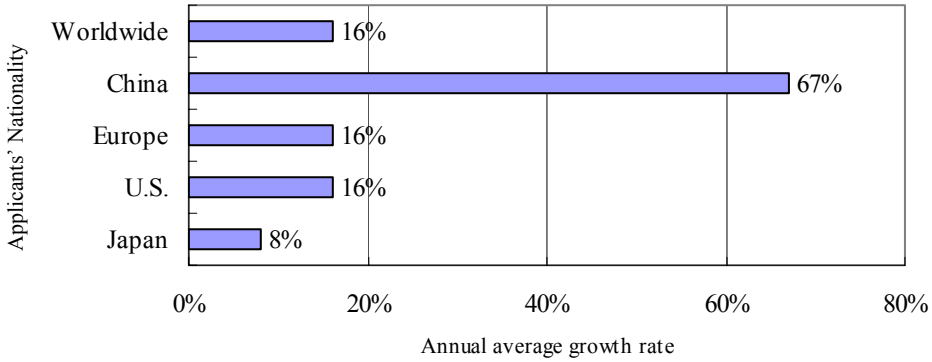
According to the Japan Patent Office, patent applications in 2000 concerning genome-related technologies (biotech core technologies and post-genome-related technologies)

[6] GCP (Good Clinical Practice) is the standard for conducting clinical tests on drugs provided by the Ministry of Health, Labour and Welfare Ordinance No. 28, enacted in April 1998.

totaled about 12,000 cases worldwide. Of the total, applications in Japan accounted for 13 percent, fourth largest after the United States (accounting for 41 percent), China (27 percent) and Europe (16 percent). Also, while these patent applications worldwide increased by 16 percent from 1991 to 2000, Japan's applications rose only by about half of the worldwide average at 8 percent.

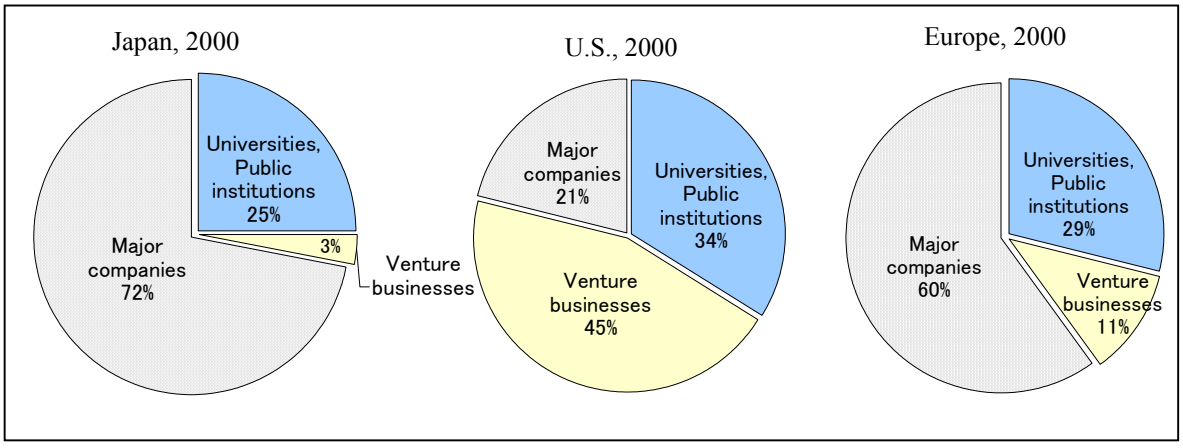
Compared with the United States, 76 percent of Japan's patent applications were filed by major companies, while in the United States, only 17 percent of such applications were filed by major companies, and 53 percent from universities and public research institutions, and the remaining 30 percent from venture businesses.

Figure 3. Average Growth Rates of Patent Applications during 1991-2000



Source: Japan Patent Office, *"Survey Report on Trends in Technological Patent Application concerning Life Science,"* 2003.

Figure 4. Breakdown of Basic Patent Applicants in Japan, U.S., and Europe



Source: Japan Patent Office, *"Survey Report on Trends in Technological Patent Application concerning Life Science,"* 2003.

The low percentage of the patent applications from universities and public research institutions vividly demonstrates discrepancies between research seeds at Japanese universities' research institutions and industrial needs. In order to correct these discrepancies, the Law for Promoting University-Industry Technology Transfer, which is also known as the Japanese version of the Bayh-Dole Act, was enacted in 1998, and TLOs (technology licensing organizations) approved by the Ministry of International Trade and Industry (currently the Ministry of Economy, Trade and Industry) and the Education Ministry (currently the Ministry of Education, Culture, Sports, Science and Technology) became eligible for subsidies. In 2000, the Industrial Technology Strengthening Law was enacted to allow TLOs to use national universities' premises. It is hoped that these measures will produce favorable results in the near future.

4-2 Technology Trends

According to the analysis by the Japan Patent Office, Japan is relatively ahead of other countries in fields of life science technologies such as glycoengineering technologies, biochemicals, microorganisms and enzyme, and bioinformatics. In these four areas, Japan enjoys high rates both in shares of patent applications and growth rates of such applications. Japan's application share in glycoengineering technologies is highest in the world, and those in the remaining three sectors – biochemicals, microorganisms and enzyme, and bioinformatics – are second highest, next to the United States. On the other hand, the sectors of gene function analysis technologies and protein functional and structural analysis technologies have still low shares but their shares are growing steadily.

Table 4. Fields in Life Science Sector in Japan in which Expectations are Placed

Areas	Features	Items	Technology Level	
			Low	High
Genome-based Drug Development (including bioinformatics, gene and protein analysis)	Combining multiple technologies, such as gene function analysis and protein analysis, bioinformatics and combinatorial chemistry, is necessary. In important cDNA related research, Japan has applied a special patent on technologies to obtain full length cDNA (full length cDNA, Helix Research Institute, Inc.: Patent 2002-17375) and has technological strength.	Applications' share	○	
		Growth rate for applications		○
		Important patents		○
		Hearing of experts	○	
Glycoengineering	Many applications for patents, including important patents, have been filed from Japan concerning glycogene library, and Japan has a good technological accumulation in this field. Japan is increasing its international competitiveness through the launch of a national project on glyconomic (glyco chain) research.ST3 Gal III, Kyowa Hakko Kogyo Co.; Patent 3131322 (1991); henkei EPO (Kirin-Amgen): Patent 2938572 (1994)	Applications' share		○
		Growth rate for applications	○	
		Important patents		○
		Hearing of experts		○
Green Biochemistry (Biochemical products, microorganism/enzyme)	Future expansion of this market can be expected. Japan has so far led the world's microorganism and enzyme research and needs to maintain its technological advantage by introducing most advanced life science to this research. Acrylamide-producing germ, method for culturing Pseudomonas (Nitto Chemical Indusry, Dr. Hideaki Yamada): Patent 1375105, Patent 1375106.	Applications' share		○
		Growth rate for applications	○	
		Important patents		○
		Hearing of experts		○
Bioinformatics	This technology is to apply IT technologies, which have kept being improved on the basis of equipment technologies, Japan's strong area, to biotechnology/life science fields. Japan is active in patent applications in this bioinformatics field.	Applications' share		○
		Growth rate for applications		○
		Important patents	○	
		Hearing of experts	○	
Nano-biotechnology	This is a field created by the fusion of nanotechnology and biotechnology. Japan is slightly behind. But, as the number of patent applications is yet small, progress in Japan's development of technologies in this field, utilizing its strength in processing technology, is expected.	Applications' share	○	
		Growth rate for applications	○	
		Important patents	○	
		Hearing of experts		○

Notes : * These life science sectors in which Japan is expected to exceed have been chosen on the basis of experts' hearings and the survey results on patent applications' trend.
* In the column of technology level, the dotted lines indicate the general technological evaluation of which level the particular sector is at.

Source: Japan Patent Office, *"Survey Report on Trends in Technological Patent Application concerning Life Science,"* 2003.

5. Trends of Foreign Company Entry into the Japanese Market

Foreign companies' entry into the Japanese biomedical market is deemed possible in four ways – by establishing corporations in Japan, by forming technical partnership, sales tie-ups and capital tie-ups. Of these four ways, corporation establishment is divided into 100 percent foreign-owned subsidiaries or joint venture firms. Main examples of these cases are listed in the following Table 5.

Table 5. Entry into Japanese Market by Direct Investment

Company Name	English Company Name	Establishment Year	Field	Situation of Establishment
Nihon Schering K.K.	Schering AG	1952	Regenerative medicine	Wholly-owned subsidiary
Nippon Boehringer Ingelheim	Boehringer Ingelheim GmbH	1961	Biotechnology-based pharmaceuticals, chemical drugs	Wholly-owned subsidiary
Bayer K.K.	Bayer AG (Germany)	1962	Biological products	Wholly-owned subsidiary; owns Bayer Medical K.K. and Bayer Yakuhin K.K.
Nippon Becton Dickinson Co.	Becton, Dickinson and Company (U.S.)	1971	Equipment, reagents	Wholly-owned subsidiary
Sigma-Aldrich Japan K .K.	Sigma-Aldrich Corporation (U.S.)	1978	Reagents for research	Wholly-owned subsidiary
Bio-Rad Laboratories Japan	Bio-Rad Laboratories, Inc. (U.S.)	1979	Equipment	Wholly-owned subsidiary
Serono Japan Co. Ltd.	Serono SA	1979	Import and sale of growth hormones etc.	Wholly-owned subsidiary
Invitrogen Japan K.K.	Invitrogen Corp. (U.S.)	1983	Import and sale of research reagents/equipment	Wholly-owned subsidiary
Sartorius K .K.	Sartorius AG (Germany)	1987	Equipment	Wholly-owned subsidiary
Genzyme Japan K.K.	Genzyme Corporation (U.S.)	1987	Pharmaceuticals, diagnostic products, research reagents	Wholly-owned subsidiary
Ventana Japan K.K.	Ventana Medical Systems Inc. (U.S.)	1987	Sale of automatic immuno-histo-chemistry equipment	Wholly-owned subsidiary; changed company name in 2000.
bioMerieux Japan Ltd.	bio Merieux S.A. (France)	1988	Reagents, automatic analysis system	Wholly-owned subsidiary; opened Saitama factory, began domestic production of cultures for bacterial testing
Thermoelectron	Thermoelectron Corporation	1989	Equipment	Consolidated from four Thermoelectron (US) Japan offices
IS Japan	Irvine Scientific Sales Co., Inc. (U.S)	1989	Cell culture mediums, reagents	Joint venture between Japan Energy Corporation (70%) and Irvine Scientific Sales Co., Inc. (30%)
Greiner Japan	Greiner bio-one (Germany)	1990	DNA chips	Wholly-owned subsidiary
Amgen Ltd.	Amgen Inc. (U.S.)	1992	Pharmaceuticals based on Biotechnology	Wholly-owned subsidiary
Tecan Japan K.K.	Tecan Group Ltd. (Switzerland)	1992	Bio-related equipment	Wholly-owned subsidiary, 042-334-8855
Japan Molecular Devices K.K.	Molecular Devices Cooperation (U.S.)	1995	Measuring equipment; reagents	Japan office became wholly-owned subsidiary in 2001
Proligo Japan K.K.	Proligo LLC (U.S.)	1996	Synthetic DNA	US head office is wholly - owned subsidiary of Degussa AG; 075-313-1974

Novartis Pharma K.K.	Novartis AG (Switzerland)	1997	Import and manufacture of pharmaceuticals for clinical use	Wholly-owned subsidiary
QIAGEN K.K.	QIAGEN GmbH (Germany)	1997	Custom DNA	Wholly-owned subsidiary
Amersham Biosciences K. K.	Amersham Biosciences UK Limited (U.K.)	1998	Related equipment, reagents	Wholly-owned subsidiary
Ciphergen Biosystems K.K.	Ciphergen BiosystemsInc. (U.S.)	1999	Import and sale of protein chip systems	Joint venture with SC Biosciences Corp. (30%)
Aventis Behring Japan	Aventis Behring LLC (U.S.)	2000	Biological products	Wholly-owned subsidiary
Actelion Pharmaceuticals Japan Ltd.	Actelion Ltd. (Switzerland)	2001	Pharmaceutical research and development	Wholly-owned subsidiary
BioCarta Japan K.K.	BioCarta, Inc. (U.S.)	2001	Import and sale of reagents for Biotechnology research	Wholly-owned subsidiary
Bay Bioscience, K.K.	e Bioscience (U.S.)	2001	Development, manufature and sales of reagents and equipment for Biotechnology research	34% foreign capital
CombiMatrix K.K.	CombiMatrix (U.S.)	2001	Products related to genetic analysis	Joint venture with Marubeni
Afymetrix Japan K.K.	Afymetrix, Inc. (U.S.)	2002	DNA chips	Wholly-owned subsidiary
Biogen Japan	Biogen Inc. (U.S.)	2003	Avonex, multiple sclerosis treatment drug	Merger agreement with Idec Pharmaceuticals was announced in June 2003.

Sources: Japan Bioindustry Association, "Statistics concerning Bio ventures," June 2003; Toyo Keizai Inc., *"Foreign-Affiliated Company Catalogue,"* 2002.

II. Business Trends by Sector

1. Genome-Based Drug Development

As a result of progress in genome research, due to the actual existence of some elements that cannot be clarified by genome information, elucidation of organism functions concerning not only DNA but also proteins has become necessary. Therefore, genome-based drugs are now being pushed mainly in antibody drugs, nucleic acid drugs and proteomic-based drugs, which will be dependent on further progress in genomic functional analysis, proteomic analysis, glyco-chain analysis and other post-genome research.

Facing intensifying competition for new drug development, many domestic pharmaceutical companies are forming alliances and tie-ups with foreign bio venture firms to make their development efforts more efficient and also spread their cost burdens and risks, while stepping up their own research and development setup. This is because in today's new drug development it is becoming even more necessary to obtain technologies and information for such development by new approaches different from conventional development methods, and it is becoming more difficult to cope only with one company's technologies and researchers.

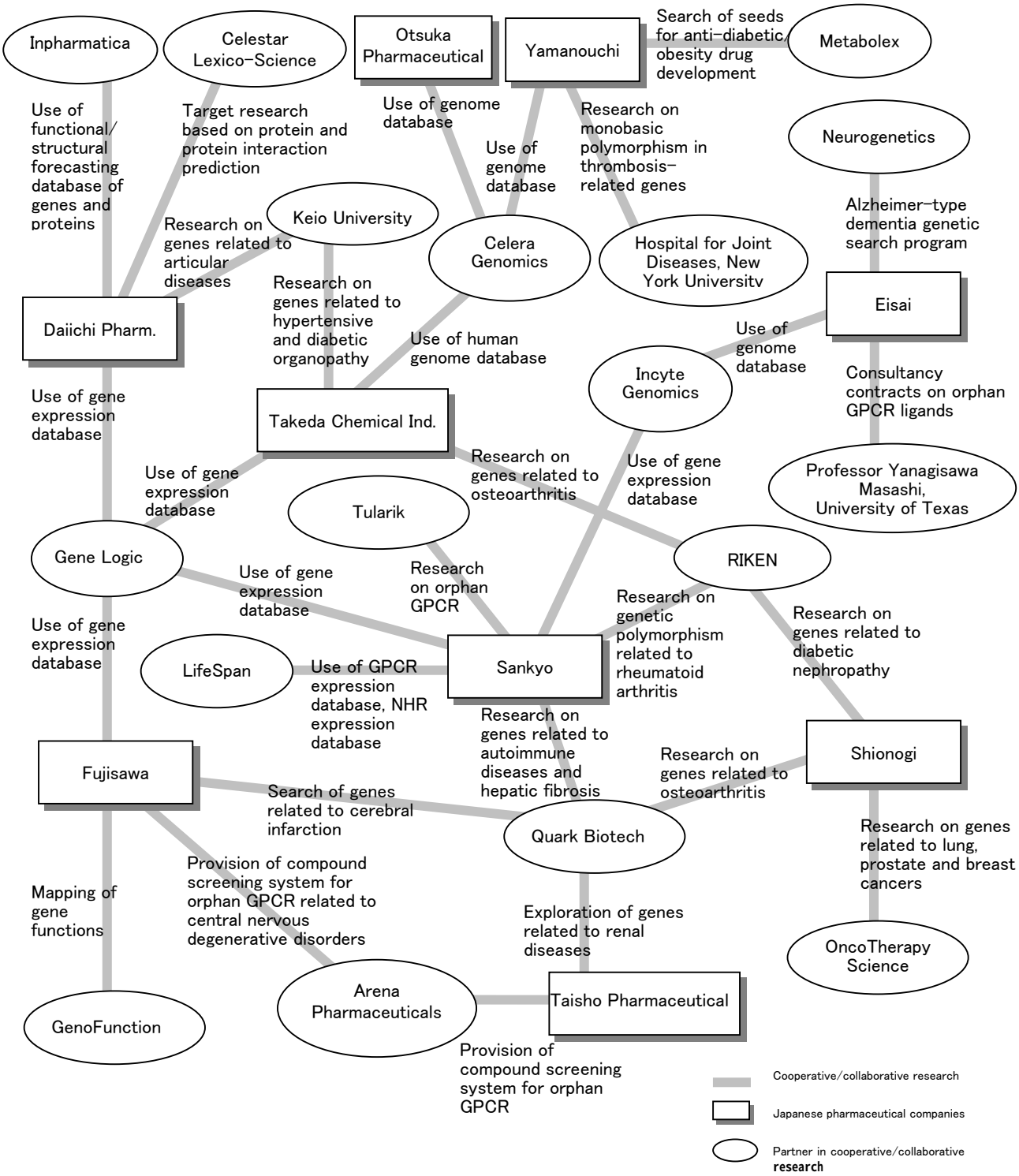
In forming R&D tie-ups, domestic companies are finding more merits in linking with firms related to areas such as investigation and function research of new genes, function research and identifying drug development target molecules. This is in view of intensified efforts in producing new genome-based drugs by identifying drug development target molecules through investigating and clarifying functions of new genes.

For instance, Takeda Chemical Industries spends about 10 percent of its research and development budget for genome-related research. With diabetes, obesity and arteriosclerosis as target areas, Takeda has formed tie-ups with U.S. corporates Celera Genomics (for database on genome sequence information) and Gene Logic Inc. (for database on gene expression information). Sankyo Co. is introducing technologies on autoimmune disease and diabetes, and Fujisawa Pharmaceutical Co. on brain infarction, both from Quark Biotech, Inc. of the U.S. In addition, Japanese companies such as Kyowa Hakko Kogyo Co., Mitsubishi Chemical and Japan Tobacco Inc. are conducting research and development under tie-ups individually with U.S. firms.

Sumitomo Chemical Co. and Sumitomo Pharmaceuticals Co. have integrated their business and established Genomic Science Laboratories. Mitsubishi Chemical established the genome-related venture business, JGS, with Fujirebio Inc. and Eiken Chemical Co., both major reagent manufacturers, and through this joint venture firm are manufacturing and selling DNA chips to be used by medical institutions for genetic function analysis. Furthermore, Mitsubishi Chemical has consolidated its medical-related business with Mitsubishi Chemical Life Science

Laboratory, Mitsubishi Pharma Corp. and JGS, to enter the genome-based drug development business.

Figure 5. Collaborative/cooperative research between pharmaceutical companies for genome-based drug development



Source: Nikkei Business Publications, Inc., *Nikkei Biobusiness, July 2003 (pp.68-69)*

Genome analysis is a two-dimensional sequence analysis, while protein analysis is three-dimensional and requires large-scale analysis too costly for a company to conduct by itself. Therefore, Japan Pharmaceutical Manufacturers Association (JPMA) formed the Pharmaceutical Consortium for Protein Structure Analysis (PCProt) and constructed its exclusive beamline at SPring-8, the powerful third generation synchrotron radiation facility in Harima Science Garden City, Hyogo Prefecture.

Of the venture businesses engaged in genome-based drug (proteomic drug) development, AnGes MG, Inc., which was listed on the Tokyo Stock Exchange's Mothers Market in September 2002, and TransGenic Inc., a venture business born at Kumamoto University to produce gene knockout mice and listed on the Mothers Market in December 2002, are the forerunners of university campus venture businesses. Other bio venture firms include aRigen, Inc., Effector Cell Institute Inc., M's Science Corp., LTT BioPharma, OrphanLink, and Sosei. Meanwhile, the largest number of biotechnology venture businesses is found in the field of drug development/discovery support.[7] They include INTEC Web and Genome Informatics Corp., Precision System Science Co., Shin Nippon Biomedical Laboratories (preclinical development business on consignment), DNA Chip Research Inc. (DNA chip business), Protein Wave Corp. (protein crystallization, screening, data gathering devices), Protein Crystal Corp. (development of protein chips with insect mori cytoplasmic polyhedorosis virus) and HuBit Genomix, Inc. (SNP analysis contract service, bioinformatics).

2. Cell Therapy

Cell therapy is a method to treat diseases like cancer that are difficult to cure with ordinary medicine, by using cells of the patient or of others. Of various cells, the hematopoietic stem cell is the source of blood and its isolation is a major issue of the therapy. Transplant of hematopoietic stem cells such as bone marrow transplant, peripheral blood stem cell transplant and umbilical blood transplant, are used to treat various cancers and blood diseases, along with anticancer drugs.

Of the major companies involved in this field, Kirin Brewery Co. introduced technologies from Dendreon Corp., and Takara Bio Inc. from Nexell Therapeutics, both of the United States, to develop cell therapy equipment.

Successful venture firms in this field include Lymphotec Inc. and Medinet Co.

[7] The number of bio venture businesses by business sector: 154 companies in research support, 46 in manufacturing. Japan Bioindustry Association, "Statistics concerning Bio Ventures," June 2003.

Lymphotec was established in 1999 based on a large-scale culturing technology of activated autolymphocytes that was developed while the company president worked with the National Cancer Center Research Institute. This technology allows removal of lymphocytes contained in the patient's peripheral blood from the body and sends it back into the body after they are activated. It is used to treat cancer and infectious diseases. On the other hand, Medinet was set up in 1995 to commercialize the results obtained by many years of basic immunological research by a former professor at the University of Tokyo's Institute of Medical Sciences. Its two main business lines are processing of immune cells for treatment and development of cell drugs.

The two companies are already registering sales as their products are already used in actual treatment, although venture businesses in biomedical fields are known for their long research and development periods and many more years may be expected before they can reap the fruit of the longtime efforts with sales and profits. However, they are not free of issues. They face many issues arising from the unique fact that their products are cells, and therefore, alive. These issues include the fact that large-scale production is not possible; in addition, it is costly because a cell culture line must be prepared for each patient. Furthermore, long-distance transport of the products is also not possible if it is to preserve the quality of the products; and it cannot be guaranteed that cells of the same quality are cultured even though the process is the same because quality assurance is difficult in case of cells. In addition to these universal issues, there are two issues unique to Japan:

1) The legal system is not fully adequate. Even in the revised Pharmaceutical Affairs Law of July 30, 2003, the definition and regulations are insufficient.

2) It is not covered by medical insurance. In other words, the patient must fully bear the medical cost. If it were to be covered by medical health insurance, the patients will bear only 30 percent of the cost. A private insurance policy, MEDCOM, is applied to this therapy.

3. Regenerative Medicine

Research concerning tissues and organs that are relatively easy to regenerate such as skin, bone, cartilage, and blood vessel is well advanced, but products have been developed only in limited areas. Products currently applied to tissue engineering (TE)[8] are found in the following categories.

- First stage products (structural functions):

[8] TE (tissue engineering) is a method to make the utmost use of regenerative function that life essentially has. It uses undifferentiated cells to artificially reconstruct necessary tissues and organs and transplant them in exchange for those that do not function properly, thereby curing the particular disease. It aims at curing the disease at its origin.

cultured skin, cartilage, cornea, tendon, muscle, fat, bladder, nerve, etc.

- Second stage products (metabolic functions):

cultured liver, kidney, pancreas, etc.

- Third stage products (genetic functions):

antimicrobial skin, functional tissues, etc.

There are various issues in turning research results into products such as safety, even for cultured skin, whose feasibility of commercialization looks very encouraging. Other issues would also include methods to obtain original cells to be used, culturing methods, and manipulation procedures. The most difficult issue is that concerning infectious diseases. There are also issues concerning effects of the biomaterial, clinical assessment, and ethics.

Of the large- and medium-size companies, Terumo Corp. (in a tie-up with Diacrin, Inc. of the U.S.) and Kyowa Hakko Kogyo Co. (research being conducted on the technology of mesenchymal stem cell utilization with Keio University's School of Medicine) are active in the market. On the other hand, Menicon Co., which entered the autologous cultured skin transplant business in 2000, announced its withdrawal in April 2003. One of the major reasons for its withdrawal from the business was the decision by the Ministry of Health, Labour and Welfare to make clinical tests mandatory for autologous cultured skin transplant as well as for allografts, which would require additional costs.

As for bio venture activities, and the application for confirmation of approval by BCS for its complex-type autologous cultured skin (product name: Autograft) was accepted by the Health, Labour and Welfare Ministry on March 27, 2003. This marks one progressive step for autologous cultured skin business from the basic research stage. BCS obtained a patent in July 2002 for its technology to produce cultured skin, following the technology transfer from a professor at Tokai University's School of Medicine. Their cell culture was from ES cells. Japan Tissue Engineering (J-TEC) has applied for approval of cultured dermal autografts and allografts, and is preparing for clinical tests on cultured epidermal autografts. It is also in the clinical application stage on cartilage regeneration. Also, OsteoGenesis, Inc., which has been working on alveolar bone regeneration using cultured bone injection, is in the preclinical stage.

Other promising areas include nerve, corneal, and cardiac muscle regeneration. Especially, with further advance of the aging society, the neural regeneration area is expected to expand. This area involves the technology to regenerate nerve cells, and applies it to the treatment of Alzheimer's and Parkinson's diseases. Venture firms in this area include Sun Bio Co. (founded by a Japanese, based in California), which aims to develop products based on research by a Keio University professor. Also, in the business using ES cells, Ripuro Cell, set up by professors at Kyoto University's Institute for Frontier Medical Sciences and the University of Tokyo's Institute of Medical Sciences, is seriously tackling this technology, but its application to

human beings is yet to materialize.

In order for regenerative medicine to be widely diffused and take root as part of normal medical technologies, not only technological advancement but also the contents of legal and ethical regulations will become important points for consideration. For example, whether regenerative medicine will be covered by insurance is a vital factor to decide whether or not the market will expand. Especially, in cases of seriously ill patients, it becomes an important factor to know whether or not insurance would cover the possible death of the patient during treatment. Therefore, many companies are taking the strategy of starting in areas of dental treatment, in which patients seem to care less even if they are not covered by insurance in their treatment through regenerative technologies.

Among the foreign companies already in the Japanese market, Genzyme Corp. of the U.S. set up a Japanese subsidiary, Genzyme Japan K.K. in 1987 and has been conducting research and development on cartilage cell therapy, cell therapy in plastic surgery fields and blood vessel regeneration using HGF (hepatocyte growth factor), in addition to the development of enzyme therapy for rare diseases. Smith & Nephew of the U.K. established its subsidiary in Japan in 1987 by starting with a Japan liaison office in 1982. It has completed clinical tests in Britain in the field of cultured dermis in tissue engineering and is providing training programs, which were developed specifically for wound management business, to workers in medical care fields.

III. Legal Systems

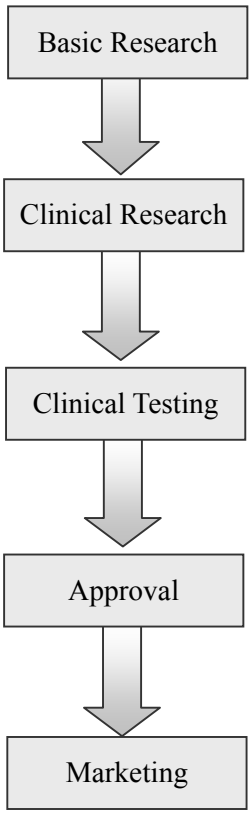
1. Pharmaceutical Affairs Law and Related Laws

1-1 Outline

The framework of the legal system concerning biomedical industry is divided mainly into two: the Pharmaceutical Affairs Law and the Medical Practitioners Law. When activity is taken as business, Pharmaceutical Affairs Law is applied and when it falls into the category of medical care and treatment by a doctor, the Medical Practitioners Law applies. The government office responsible for basic research is the Ministry of Education, Science and Culture, while the Ministry of Health, Labour and Welfare is responsible for matters concerning clinical research and thereafter. Legal regulations concerning industrialization and commercialization are mainly covered by the Pharmaceutical Affairs Law.

Industrialization and commercialization of biomedical drugs and medical equipment must generally go through the process of basic and clinical research, clinical testing, approval and marketing with various formalities required at each stage.

Figure 6. Main Regulations and Guidelines concerning Industrialization of Biomedical Drugs and Equipment



- The Ministry of Education, Culture, Sports, Science and Technology issued a guideline concerning research on specified embryos, ES cells and human genome as they involve ethics in human life or bioethics and safety. The guideline concerning the establishment and use of human ES cells was issued in September 2002.
- Under a guideline by the Ministry of Health, Labour and Welfare, it is required to obtain prior approval of the health minister to conduct clinical research in Highly Advanced Medical Technology fields, such as gene therapy.
- As for regulations in conducting clinical research on regenerative medicine, various guidelines have been issued, in addition to the Medical Practitioners Law and the Pharmaceutical Affairs Law. The guideline on ethics concerning clinical research was issued in July 2003.
- Applications for confirmation with the Ministry of Health, Labour and Welfare are required to conduct clinical tests. On the basis of the applications, consultations on the proposed clinical tests will be held so that clinical tests will be conducted while respecting the result of consultation.
- To obtain approval of drugs and medical equipment, applications for approval to manufacture them must be submitted to the Health, Labour and Welfare Minister for examination.
- Materials for applications must be collected, in principle, according to the standards stipulated by the Pharmaceutical Affairs Law, and GLP (Good Laboratory Practice) should serve as the appropriate standard for safety testing, and GCP (Good Clinical Practice) as the standard for clinical testing.
- Surveys after the products have been put on the market are required as compulsory for makers and importers of drugs, according to the GPMSP (Good Post-Marketing Surveillance Practice) rules for drugs, while such surveys are encouraged for medical equipment, according to the GPMSP rules for medical equipment, but not mandatory.

1-2 Main Issues concerning Legal Regulations

(1) Shortening of process for clinical tests

Clinical tests used to be required in Japan even for successful drugs already approved abroad in order to market them in Japan. This caused the approval process for foreign-made new drugs to take much longer time of up to five years from the time of filing applications to obtaining approval. Therefore, even introduction of foreign-developed lucrative drugs with a large potential market in Japan was often delayed. However, amid global standardization of clinical testing led by ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) among Japan, the United States and the European Union, Japan has also made progress in reforming regulations. From 1998, new drugs already approved abroad came to be exempted from some of the clinical tests required, and as a result, drugs already approved outside Japan now can obtain the Japanese government approval in one to one and half years.

(2) Main Points of the Revised Pharmaceutical Affairs Law Enforced in July 2003

Revisions of the Pharmaceutical Affairs Law are basically to be put into force in 2005, but some of the revisions were promulgated in July 2003 ahead of the 2005 revisions in Law 96, "Law to Revise Part of the Pharmaceutical Affairs Law and Bleeding and Blood Donor Supply Service Control Law". As a result of the revision, changes were made concerning genome-based drug development, regenerative medicine and cell therapy on the following two points:

1) Clinical tests led by doctors become possible

Doctors and medical institutions can file clinical test applications, which only pharmaceutical companies were allowed before the revision, and as a result, it became possible for drug makers to provide new drugs before approval to medical institutions. This revision is expected to encourage introduction into the Japanese market of foreign-developed drugs that have already been approved abroad, but pharmaceutical companies had been reluctant to develop in Japan because of questionable profitability. It is also expected that drugs already approved will be given trial adaptations. Also the revision now enables clinical data gathered in universities to be used when applying for approval of new drugs, which in turn encourages creation of bio venture startups on university campuses.

2) Safety standards for bio-derived products

New categories of "bio-derived products" and "specified bio-derived products" have been created over and above ordinary pharmaceutical products to take safety measures according to their characteristics. Specifically, on the basis of the products' potential risk of

infectious diseases when they are applied, the products made with materials derived from human and animal cells and tissues are categorized as bio-derived products, and especially among them those that require special care are grouped as specified bio-derived products. The "bio-derived products" include 131 ingredients such as genetically modified drugs, self-derived products and vaccines, and in "specified bio-derived products" there are 51 designated ingredients including human blood products and human cellular tissue drugs. Under the safety measures, drug makers of "specified bio-derived products" are required to preserve the products for 30 years.

In the revisions of the Pharmaceutical Affairs Law scheduled to be enforced in 2007, there are plans to shift the current manufacturing approval system to a marketing approval system and to lift the ban on consigned production. These movements are expected to bring about major changes to the biomedical industry's business models.

(3) Further shortening of the process for clinical tests

In April 2004, an incorporated administrative agency, called Pharmaceuticals and Medical Devices Organization, is planned to be established. With the launch of this organization, clinical testing consultations, applications for drug approval and identical checkups of medical equipment, all of which used to be conducted by separate facilities, will be managed under a single administrative organization. Along with the introduction of the fast track system (by which prior clinical test consultations and prior screenings are combined), this is expected to improve efficiency and contribute to shortening the time needed for developing new drugs.

(4) Ethical standards concerning human cloning and human embryo stem (ES) cells

The "guideline concerning the establishment and use of human ES cells" was issued in 2001 by the Ministry of Education, Culture, Sports, Science and Technology, and in 2002, Kyoto University's human ES cell research plan was approved by the ministry. Currently the technical committee on bioethics of the government's Council for Science and Technology Policy is studying a new set of safety standards on how to handle human embryos in regenerative medicine that uses ES cells.

Table 6. Regulations by Countries concerning Human Clones and ES Cells

Country	Policies
France	・ "Bio-ethics Law" (enacted in 1994): Producing human clones is banned; research on human embryos is also banned, except for observation purposes. ・A revision bill to ban cloning of human embryos was submitted to Parliament; a revision bill to allow research on the establishment of ES cells from embryos was submitted to Parliament.
Germany	・Cloning of human embryos and producing human clones are banned by law. ・ES cells are strictly restricted, but a law intending to allow import of human ES cells was enacted on July 1, 2002. As a result, importing human ES cells became possible, if permission was obtained.
U.K.	・Producing human clones is banned by law. ・The use of human embryos for research purposes and cloning human embryos for research purposes may be permitted upon application. Cloning of human embryos for research purposes was permitted in 2001, and although conditions are strict, it is possible to establish ES cells from cloned human embryos.
U.S.	・A presidential order not to approve subsidizing research to create human clones has been issued. ・A bill to ban human cloning was passed by the House of Representatives in 2001 and is currently being debated in the Senate. ・Establishing new human ES cells is not allowed, but research using already existing human ES cells may be allowed and public subsidies may be provided.
Canada	・Cloning human embryos is banned by the Health Minister's order. ・A bill to restrict creating human clones was submitted to Parliament in 2002. ・Canadian Institute of Health Research (CIHR) compiled a guideline in March 2002, which may allow the establishment of human ES cells upon applications.
Japan	・Creating human clones is banned by law; cloning of human embryos is restricted, as specially designated embryos, by guideline based on law; research on ES cells are allowed under strict conditions based on a newly made guideline. ・The Clone Technology Regulation Law (or the law to regulate cloning technologies concerning humans) was enacted in November 2000.

Source: Japan Patent Office, *"Survey Report on Trends in Technological Patent Application concerning Life Science,"* 2003.

(5) Expansion of Coverage by Health Insurance

The Ministry of Health, Labour and Welfare decided in June 2003 to designate certain cases of regenerative medicine for the first time as "Highly Advanced Medical Technology (HAMT)", for which part of the medical costs will be covered by health insurance. Those cases involve therapy to make new blood vessels by transplanting vascular stem cells to the patients, conducted by the Kansai Medical University Hospital and two other hospitals. In these cases, the patients will eventually have personal medical costs reduced from more than ¥1 million to somewhere between ¥300,000 and ¥500,000. The lighter medical costs for patients are expected to stimulate the needs for regenerative medicine and expand the market.

2. Various Systems to Protect and Utilize Intellectual Property

In the biomedical industry, the impact one basic patent could have on competitiveness is so large that it is important to strategically secure intellectual property. Explanations of the basic systems and their characteristics to protect and utilize intellectual property follow:

(1) The Patent Law (revised in 1975)

With the revision of the Patent Law in 1975, patents are not only granted to "manufacturing methods" but also to "materials". However, "medical conducts" are yet to become subjects for patents. In response to the needs of the industrial world, the Japan Patent Office has begun studying the possibility of granting patents to regenerative medicine and other advanced medical technologies.

In Japan, patents are given to the first applicant in case two or more applications are filed on the same invention.

(The Japan Patent Office web site: http://www.jpo.go.jp/index.htm)

(2) Basic Law on Intellectual Property (enacted in December 2002)

The Basic Law on Intellectual Property was enacted in 2002 for Japan to become an intellectual property-advanced country by 2005. The law stipulates basic ideas for the creation, protection and utilization of intellectual property and its realization, and provides for the establishment of the Intellectual Property Policy Headquarters in the Cabinet to carry out related policies. The headquarters has already begun working on solutions to the problems under the current situation. For example, it implemented revision of the examination standards concerning "methods of operating on, treating or diagnosing humans" in August 2003. Following this revision, it is stipulated that methods to manufacture drugs by recombinant DNA technologies and medical equipment such as cultured skin sheets become subjects for patents, even if they are to be returned to the same person.

(The Basic Law on Intellectual Property web site:
http://www.kantei.go.jp/foreign/policy/titeki/hourei/021204kihon_e.html)

(3) Japanese Version of Bayh-Dole Act: "Law on Special Measures for Industrial Revitalization Article 30" (enforced in October 1999)

In the past, intellectual property rights derived from consigned research conducted with government funding used to belong 100 percent to the country. However, with this law's enforcement, such intellectual property rights obtained in research done with government funding may be transferred to private companies. In order to manage such rights, "intellectual property headquarters" will be established in major national, public and private universities.

Also, in cases where universities conduct research upon contract with the government and public corporations, intellectual property rights will be arranged so that they will belong to the universities. As a result, the law is intended to allow intellectual property to accumulate in universities and not the country, so as to encourage research results to be circulated quickly to society through TLOs (technology licensing organizations) and others.

(4) TLO Law: "Law for Promoting University-Industry Technology Transfer" (enforced August 1998)

The importance of TLOs to promote patenting the results of university research and licensing those technologies to business corporations came to be recognized acutely after it was realized that there was a serious problem in universities lacking an intellectual property unit to manage patents, as corporations had. With this shared understanding, "the Law for Promoting University-Industry Technology Transfer" (under the jurisdiction of the Ministry of International Trade and Industry and the Ministry of Education, Culture, Sports, Science and Technology) was enacted in May 1998 and enforced in August that year with the aim to support the opening of TLOs at the nation's universities through policy measures. As of the end of August 2003, there are 34 authorized TLOs eligible to receive subsidies and other government support policy measures.

In the Ministry of Health, Labour and Welfare, research results by their national labs, research institutes and incorporated administrative agencies are significantly contributing towards the improvement of medicine and welfare, as well as the work environment. From this point of view, they have also established a technology transfer organization in the Japan Health Sciences Foundation and are trying to build up the system and environment to promote technology transfer to business corporations.

3. Government's Industrial Promotion Measures

It is only in several years recently that nation-level measures to promote the nation's bioindustry have been launched and developed on a full scale.

(1) Millennium Genome Project (November 2001, the Prime Minister)

Under the government-led, academic-industry-government joint project, "Millennium Project", in which more than two ministries make inter-ministerial efforts to tackle issues in the fields of advanced information technologies, aging population and environment. "Millennium Genome Project" was launched to conduct research in tailor-made medicine and regenerative

medicine to achieve goals in the aging population field.

The goals of this project are to put tailor-made medicine to practical use by identifying the genes of major diseases of dementia, cancer, diabetes and hypertension and launch development of new epoch-making drugs. It also aims to apply knowledge from research on functions related to development of organisms to regenerative medicine of bones and blood vessels, by utilizing self-restoring functions that will not cause rejection. In February 2003, an interim report was submitted by the project's evaluation and advisory council.

(2) Pharmaceutical Industry Vision (August 2002, The Ministry of Health, Labour and Welfare)

Worked out by the Ministry of Health, Labour and Welfare, this vision presents a future when genome-based drug development and tailor-made medical treatment will be widely conducted in around 2010, and proposes subjects to strengthen the Japanese pharmaceutical manufacturers' international competitiveness and country's measures to support the efforts. Its "action plan" lists such activities as a disease-related protein analysis project, development of the Basic Pharmaceutical Technology Research Facility (named tentatively), promotion of measures to utilize patents, acceleration of practical use through the Pharmaceuticals and Medical Devices Organization (tentatively named), a large-scale clinical testing network, and review of the approval and permission system for pharmaceutical products and medical equipment.

(3) Biotechnology Strategy Guidelines (December 6, 2002, Biotechnology Strategy Council)

The Biotechnology Strategy Guidelines regard this biotech industry as a national strategic industry, and to develop it as such, the Guidelines call for the following three strategic measures to be tackled: considerable improvement of research and development (more than doubling the R&D budget over five years, etc.), drastic strengthening of the industrialization process (expanding tax measures to support startups, reviewing regulations on startups, etc.), and thorough public understanding (drastically stepping up the government's efforts to provide information concerning safety of genetically modified food, etc.). The Bio Action Plan 2002 calls for the powerful promotion of the biotechnology program in line with its 50 action guidelines, 88 basic action plans and 202 detailed action plans.

(4) Bioindustry Cluster Policy

National policies to promote building bioindustry clusters such as the urban revitalization project by the Cabinet Office, the industry cluster plan by the Ministry of Economy, Trade and Industry, and the intelligent cluster creation project by the Ministry of Education, Culture, Sports, Science and Technology are developing at local levels. Measures by local governments and regional economic organizations are also being taken (For details, see V. Bioindustry Cluster.).

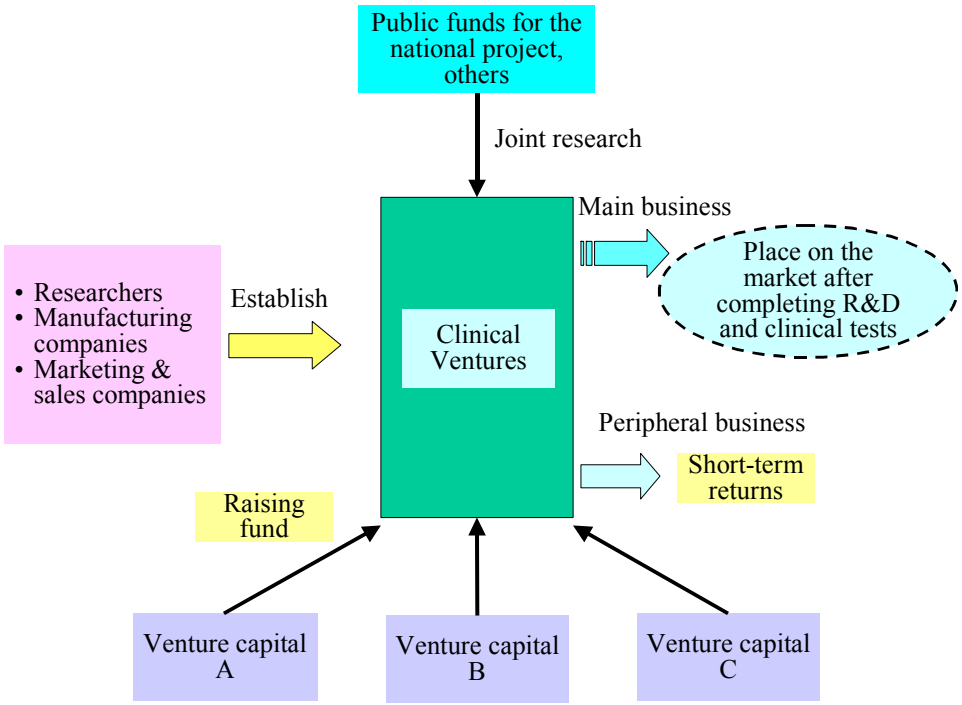
IV. Business Models

On the basis of hearings from companies involved in this industry, we present some business models in several areas of the biomedical-related industries and businesses in Japan. Business models in this field are constantly changing, as venture businesses are playing the leading role in this field, and therefore these business models are not firmly established.

1. Business Model for Clinical Ventures

Quite a few clinical ventures are operating for several years since their startup with funding from venture capitals carrying out R&D, but without producing any sales. Since it is difficult for these ventures to spare their resources for marketing, a typical business model in this field is that these ventures, after finishing the clinical tests, usually deliver their products to hospitals and other end users through specialized companies under consignment, such as major and medium pharmaceutical companies and bio-trading companies.

Figure 7. Clinical Ventures' Business Model

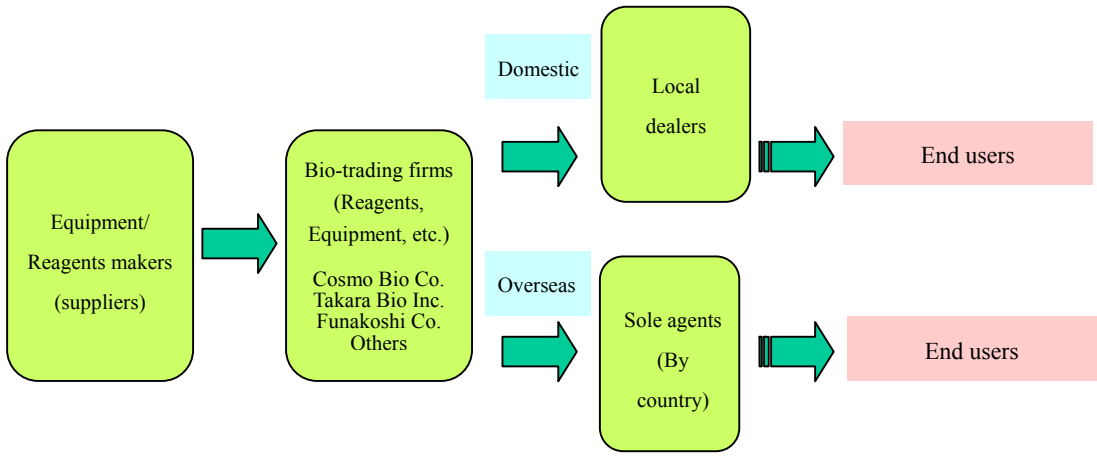


2. Basic Research/Early-Stage Business

Many of the basic research-related business target niche markets. In the basic research stage, products such as reagents and research equipment are delivered from the manufacturers and technology trading firms operating in wide areas, through local dealers, and to end users. Local wholesales play big roles in local languages, financial matters (settlement system), handling complaints and claims, and other matters.

On the other hand, there are still no business models established for clinical stages of tissue engineering, cell therapy and genome-based drug development.

Figure 8. Business Model at Basic Research/Early Stages

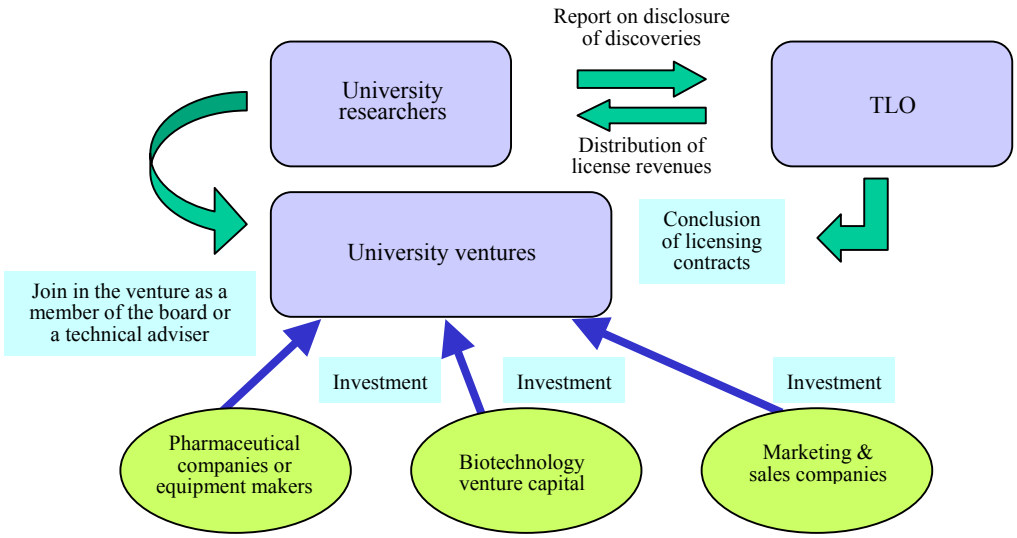


Note: Local dealers are responsible for collecting payments (settlement system) and handling complaints and claims.

3. Business Model for University Ventures

Researchers who belong to universities and public research institutions report to their university TLO (technology licensing organization) or local TLOs when they come up with new ideas or obtained research results, and then decide on the distribution of license revenues. In establishing a venture company, the researchers concerned must obtain approval of the organization they belong to if they are government employees, and then join in the management of the venture as a member of the board or a technical adviser. When establishing the venture, they often receive support from other companies on manufacturing, marketing and sales personnel and funding. In addition, they receive funding from venture capitals.

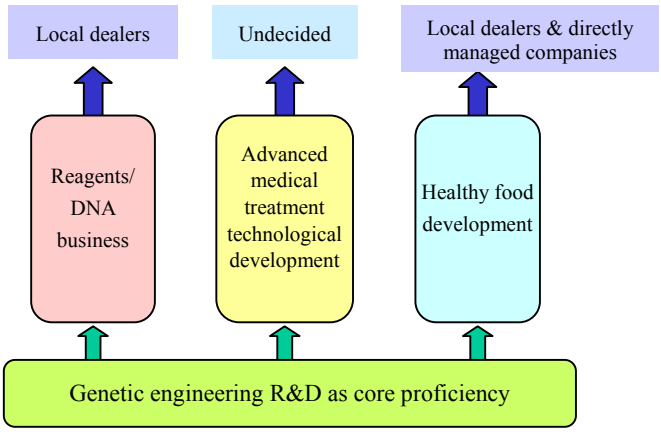
Figure 9. Business Model for University Ventures



4. Business Model for Medium Biomedical Companies

For medium biomedical companies with their roots in food biotechnology, it is advantageous for them to develop reagent and DNA business as firms specializing in basic research by using their genetic engineering R&D capability as core proficiency, rather than go directly into clinical-related business. In this business model, the medium companies enter the clinical bio-business only after they have established the foundation of basic research business.

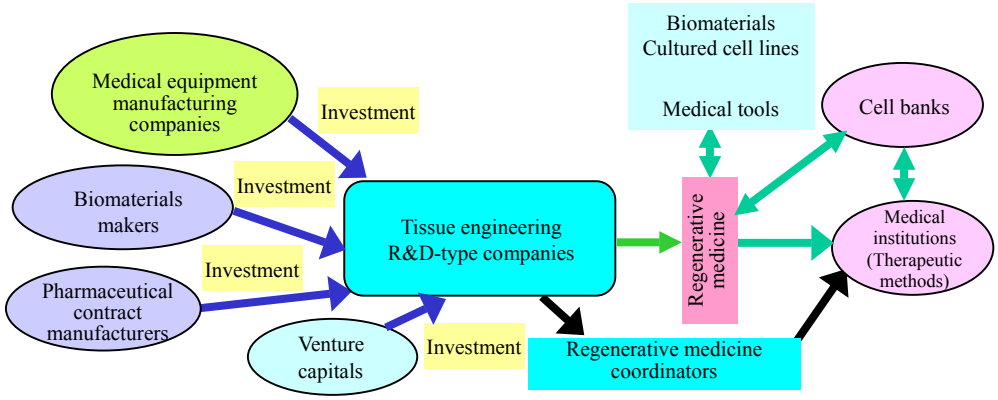
Figure 10. Business Model for Medium Biomedical Firms



5. Business Model for Tissue Engineering Ventures

In the field of tissue engineering (TE), research and development for regeneration of human tissue such as skin, bone and cartilage, has progressed to the level where commercialization of the R&D results will be realized in the very near future. Although basic technologies belong to the universities that developed them, it is very important to obtain know-how about related biomaterials and pharmaceuticals. It takes a very long period to obtain the approval from the Ministry of Health, Labour and Welfare (about five years in case of TE, because it requires submission of applications for clinical test verification). However, even after it is approved, TE will not be used widely unless it is used properly in actual medical treatments. TE venture firms should seek to develop business by nurturing regenerative medicine coordinators and working closely with highly specialized doctors and medical institutions.

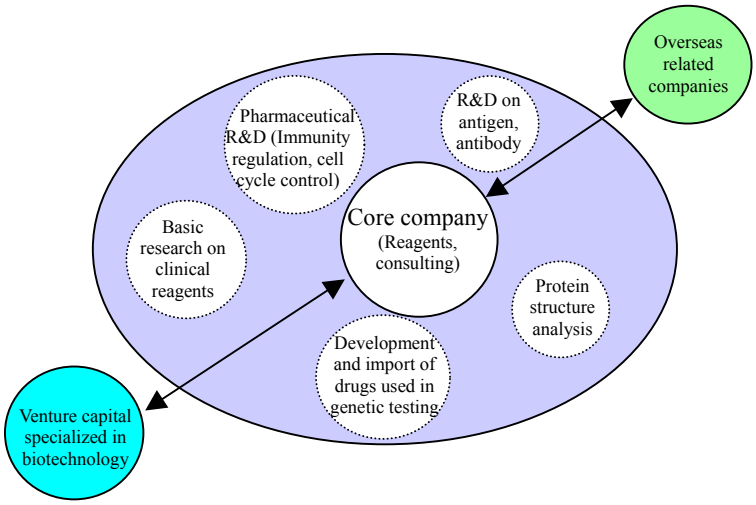
Figure 11. Business Model for Tissue Engineering Ventures



6. Network-Type Business Entity

In the model of companies developing reagents, they let their bio venture firms in related areas spin off or discover and support prominent venture firms. These type of companies also take over marketing and sales that R&D-type companies are weak in, and also establish consulting business. Through their own experiences in marketing their products, these companies also set up venture capitals specialized in biotechnology to nurture bio ventures from an angelic standpoint. Since the above-mentioned spun-off sections are organically linked as autonomous enterprises, they have the characteristics of a network business entity.

Figure 12. Business Model for Network-Type Business Entities

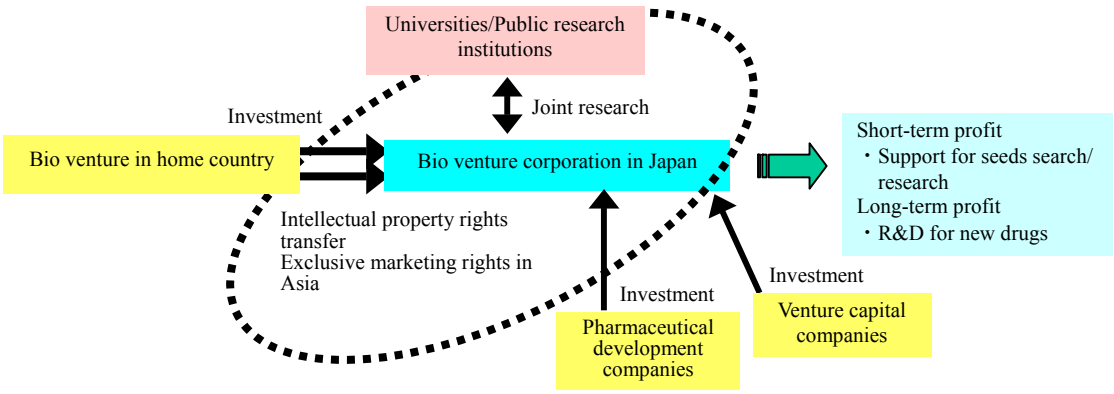


7. Business Development in Japan through Technology Transfer by Foreign Venture Companies

When a foreign bio venture wants to start business in Japan, there will be fewer risks by setting up a joint venture corporation with a Japanese partner. Although mutual trust is a precondition, there are several foreign companies that have had very favorable results by providing Japanese corporations with intellectual property rights and exclusive marketing rights in Asia and giving them autonomy including fund raising. In developing business through joint ventures, selecting good partners is extremely important.

It is a worldwide trend that productivity of research and development at companies' central research laboratories is declining. In the biomedical field, in contrast to the growing R&D expenditure, the number of new drugs developed from such expenditure has decreased sharply. At the center of the process are design and tests, not scientific technologies. What is important in each of these analyses of protein structures, bioinformatics, research equipment and devices is the designing process.

Figure 13. Business Model for Technology Transfer-Type Foreign Venture Companies



Also, as seen in the academic-industry collaboration such as university ventures, partnership and collaboration between several organizations are becoming common, and new patterns of cross-boarder alliances and strategic partnerships are becoming more important. Forming consortiums and launching new projects are becoming active and building up technology platforms is a key issue facing the biotechnology industry.

V. Bioindustry Clusters

Bioindustry clusters are now being formed in various parts of Japan. Important factors for building clusters or collections of related industries are “mutual dealings,” “sharing technology base” and “sharing customers.” It is difficult to understand the situation of clusters only by existing industrial groupings. Especially, the current situation of clusters of biomedical-related companies has not been grasped so far. However, as such industrial cluster plans and regional projects have been promoted by the leadership of the central government and local governments in recent years, it is becoming possible to comprehend these industries’ trends and situations.

1. Hokkaido Region

The bioindustry cluster in Hokkaido is made up mainly of food and agriculture-related bio ventures. However, in recent years, a new trend is emerging as more medical and environmental bio ventures are starting up. University ventures are also gradually setting up shop, with the Center for Business Creation, Otaru University of Commerce playing a leading role. “Hokkaido Bio-Cluster” (Secretariat: Northern Advancement Center for Science & Technology or NOASTEC, Hokkaido Bureau of Economy, Trade and Industry) has 63 companies as members of the Hokkaido Bio-Cluster Forum. Their aims are to promote vitalization of the bioindustry in Hokkaido by networking bio-related works in Hokkaido, sharing technological information, and matching firms as part of the Hokkaido Super Cluster Promotion Project. Under this strategy plan, the “Hokkaido Bio 21 Council” was inaugurated. Another organization, Hokkaido Bio-Industry Association, was established in 1985 with the purpose of promoting bioindustry utilizing Hokkaido’s characteristics. Especially, the recently established technology licensing organization, Hokkaido TLO (opened in December 1999), and the community-based, independent venture capital, Hokkaido Venture Capital (August 1998), are expected to play important roles.

2. Kanto Region

An industrial cluster can be found in the Tokyo Metropolitan area as “Metropolitan Biotechnology-Related Startups Network” (Secretariat: Japan Bioindustry Association). The

number of companies that registered with the network increased from 170 at the time of its launch to 186 as of August 2003. Of the total, 100 companies are located within Tokyo. Particularly, in 2003, the "Genome Bay Tokyo Project" was launched along the Tokyo Bay waterfront area to develop it into a major cluster of tailor-made medicine and bioinformatics. It must also be noted that support companies in this field are spontaneously gathering to form a support group in Toranomon Pastoral, a hotel in central Tokyo.

In Chiba Prefecture, where Kazusa DNA Research Institute, Chiba University, the University of Tokyo Kashiwa Campus, and the National Cancer Center and other institutions are located, "Chiba Bio Life Science Network Forum" (Secretariat: Commerce, Industry and Labor Department, Chiba Prefectural Government) was inaugurated and the move to promote industry-academia-government collaborations is already under way, with 64 member companies as of August 2003. On the KAZUSA HILL is Kazusa Academia Park, where a cluster of biotech, telecommunications and other high-tech research and development functions are being built, with Kazusa DNA Research Institute serving as its core. Because of the advanced trunk highway networks, it is now easily accessed from central Tokyo and Narita and Haneda airports.

In Ibaraki Prefecture, "Tsukuba Biotechnology and Genome Research Promotion Council"（Secretariat: Department of Commerce, Industry and Labor, Ibaraki Prefectural Government） was established in 2002, and at Tsukuba Science City, which will serve as the core of the project, research to improve efficiency of food production and develop new drugs are underway.

In Kanagawa Prefecture, Yokohama City is promoting "Yokohama Science Frontier" (Contact: Policy Division, Management and Planning Bureau, City of Yokohama) at Keihin Waterfront Area, with research focused on proteome and biotech tools, and in the main area of the Frontier are located 38 companies, 18 of them housed in Yokohama Joint Research Center and the other 20 in Leading Venture Plaza. As part of the city's efforts to promote redevelopment of the Keihin Waterfront Area, the Frontier project aims to create a place for academic-industrial-government collaboration in the area, with the Institute of Physical and Chemical Research (Yokohama Institute, RIKEN) playing the central role, and to develop new technologies and industries by undertaking every process from planning to development of products and manufacturing. A community-based joint research project to "develop an analysis and evaluation system for functional proteins" on contract from the Japan Science and Technology Agency, began in 2001. Kihara Memorial Yokohama Foundation for the Advancement of Life Sciences, as the core institution of the project, is working in conjunction with local universities and public research institutes, as well as local companies, to research and develop new drugs through analysis of genome and proteins.

3. Chubu Region

“Tokai Bio-Factory Research Society” is considered to serve as one base for the biotech cluster in the Tokai area. This association was established in June 2002 as a group responsible for life science research in the industrial cluster plan known as “Tokai Factory Creation Project.” It is made up of Tokai Bio venture Network and Tokai Bio venture Support Companies’ Network, with some 500 researchers and 26 supporting companies participating (as of August 2003). Launched at the initiative of the Chubu Bureau of Economy, Trade and Industry, it has set up a secretariat among the industrial, academic and government sectors and private companies such as the Medical & Biological Laboratories Co., a reagent and diagnostic agent producer to conduct exchange activities. An incorporated nonprofit organization “Bio Factory Central Japan” (Secretariat: Chubu Science and Technology Center) was established in October 2003, combined with “Chubu Bio-industry Promotion Group” (established in 1986).

In Shizuoka Prefecture, there is a large cluster of medical service-related industries, such as pharmaceuticals, medical equipment and food industry. The shipment values of both pharmaceuticals and medical equipment and goods from this area are second largest, according to the Survey of Pharmaceutical Industry Production 2002, with about 50 of related companies and offices located in this area. Shizuoka Cancer Center opened in the autumn of 2002, and its research institute is set to open in 2005. In addition, many universities and research institutes are located in Shizuoka, while the National Institute of Genetics is also located as an international foothold of genomic analysis and related research. Against this background, “Fuji Pharm Valley Project” (Secretariat: Pharm Valley Center, Shizuoka Organization for Creation of Industries) has been set up and 304 individuals are participating as members of the Pharm Valley Research & Development Forum, a grouping of organizations and individuals from the industrial, academic and government sectors. Highly advanced research combining basic research and clinical research are being conducted with the leadership of Shizuoka Cancer Center, while nurturing of entrepreneurs is also under way using the bio-incubation facilities.

In Toyama Prefecture, where pharmaceutical makers have always existed, there are some 50 pharmaceutical manufacturers, large and small, including Toyama Chemical Co. and Nici-iko Pharmaceutical Co. Toyama Prefectural Government has set up the project headquarters within the government that worked out Toyama BioValley Development Plan (Secretariat: Toyama New Century Industrial Organization). It also holds the Bio Valley workshop to promote research in the latest biotechnology. Fifteen companies are participating in the Toyama BioValley Development Plan. It conducts comprehensive research and development activity on micro-array chips in attempts to establish rapid diagnosis of infectious diseases, and develop personalized medical treatment systems and new drugs as well as their commercialization.

4. Kansai Region

“Association for the Promotion of Bio-Industry in Kinki Region” (Secretariat: Osaka Science & Technology Center) was established in 1985 with the initiative of the Osaka Bureau of International Trade and Industry (currently, the Kansai Bureau of Economy, Trade and Industry). It covers all areas of biotechnology and has 93 bio-related companies, including pharmaceutical manufacturers and sake brewers, as its members. Since April 2001, the organization has been playing the role as the prime mover behind the Kinki Bio-Related Industry Project to encourage closer cooperation among the industrial, academic and government sectors in biotechnology in this region. And, with the key phrase of “industrialization of advanced technology seeds” as slogan, it is also promoting creation of new ventures and innovation of medium and small enterprises.

In Kobe City, clustering of biomedical venture companies, mainly in regenerative medicine, has been progressing at an accelerated pace on the basis of the city’s “Medical Industry Development Project” (Secretariat: Planning and Coordination Bureau and Industry Promotion Bureau, City of Kobe). The number of companies that entered Kobe KIMEC Center Building, Kobe International Business Center (KIBC), Pilot Enterprise Zone (PEZ), Kobe Incubation Office (KIO) and Translational Research Informatics Center (TRI) reached 39 as of August 2003, and is still increasing. In this project site, construction work and expansion of core facilities such as RIKEN Center for Developmental Biology (RIKEN CDB) and Institute of Biomedical Research and Innovation (IBRI) have been progressing to make translational research, or bridging basic medicine level research to clinical levels possible. Furthermore, the Kobe Medical Industry Development Project Study Group had as many as 379 companies as its members as of July 2002. The city is exerting to push research and development of state-of-the-art medical technologies and help create new businesses, by promoting collaboration among domestic and foreign medical-related companies, universities and research institutions at Port Island 2nd Stage as the main project site.

Osaka is traditionally the nation’s center of pharmaceutical industry, with many pharmaceutical-related industries, including manufacturing and wholesale companies, gathered. Notably, five of the country’s largest 10 pharmaceutical companies are headquartered in Osaka. With such a great potential as its background, Osaka Prefectural Government’s “Saito Life Science Park” (Secretariat: Saito Bio Promotion Division, Osaka Prefectural Government, Saito {International Cultural Park} Promotion Council) is now trying to attract companies to participate in the project while, at the same time, is working on the construction of its major facilities. In its neighborhood are Osaka University’s Faculty of Medicine, Graduate School of Medicine and other institutions, and a considerable number of bio venture companies are located in this area although the exact number is not known. The Life Science Park is one of the

main parts of Saito, or the International Cultural Park, which combines international academic and research functions and cultural exchange functions and aims to develop it into a major life science research center with close cooperation with neighboring research facilities. The construction of the National Medical and Pharmaceutical Basic Technology Research Institute is planned in this Life Science Park.

At "Kansai Science City", located in an area bordering Osaka, Kyoto and Nara prefectures, the Intelligent Cluster Promotion Headquarters is playing a central role to build such a cluster. Twenty-seven companies have set up shop in the laboratory building of Keihanna Plaza, a core organization, with nine other companies conducting joint research. Having been established as a core for cultural, academic and research exchanges at Kansai Science City, it promotes industry-academia-government collaboration and supports efforts to create new industries.

5. Chugoku Region

Some 20 to 25 companies are participating in the "Hiroshima Central Bio-Cluster Project" (Secretariat: Intelligent Cluster Headquarters of Hiroshima Prefectural Institute of Industrial Science and Technology, Hiroshima Industrial Promotion Organization) and about five of them have signed contracts to conduct joint research. On the basis of bio-related technologies accumulated at Hiroshima University and other institutions, the project aims at formulating a technology innovation-type cluster, with Hiroshima Prefectural Institute of Industrial Science and Technology as its core.

6. Shikoku Region

Kagawa Prefecture (Commerce and Labor Department) is working to build a glyco-biocluster, known as "Kagawa Rare Sugar Cluster," based on research on rare sugars (biologically functional monosaccharides), which was adopted as one of the government's Intelligent Cluster Creation Projects (Secretariat: Kagawa Industry Support Foundation). Kagawa University and Kagawa Medical University are aiming to form the research and development core as the two main institutions. Utilizing special measures in the government's glyco-biocluster special zone (approved in April 2003), the two universities are now recruiting foreign researchers to work on rare sugars.

In Tokushima Prefecture, a similar Intelligent Cluster Creation Project (Secretariat: Tokushima Industrial Promotion Organization) is being promoted as the creation of health and

medical service cluster led by health technology." With the development of diagnosing equipment and of treatment technologies as the cluster's main research topics, it aims at promoting industrialization of the outcome of their joint research. In Tokushima City, there is one of the only two genome research institutes established in Japanese universities–Institute for Genome Research at the University of Tokushima, the other being at the University of Tokyo's Institute of Medical Science.

7. Kyushu Region

Fukuoka Prefecture formulated the "Fukuoka Bio Valley Project" (FBV Project) in April 2001. Bio Project Promotion Office of Kurume Research Park, the management organization for the venture incubation facility, set up in 1989, is functioning as a secretariat. FBV Project Promotion Council has 76 companies as its members. It aims to collect bio-related companies and research institution in the southern area of Fukuoka Prefecture and create new industries based on biotechnology as the core. In September the same year, "Fukuoka Bio Valley Project Promotion Council" was established as the central institution of this project. In Kurume City and its surrounding area of the prefecture's southern part there is a cluster of many traditional sake brewers and other brewing industries. However, this project aims at developing new biomedical ventures from this area by making use of potential of the local universities and public research institutions.

Apart from Fukuoka Prefecture, an industry-academia-government collaboration venture, Trans Genic Inc., established in 1998 as part of "Kumamoto Prefecture's Life Science Center project", and Eugene, set up in 2001, by professors of Kumamoto University's Institute of Molecular Embryology and Genetics, are engaged in projects.

Figure 14. Clustering of Biotechnology-Related Companies by Prefectural Breakdown
(As of August 2003)

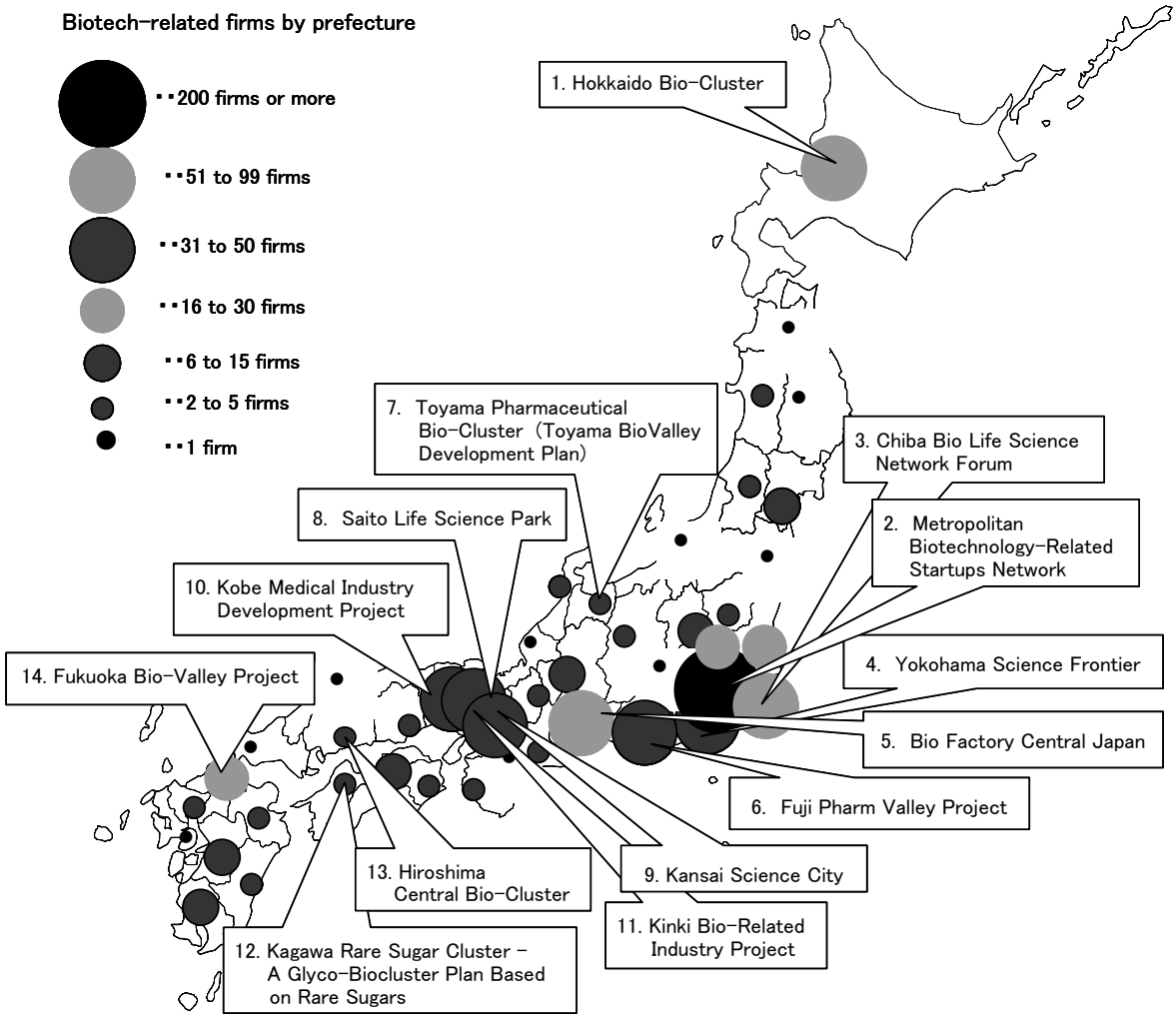


Table 7. Japan's Major Bio-Clusters Networks Outline (As of August 2003)

1. Hokkaido Bio-Cluster	
Core Body	Hokkaido Bio-Cluster Forum (http://www.noastec.jp/biocluster/) Northern Advancement Center for Science & Technology (NOASTEC), Hokkaido Bureau of Economy, Trade and Industry
Number of Companies	63
Outline	Food and agriculture-related bio ventures make a majority, but medical and environmental bio ventures are increasing. Active roles are expected to be played by recently established Hokkaido TLO and Hokkaido Venture Capital.
Source	Number of Hokkaido Bio-Cluster Forum Member Companies (Home page)

2. Metropolitan Biotechnology-Related Startups Network	
Core Body	Metropolitan Biotechnology-Related Startups Network (http://www.shutoken-bio.net/) Bioindustry Promotion Council, Kanto Bureau of Economy, Trade and Industry
Number of Companies	186
Outline	As part of the central government's industrial cluster project, this was organized in July 2002 as a platform to nurture and support bio ventures with the leadership of the Kanto Bureau of Economy, Trade and Industry. Of the 186 companies registered (as of August 2003), 100 are concentrated within Tokyo.
Source	Metropolitan Biotechnology-Related Startups Network (Home page)
3. Chiba Bio Life Science Network Forum	
Core Body	Commerce, Industry and Labor Department, Chiba Prefecture (http://www/chiba-bio-net.com/)
Number of Companies	64
Outline	This seeks to bring together biotechnology, information communication and other high-tech R&D functions, with the Kazusa DNA Research Institute, the National Cancer Center, Chiba University, the University of Tokyo Kashiwa Campus as its cores, on Kazusa Hill, which can be accessed easily from central Tokyo, and Narita and Haneda airports.
Source	Kazusa Akademica Park, its 21 companies (Home page & hearing)
4. Yokohama Science Frontier	
Core Body	Planning Division, Planning and Coordination Dept., City of Yokohama (http://www.city.yokohama.jp/me/keiei/seisaku/keihin/kenkyu/)
Number of Companies	38
Outline	In order to promote redevelopment of the Keihin Waterfront Area, this creates a place for industry-academia-government collaboration, led by the Institute of Physical and Chemical Research (RIKEN) Yokohama Institute, and aims to create new technologies and industries mainly in proteome and bio-tools.
Source	Companies at Yokohama Joint Research Center (18 firms), Leading Venture Plaza (20 firms) (Hearing and Yokohama Industrial Development Corp. home page)
5. Bio Factory Central Japan	
Core Body	Tokai Bio-Factory Society (http://www.bioface.or.jp/) Chubu Bureau of Economy, Trade and Industry, private companies, university researchers make up the secretariat. "Bio Factory Central Japan" was established in October 2003, combined with "Chubu Bio-industry Promotion Group". (http://www.shatchy.ne.jp/cstc/index/bio/bio2.htm)
Number of Companies	26
Outline	This started as a life science group of the industrial cluster plan called "Tokai Factory Creation Project" in June 2002. It is made up of Tokai Bio venture Network and Tokai Bio venture Support Companies' Network, with some 500 researchers and 26 supporting companies participating.
Source	Bio Factory Central Japan
6. Fuji Pharm Valley Project	
Core Body	Pharm Valley Center, Shizuoka Organization for Creation of Industries (http://www.scchr.jp/pvc/)
Number of Companies	304 people participating in this project
Outline	There is a large collection of pharmaceutical, medical equipment and food processing industries in Shizuoka Prefecture, with both pharmaceutical and medical equipment production being the second largest in Japan. It aims to promote advanced research combining basic and clinical science, with the Shizuoka Cancer Center playing central roles.
Source	Pharm Valley Research and Development Forum members (Names of the organizations and individuals in the industrial, academic and public sectors, their lists are not disclosed in principle.) (Hearing)

7. Toyama Pharmaceutical Bio-Cluster (Toyama BioValley Development Plan)	
Core Body	Toyama New Century Industry Organization (http://www.tonio.or.jp/gijutsu/clus/)
Number of Companies	15
Outline	Comprehensive R&D activity is conducted here on micro-array chips mainly with Toyama Medical and Pharmaceutical University and Toyama Prefectural University, with an aim to realize speedier diagnosis of infectious diseases and develop personalized medical treatment system and new drugs and their commercialization. This is to make most use of potentials accumulated by the pharmaceutical industry that exist in Toyama since olden days.
Source	(Home page)
8. Saito Life Science Park	
Core Body	Saito (International Cultural Park) Promotion Council (http://www.saito.tv/) International Culture Park Corp. (Urban Development Corp. Kansai Branch) (http://www.saito-udc.jp/saito/) Saito Bio Promotion Division, Planning & Coordination Dept., Osaka Prefecture (http://www.pref.osaka.jp/osaka-pref/kikaku/saito/index.html) Japan Biotechnology Business Competition (http://mic.e-osaka.ne.jp/biocompe/)
Number of Companies	2
Outline	Five of the nation's 10 largest pharmaceutical companies are headquartered in Osaka, where drug making industries have traditionally been concentrated. With such potential as its background, this project seeks to form a life science research base that keeps close collaboration with surrounding research institutions. The national Fundamental Pharmaceutical Technology Research Institute is planned to be built in this Life Science Park.
Source	Efforts to attract companies to this site are currently under way. The number of companies is that of September 3, 2003. (Hearing)
9. Kansai Science City	
Core Body	Intelligent Cluster Promotion Headquarters, Keihanna Interaction Plaza, Inc. (http://www.kri.or.jp/)
Number of Companies	27
Outline	This will promote collaborations among industrial, academic and public sectors and support creation of new industries mainly at Keihanna Plaza, which was built as the base for cultural, academic and research exchange at the Kansai Science City located in a vast area bordering Osaka, Kyoto and Nara.
Source	Companies hosed in the laboratory building. (In addition, nine more companies are conducting joint research.) (Home page)
10. Kobe Medical Industry Development Project	
Core Body	Kobe Medical Industry Development Project (http://www.city.kobe.jp/cityoffice/06/015/iryo/) Project Research Office, Planning and Coordination Bureau, Corporate Relations Division, Industry and Agriculture Promotion Bureau, the City of Kobe
Number of Companies	39
Outline	With research focus on regenerative medicine, this project encourages collaborations among medical service-related companies, both domestic and foreign, and universities and public institutions. By doing so, it promotes R&D of most advanced medical technologies and seeks to create new businesses. Expansion of RIKEN Center for Developmental Biology (RIKEN CDB) and Institute of Biomedical Research and Innovation (IBRI) have progressed and translational research have become possible.
Source	The 39 companies are those housed in Kobe KIMEC Center Building, Kobe International Business Center (KIBC), Pilot Enterprise Zone (PEZ), Kobe Incubation Office (KIO), and Translational Research Informatics Center (TRI). In addition, there are 379 companies belonging to the Kobe Medical Industry Development Project Study Group (As of July 2003). (Home page and hearing)

11. Kinki Bio-Related Industry Project	
Core Body	Kinki Bio-Industry Development Organization (http://www.kinkibio.com/) Kansai Bureau of Economy, Trade and Industry
Number of Companies	54
Outline	This encourages collaborations among industry, academia and government in the biotechnology fields in the Kinki Region, and promote creation of new ventures and innovation of small and medium enterprises, with the key phrases of "industrialization of advanced technological seeds."
Source	(Home page)
12. Kagawa Rare Sugar Cluster – A Glyco-Biocluster Plan Based on Rare Sugars	
Core Body	Rare Sugar Project Team, Takamatsu Region Intelligent Cluster Headquarters, Kagawa Industry Support Foundation (http://rs.kagawa.com/info.html)
Number of Companies	6
Outline	With Kagawa University and Kagawa Medical University as main institutes, this project conducts analysis of architecture and development of mass production methods of rare sugars, and development of pharmaceuticals and other rare sugar-based products, and aims at establishing glycol-life-science and developing new glycol-bio industries.
Source	(Home page)
13. Hiroshima Central Bio-Cluster	
Core Body	Intelligent Cluster Headquarters, Hiroshima Prefectural Institute of Industrial Science and Technology, Hiroshima Industrial Promotion Organization (http://www.sanken.gr.jp/ *under construction)
Number of Companies	20～25
Outline	On the basis of bio-related technologies accumulated at Hiroshima University and other institutes, this projects aims at forming a technology innovation-type cluster to support development of medical service products and pharmaceutical drugs, with Hiroshima Prefectural Institute of Industrial, Science and Technology as its core.
Source	About 5 companies that have signed joined research contracts. (Hearing)
14. Fukuoka Bio-Valley Project	
Core Body	Fukuoka Bio Valley (FBV Project Promotion Council) Bio Project Promotion Office, Kurume Research Park Co., Ltd. (http://www.krp.ktarn.or.jp/fbv/)
Number of Companies	76
Outline	This project seeks to bring together bio-related companies and research institutions to southern Fukuoka Prefecture, particularly around Kurume City, where sake brewers and other brewing companies are concentrated, and develop new biomedical industries. FBV Project Promotion Council has been established as the main organization to promote this project.
Source	FBV Project Promotion Council member companies (Hearing)

VI. Examples of Foreign Capital's Entry

1. 100%-Owned Subsidiary in Japan

Actelion Pharmaceuticals Japan Ltd.

Established : October 2001

Capital : ¥95 million

Employees : 32 (As of January 1, 2003)

URL : http://www.actelion.co.jp/ (in Japanese)
http://www.actelion.com/ (in English)

Head Office : Actelion Ltd. (Switzerland)

Established : December 1997.

A R&D-oriented company established by a former Roche researcher in the circulatory system field, it aims at discovery and development of epoch-making new drugs for endothelial cell-related diseases. Major products include Tracleer (generic name: bosentan) for hard-to-cure pulmonary arterial hypertension, and Endothelin Receptor Antagonists, the world's first orally administered PAH drug. Besides its headquarters in Allschwill/Basel, Switzerland, it has subsidiaries, all 100 percent-owned, in 14 countries.

< Form of market entry >

100%-owned corporation

< Background of market entry >

- Actelion Pharmaceuticals Japan Ltd. (Actelion Japan) was established as a 100 percent-owned subsidiary of Actelion Ltd. in October 2001 to obtain an early approval of Tracleer and tezosentan in Japan and the Asian region, as well as to market them.
- It's entry into Japan is based on Actelion's global strategy and is one of the three pillars in the world, next to the European Union and the United States. The reasons are 1) the attractive size of the Japanese pharmaceutical market, second largest in the world, next only to the United States, 2) because success in Japan means "proof of high quality" that can be accepted throughout the world, and 3) because Japan can become the foothold for entering the Southeast Asian markets.

< Process of establishing a foothold in Japan >

- Actelion Japan was established as a 100 percent-owned subsidiary from the very beginning. The parent company chose to enter the market on its own in view of its products' nature as niche products whose demand is very strong. Its judgment was that 1) different handling, according to individual products, becomes necessary as different marketing channels are

needed according to specific purposes, and 2) its presence in Japan is indispensable to future expansion of the business into Southeast Asia.

- The president of the Actelion head office in Switzerland personally asked the current Actelion Japan president, Satoshi Tanaka, to take the post. Following this, preparations were made mainly by the Actelion Japan president until its subsidiary in Japan was established after going through about two months as a representative office.

< Business development >

- Its policy is to conduct research and development, application for approval, and marketing independently. It filed an application for approval of Tracleer in April 2003. It conducted clinical tests on its own to apply for approval and in January 2003, Tracleer was designated as a drug for rare diseases. Clinical tests were completed in a year from April 2002 to March 2003, a relatively short period for clinical tests mainly because of the drug's "strength" – because it was a niche product with a strong demand, it was easy to obtain cooperation in clinical tests from medical institutions and patients. It is expected to be approved in the autumn of 2003.
- As for its outlets, the company judged that, because Tracleer, a drug for treating pulmonary arterial hypertension, is a niche product, it is possible to establish outlets with few selected MRs and set up its own sales channels. The MR system is called a "virtual office" with each MRs linked to its office to share information, using mobile PC terminals.

< Factors of success >

Three major factors necessary for biomedical companies to succeed in the Japanese market are: 1) excellent seeds in niche areas, 2) employ capable people, and 3) transfer discretionary authority to the Japanese corporation.

1) Excellent seeds in niche areas

- In the clinical test stage, it is easy to obtain cooperation from medical institutions and patients, because this company's drug is for rare diseases. As for marketing, small-scale marketing is possible, and its outlets and customers can be identified as its product is for niche markets.

2) Employing capable people

- To employ capable people is a major issue when a company is entering a new market. The company actively hired experienced people in their 50s and older. It hopes their extensive human networks and precious know-how will be accumulated in Actelion Japan.
- The company could minimize obstacles for foreign companies' entry into the Japanese market, such as regulations unique to the Japanese market, business practices particular to this industry and cultural differences, by making most use of those veteran Japanese employees' know-how and networks. In order to make this effective, and to prevent information from being held by a handful of executives, it is encouraging to share necessary

information among employees while helping to create an atmosphere and corporate culture that would allow employees to freely speak out their views.

3) Transfer of discretionary authority to the Japanese corporation

- In addition to the above two factors, it is another important factor for the company's success that Actelion Japan, a corporation in Japan, be given the maximum discretionary authority. If it has to ask for decision and instructions from the head office whenever it receives business proposals and inquiries from other companies, it would be very difficult to win the trust from its potential business partners and customers as well as to close business deals. It is important to think that to have executives dispatched from the home office is not always the best way but to have a system that would enable the corporation to make appropriate decisions promptly according to the condition of the Japanese market.

< Future >

It is considering the possibility of joint research with Japanese companies and universities. Actually, it has received proposals of joint research from universities. It hopes to be able to introduce new drug technologies from Japan to Switzerland, and not only to introduce drugs from Switzerland to Japan. The head office in Switzerland has also high hopes for such contributions from the Japanese corporation.

2. Alliance among Venture Companies

Stem Cell Sciences KK (SCS KK)

Established : April 2002
Capital : ¥180 million (As of August 19, 2003)
Employees : 11 (As of the end July, 2003)
Shareholders: Stem Cell Sciences Ltd. 48.8 %
Sosei Co., Ltd. 26.0 %
Venture capitals (9 companies) 19.3 %
Individuals (employees, others) 5.9 %
* Initially, SCS had 58 percent and Sosei 35 percent, but later, the capital was increased twice. The stock price was 50,000 yen per share at the time of the company's inauguration, but after two capital increases, the fund was raised to 750,000 yen per share.
URL : http://www.scskk.com/ (in Japanese)
Head Office : Stem Cell Sciences Ltd. (SCS) (Australia)
Established : December 1994.

A bio venture specialized in embryonic stem cell research. Its CEO is Peter Mountford, Ph.D. The company was given from Professor Austin Smith at the Institute of Stem Cell Research (ISCR) of Edinburgh University in Scotland, the exclusive global right to put to practical use of the results of research at the institute from 1991 onward, on stem cells' growth and differentiation. Major research items include research on regulation factors concerning growth and differentiation of target stem cells, probe and research of new genes and compounds concerning regulation factors, and research and development of stable production of high-purity cells applicable to cell transplant therapy.

< Form of market entry >

Establishment of a joint venture company with venture firms

< Background of market entry >

- Stem Cell Sciences Ltd. (SCS) set up a joint venture firm, Stem Cell Sciences KK, with Sosei Co. to launch business in Asia, using biomedical patents it owns.
- SCS owns 14 patents on basic research, but it takes further research to turn the patents into business. In selecting the foothold for developing business in Asia, the parent company chose Kobe City, where RIKEN Center for Developmental Biology (RIKEN CDB) is located, for establishing its Japanese subsidiary. The primary condition for the search was that there is a possible partner that can conduct joint research. SCS concluded that, in view of its size and strength, it is best to establish a joint venture company with a Japanese company, in order to conduct joint research with RIKEN CDB. Subsequently, SCM sounded Sosei with the proposal to establish a joint venture.
- Sosei's main business line is development of pharmaceutical products. It is conducting development of its seventh item through introduction of drugs from abroad and joint research with Japanese and foreign pharmaceutical companies and universities (as of March 2003). This company is utilizing extensive global network in building up in its technology transfer business for improving its development pipelines and promotion of development.

< Business development >

- On the basis of the intellectual property rights owned by SCS, the joint venture utilizes Sosei's business infrastructure. It conducts joint research with RIKEN CDB and other research institutes to develop new fundamental technologies concerning stem cell research. Based on these fundamental technologies, it envisages developing cell drugs and producing, marketing and importing related cells as its core business. At the same time, it will also give permission to use the patents it holds to pharmaceutical companies and sell cell plates to support its research for new drug development.
- SCS KK participates in various national projects.
- In the Japan Science and Technology Agency's Intelligent Cluster Creation Project (four

research groups in the Kansai Region), it conducts joint research with RIKEN CDB and Sasai Group.

- Kobe Community-Based Joint Research Project. Under the Kobe Medical Industry Development Project, it defrays the personnel cost for the collaborated research by the Institute of Biomedical Research and Innovation (IBRI) and RIKEN CDB and loans its researchers. It is under the condition that it will share intellectual property rights to the research results from this project and be given a priority right to put it into practical use. It aims at establishing technologies for differentiation-induction of endoderm cells from ES cells.
- Kobe City's "Translational Research toward Creation of Biomedical Cluster including Regenerative Medicine," has been adopted as a special zone (2002~2006, budget: approximately ¥500 million per year per area). It covers the personnel cost for the project and provides researchers on loan for collaborative research between RIKEN and Kyoto University. The project focuses on research for creation of effective nerve cells and nerve cell transplant and analysis of clinical effects.
- Dr. Shinichi Nishikawa, deputy director of RIKEN CDB, Stem Cell Sciences' joint research partner, has a close relationship with Professor Smith of Edinburgh University through advanced biomedical research. Meanwhile, Dr. Hitoshi Niwa, who replaced departing SCS CEO Dr. Mountford, at the university's Institute of Stem Cell Research as researcher, now leads the institute's research team of pluripotent stem cells and is conducting joint research with Stem Cell Sciences.

< Factors of success >

One of the important factors for biomedical companies to succeed in the Japanese market is to have outstanding technological power.

1) Outstanding technological power

The company thinks it was its outstanding technological power that made the smooth fund raising possible through the three capital increases.

2) Strategic management (both main business and side business)

- Venture capitals in Japan are looking for "Japanese type" venture companies. This means they want management that produces profits in a short period of time. Stem Cell Sciences is earning short-term profit through sales of cell plates, serum-free media and other products.
- The main products are currently in their research stages and are not in a condition to produce profits. In order to cover this situation, a side business becomes necessary. However, a side business that requires new research would be useless. Stem Cell Sciences secures a certain level of profits, without spending extra for research, by utilizing results obtained in the process of research of the main business products for its side business.
- Specifically, in the support service for clinical research and tests at medical departments and

school of medicine, this company may enter the regenerative medicine business by supporting improvement of quality and productivity of clinical tests in universities. It is difficult for new-comer companies without practical achivement in Japan to apply clinical tests and it will take an extremely long time to become eligible. Stem Cell Sciences plans to begin business by initially supporting clinical research in universities, and after gaining results, enter the full-scale clinical market. It thinks that side business not only produces profit but also helps build up its track record.

3) Alliance with Japanese companies

Japanese pharmaceutical companies thus far have been protected by the governmental price regulations for drugs. Therefore, for them, it has been a stable industry and there has not been much movement of talented people in this industry. SCS will try to expand its business chances by cooperating and allying with Japanese companies.

< Future >

- SCS will aim to commercialize the results of its major research. It hopes to continue to expand its cooperation and tie-ups with universities and medical institutions.
- From Sosei's standpoint, SCS may enter tie-ups with other foreign companies, if they do not compete with Sosei.
- Kobe City has started sister city exchanges with Edinburgh, Scotland. With this city Kobe-Edinburgh relationship as a core, SCS hopes to promote scientific collaborations between Japan and U.K.
- It is SCS's dream to open a Regenerative Medicine Center, using mainly Stem Cell Sciences' technologies, on the basis of the advanced medical industry special zone in the Kobe Medical Industry Development Project.

3. Joint Venture with Specialized Biomedical Trading Firm

Ciphergen Biosystems K.K.

Established : April 2002
Capital : ¥125 million (As of August 2003)
Shareholders : SC BioScience Corp. 30% (70% at the time of establishment)
Ciphergen Biosystems, Inc. 70% (30% at the time of establishment)
Employees : 12 (As of the end of August 2003)
URL : http://www.ciphergen.co.jp/ (in Japanese)
http://www.ciphergen.com/ (in English)
Head Office : Ciphergen Biosystems, Inc. (United States)

Established : December 1994.

Main business is marketing and sales of a protein analysis system, "SELDI System" (Japanese product name: "Protein Chip System"), and consigned analysis service. This system is applicable to diagnosis using multi-markers to measure serum and other proteins ' "variety and the amount of expression." At the American Association of Cancer Research (AACR), the number of protein chips-related announcements made has been increasing, from 14 in 2001 and 26 in 2002 to 46 in 2003, and is becoming the de facto standard. Currently, more than 200 units have been delivered throughout the world. The company was listed on NASDAQ in 2000.

< Form of market entry >

A joint company established with a general trading company (which later spun off into a specialized biomedical trading firm).

< Background of market entry >

- Sumitomo Corp. was looking for new business close to genome-based drug development, while it established a sales company for biotechnology-related equipment and was pushing import sales of biotech equipment and tools such as bio reactors. In 1998, the company was introduced to Ciphergen Biosystems, Inc.'s protein analysis system by Mr. Yoshihiro Otaki, then head of bio investment business department at Japan's largest venture capital, JAFCO (he is currently the president of BioFronteers Partners). The product was the most advanced system with the world's first functions, and enjoyed high evaluation from Japanese research institutions. Realizing that protein chips will be the main product, replacing DNA chips, Sumitomo began negotiations to market the Ciphergen products in Japan.
- At first, Ciphergen did not show much interest in the Japanese market, but because reaction to the product was very favorable, Sumitomo tried hard to persuade the U.S. company to do business with Japan. Eventually, Sumitomo Corp. agreed to invest $2 million to Ciphergen and also to set up jointly its Japanese company, Ciphergen Biosystems K.K. (Ciphergen Japan). They also agreed that Sumitomo Corp. (later spun off as SC BioScience Corp.) sends its executive as the president of Ciphergen Japan.
- Later, Sumitomo Corp. established SC BioScience Corp. in 2000 to expand its biotechnology business and transferred all of its biotechnology business to SC BioScience.

< Business Development >

- In March 1999, Ciphergen Japan was established, and marketing of protein analysis system "SELDI System" began. The company was housed in a rental lab, run by Nippon Roche Institute at the time of its launch, and later moved to Yokohama Business Park.
- The Protein Chip System, made up of a protein chip reader, its exclusive analysis software, a computer, and expendable supplies, costs 40 million yen. Its sales have been steadily

growing, from three units in 1999 to eight in 2000, six in 2001 and 14 in 2002.

- Sales activities are concentrated on university research institutes, public research institutions, and pharmaceutical companies. The system has been delivered to the National Cancer Center, Chiba University Medical Department, Jikei University School of Medicine, Osaka University Faculty of Medicine, the Institute of Physical and Chemical Research, and several pharmaceutical companies. In addition, joint research is conducted with several university laboratories.
- Business activities toward local universities and research institutions are being conducted directly by the Tokyo head office. However, local agents take care of follow-up, once the business deals are made.

< Factors of success >

1) Entry into the market by establishing a joint venture

The biggest factor for success is the fact that a joint venture was established to enter the Japanese market. When it is handled by a general agency, it often ends up splitting between the products side and the sales side, when sales do not fare well. However, in a joint venture firm, both the production side and the sales side can cooperate to achieve their goals, being in the same boat heading for the same destination, by discussing and exploring ways to improve their ways of doing business and carrying out what they have talked about.

2) Investment in the parent company

As a condition for Ciphergen's entry into Japan, Sumitomo Corp. invested $2 million into Ciphergen U.S. first. This financing by Sumitomo Corp. is said to have primed the pump and induced other investors to invest in Ciphergen. As a result, Ciphergen U.S. was listed on the NASDAQ exchange in 2000.

3) Name value of Sumitomo

The name of Sumitomo Corp. as the parent company of SC BioScience serves as a standard of trust when Ciphergen Japan conducts business activities in Japan. Those who are buying the product, which is very expensive, apparently want to make sure that the company can provide good after-sale service. On the other hand, Sumitomo Corp. strictly examines the potentials of the company that it plans to invest in. Its criteria for deciding to invest are whether the management is reliable, whether it owns patents, whether it has strong competitive strength in technology, whether it has a clear image of its target market, whether it has competitive products, and whether it has the attitude of learning Japanese culture, including the language.

4) Securing high quality talented people

Mobility in the Japanese pharmaceutical industry is not yet very high. However, in 2002, when Nippon Roche took over Chugai Pharmaceutical Co., talented people were released, and Nippon Roche was able to hire several of them.

5) Utilizing Sumitomo network

When a foreign bio venture enters the Japanese market on its own, it is expected to face big issues such as obtaining a laboratory, hiring good talented staff, and procuring funds (or obtaining loans from banks). One of the factors that contributed to the success of this company was that it could have Sumitomo Corp.'s appropriate support in leasing a lab, hiring staff, and obtaining funds, although in the case of sales, Sumitomo does not have sales channels.

< Future >

- Ciphergen Japan began protein biomarker discovery business in November 2002. Ciphergen Japan plans to open a Biomarker Discovery Center (BDC), its fourth in the world, in its Yokohama Laboratory with a capacity of, for the time being, 7,580 assays per month to conduct protein analysis service on consignment.

VII. Advice for Entering the Japanese Market

1. Promising Fields

In basic research and research support fields, there are promising areas such as biomedical research equipment, reagents markets related with genome analysis and protein analysis, various contract services and bioinformatics. On the other hand, in clinical and pharmaceutical fields, not only drug discovery and development but also genomics and proteomics, research tools and equipment, and related services are all believed to be promising markets to enter. Although these markets are niche areas for the time being, all of these fields are expected in mid- to long-terms, to expand enough to succeed in entering such markets.

(1) Genome-based drug development

As competition intensifies in developing new drugs, research and development costs are also increasing rapidly, and this trend is observed in almost all advanced countries. Efficiency in new drug development is essential and alliances and tie-ups with foreign companies are becoming quite active to improve efficiency and competitiveness. Genomics, proteomics, glyco-chain analyses and other biomedical and related businesses are becoming more important.

(2) Regenerative medicine

Regenerative medicine technologies in Japan are said to be advanced, but even in the most advanced fields, they are still in the stage of "clinical tests being applied for approval." Also, as their fields are divided into very small areas, there is enough room for new comers to enter these markets. There are also good chances for success for those that opt for cross licensing, joint ventures and even mergers and acquisitions. Many of the ventures in this field have their clinical tests pending approval, with some of them expecting to win approval from the Ministry of Health, Labour and Welfare within 2004.

When technologies of regenerative medicine are applied clinically, they will come under the control of the Medical Practitioners Law and the Pharmaceutical Affairs Law. Also, in the case of ES cells, careful attention must be paid to the Ministry of Education, Culture, Sports, Science and Technology's "Guidelines for Derivation and Utilization of Human Embryonic Stem Cells."

(3) Clinical support business

In relation to the biomedical fields mentioned above, the existence of Contact Research Organizations (CROs) is very important to clinical biomedical ventures. There are

about 50 CROs in Japan, but the number is far smaller compared to the United States. In Japan, pharmaceutical companies used to conduct clinical tests on their own, and only in the 1990s, outsourcing began to take over those parts. This market is still small, and is relatively lagging behind the United States, where this business started in the late 1970s. This means the market has great potential.

2. Market Entry Business Models

(1) Tie-ups between venture companies

Stem Cell Sciences KK is a joint venture established in Kobe City between Australia's Stem Cell Sciences Ltd. and Sosei Co. on the assumption that it would conduct joint research with the RIKEN Center for Developmental Biology (RIKEN CDB), located in the Kobe Medical Industry City (Development Project). The joint venture in Japan has been given its own discretionary authority from its parent company and is conducting autonomous business management.

(2) Join venture set up with a trading company

Ciphergen Biosystems, Inc., a U.S. biomedical venture, obtained Sumitomo Corp.'s investment into the U.S. venture prior to its entry into the Japanese market. The joint venture established in Japan by Ciphergen and Sumitomo is developing business in cooperation with SC BioScience, a Sumitomo spin-off. A joint venture, unlike a general agent, enables people from both companies to work in close cooperation to achieve their shared goal, with feedbacks from workers to improve their products and pin-point targets in their markets. Especially when a partner of the joint venture is a major trading company, the joint venture will be able to enjoy the favorable effect of partnership with the trust and confidence of the major trading company. When a foreign bio venture enters the Japanese market on its own, it usually faces big issues such as obtaining a laboratory, hiring personnel, and raising funds. It is very reassuring to have a trustworthy Japanese partner.

(3) 100% - owned subsidiary - A company with certain level of status established in home country

Actelion Ltd. headquartered in Switzerland, is a well-developed medium biomedical company with branches set up in 14 countries, despite it being established only in 1997. It has entered the Japanese market, with its eyes already on future business developments in Asian markets. When it established its subsidiary in Japan, the company had directly asked the current

president of the Japanese unit to take the post in view of the need of talented Japanese staff and executives to develop business in Japan. In addition to the fact that it has prominent, competitive seeds in niche markets, it is also important that the Japanese subsidiary is given considerable discretionary authority to make decisions, which makes operation in Japan successful. In this case, how to make good use of talented Japanese people is also a vital point to success.

(4) Technical tie-up with major and medium pharmaceutical companies

Many cases are found in Japan where major and medium foreign pharmaceutical companies, usually suppliers, are chosen as partners in technical tie-ups with Japanese biomedical companies as their sales companies. These cases include tie-ups between Italy's MolMed S.p.A. and Takara Bio Inc. (gene therapy for leukemia, others), Belgium's Innogenetics and Nipro Corp. (diagnostic agents for nerve tissue diseases) and AntiCancer Inc. of the U.S. and Nosan Corp. (metastatic cancer model mice).

Major and medium pharmaceutical companies in Japan, on the other hand, are looking for foreign venture companies that can undertake development projects that they cannot do on their own. It is important for foreign biomedical ventures wishing to conclude such tie-ups with those Japanese companies to have excellent technologies for which patent rights have been granted. Especially in clinical fields, it is easier to get into tie-up deals if clinical tests in their development projects are already in the stage close to clear Phase III.[9]

It is essential to conduct market surveys in advance because pharmaceutical companies have their own, different areas as their forte or strong points.

3. Points for Entering Japanese Market

(1) Distribution system issues

In the distribution system of pharmaceutical products in the Japanese market, products usually go from suppliers through nationally operating technology-specialized trading firms to local dealers before reaching end users. Because of the issues involving language, payment terms, and claims and complaints, the roles played by local dealers are important. In order to market products nationally on a continuous basis, it is an important point to maintain favorable relationships with local dealers.

[9] There are three stages, Phase I, Phase II and Phase III, in clinical study and clinical trials.

(2) Points when establishing a company in Japan

In the beginning, it is important to market products through sales tie-ups with Japanese pharmaceutical companies and specialized trading firms that have their established sales networks and markets. It is also necessary to have a clear strategy on whether to follow international business practices or organize a very "Japanese" company by thoroughly learning and following traditional Japanese business practices.

(3) Points when choosing location of company

In case the foreign company is being established in Japan on the assumption that it will tie up with local research institutions, it is necessary to be located close to research-oriented universities with a medical department, or public research institutions, or special facilities and equipment. Needless to say, it is also vital to maintain close communication with core researchers at universities and research institutions. To have the corporation located in public venture incubation facilities such as Venture Incubation Factories (VIFs) will not only help to save costs but also easily obtain useful information provided by the local government.

For example, in the Osaka area public facilities such as the National Cardiovascular Center, Biomolecular Engineering Research Institute, Osaka Bioscience Institute, Osaka University Hospital, and Fundamental Pharmaceutical Technology Research Institute (to be opened in spring, 2004) are located. In the Kobe area there are institutions such as RIKEN Center for Developmental Biology (RIKEN CDB) and Institute of Biomedical Research and Innovation (IBRI). The National Institute of Advanced Industrial Science and Technology has its Tissue Engineering Research Center in Hyogo Prefecture's Amagasaki area.

To conduct translational research in Japan, it is advisable to locate the corporation near major universities' medical departments or the translational center in Kobe Medical Industry Development Project's Institute of Biomedical Research and Innovation.

Furthermore, utilization of the synchrotron radiation facility, SPring-8, one of the world's largest set up in Hyogo Prefecture's Harima Science Garden City, and availability of PET facilities (Tokyo Metropolitan Institute of Gerontology and Kobe's Institute of Biomedical Research and Innovation have medical research facilities) should be considered.

Meanwhile, it is also advisable to make a study of industrial clusters being built in various parts of the country before deciding on the location of the company. And it is important to pay attention, not only to biomedical ventures, but also related industries and support industries in the area where the corporation is to be located. Availability of services to test-manufacture and develop equipment and other specialized services are also necessary points to check before deciding on the location of the corporation. Also, having the corporation located in public incubation facilities at relatively inexpensive prices and rental laboratories will help in obtaining a variety of useful information and in cutting operation costs.

Note : Following university facilities and institutions have translational centers: Kyoto University Hospital's Translational Research Center; Advanced Clinical Research Center in the University of Tokyo's Institute of Medical Science; Nagoya University Hospital's Center for Genetic and Regenerative Medicine; Osaka University Hospital's Center for Advanced Research Projects; Kyushu University Hospital's Center for the Integration of Advanced Medicine and Innovative Technology; Keio University School of Medicine Shinanomachi Research Park; Tokyo Women's Medical University's Advanced Life Science Institute, and Jikei University's Institute for Integrative Medical Research., etc.

(4) Points when selecting business partners

Business partners, when entering the Japanese market, can be chosen from among major and medium pharmaceutical companies, bio-specialized trading firms, bio ventures and venture capitals specialized in biotechnology, and universities and public research institutions. In addition, other various unconventional organizations, such as Non Profit Organizations (NPOs) can be business partners in Japan. In selecting a business partner, not only reputation within the bio-business circles but also wider reputation within industrial clusters in the community is worth considering. Especially in the case of university and public research institutes and NPOs, the results of collaboration are more dependent on personal factors such as researchers and managers than on the organizational strength. On the other hand, the Japanese side evaluates the prospective foreign partner for business tie-up or joint venture on items on their selection criteria such as good management, whether the partner has patents, whether it has technological competitiveness, whether it has a clear target market and competitive products, and whether the foreign company shows interest in learning Japanese culture, such as the Japanese language.

How to access prospective business partners is shown in the next section, "4. Access." It is important to have the opportunity to meet them face-to-face at an early stage. It is a key point to make good use of various academic societies' conventions, trade fairs and exhibitions, as well as various other occasions for exchanges presented by industrial associations and local organizations. In particular, as shown in Chapter VIII, Reference Materials, many fairs and exhibitions of biotechnology-related fields are organized in Japan. There are also a good number of foreign companies that participate in these events and, while introducing their new technologies, they try to build up contact networks with Japanese companies participating in those exhibitions as well as with visitors.

Tie-ups are basically formed to supplement each other's lack of resources, or weak points. For example, Japanese companies looking for business partnership with foreign companies with good technological seeds will often seek to share intellectual property rights or obtain exclusive rights to market them. Also, they may want to spread technologies developed by Japanese companies to the world through business partnership, or expect the foreign partner to play coordinating roles to promote joint research with research institutions in the Western countries.

4. Access

(1) Bio venture capitals

Venture capitals specializing in biotechnology in Japan have a history that is relatively new and these bio venture capitals are expected to increase rapidly as seen in examples of the recently established three venture capitals. As they look for various types of tie-ups and partnerships, approaches by these three new venture capitals and their methods of nurturing bio ventures greatly differ. Some give comprehensive guidance to venture startups on the basis of their financing, while others conduct very typical hands-on management of startups by having their executives become the ventures' top management or CEOs.

These venture capitals are offering guidance in forming tie-ups and partnerships with foreign companies to major and medium Japanese biotechnology-related companies. They are:

- BioFrontier Partners, Inc. (established in March 1999)
- MBL Venture Capital Co. (mblVC, established in January 2000)
- Biotech-Healthcare Partners, Inc. (established in July 2000)

These venture capitals have been investigating researchers at universities and various technological seeds since their launch, and have accumulated considerable amount of national and international information. All of these companies are looking not only for clients but also their venture capital partners.

Major venture capitals have also started spending greater resources in the biotechnology fields.

(2) Contacts with general trading companies

Many of the general trading houses are recently showing greater interest in expanding business in biotechnology markets. Their basic business is agency business, but recently they are making more direct investment in bio ventures and venture capitals. Some of them also provide service to discover venture seeds overseas and give information regularly to major and medium pharmaceutical companies.

Mitsubishi Corp. has set up a membership organization called Cosmos Alliance, to provide bio-business information. This is an example of the third category described in the above. Mitsui & Co. has selected gene diagnosis as its core biotechnology business, while Itochu Corp. has launched new drug development in proteomics. Sumitomo Corp. set up its strategic investment companies (biotechnology specialized trading firms: SC BioScience Corp. and Summit Pharmaceuticals International Corp.) and through them is investing in foreign ventures and supporting business developments in Japan.

Therefore, it is another option for foreign companies to use these trading companies' various functions and networks to enter the Japanese market.

(3) Contacts with foreign local government offices in Japan

Many governments of foreign states and provinces have their representative offices in Japan. One of the major purposes of their activities in Japan is to promote business collaboration with Japan. Many companies contact them and ask for their advice in finding business partners and locations for their investment. There are several successful examples in this approach.

(4) Information at regional levels: contacts with clusters

Various industrial cluster plans and other projects are being promoted by the regional Bureaus of Economy, Trade and Industry and prefectural governments, and versatile exchanges of research are taking place as part of such moves. Several local governments are making particular efforts to develop industrial clusters in their towns and cities and eager to attract foreign companies' investment there. They are also eager to publish their information in English and on the Internet. This makes it possible for potential foreign investors in Japanese biomedical ventures to access their websites before they decide to enter the Japanese market.

(5) TLO (Technology Licensing Organization)

The history of the technology licensing organization (TLO) in Japan is relatively new, but a great deal of information about technology seeds is concentrated in the TLO. As a national organization of the TLO, the Japan TLO Association has been established, and all TLO websites can be accessed from the following address.

The Japan TLO Association http://www.jtloa.gr.jp/ (in Japanese and English)

(6) Academic Societies

Academic societies in the Regenerative Medicine field include the Japanese Society for Regenerative Medicine, the Japanese Society for Tissue Engineering and the Japanese Society for Artificial Organs. Those societies in the fields related to information technology include the Japanese Society for Bioinformatics, the Japanese Society for Medical and Biological Engineering (a study group concerning molecular and cell therapies), and many others concerning medical images and medical information.

- The Japanese Association of Medical Sciences
  http://www.med.or.jp/jams/ *The largest academic society in Japan.
- The Japanese Society for Artificial Organs
  http://jsao.bcasj.or.jp/ (in Japanese)
- The Japanese Society for Regenerative Medicine
  http://wwwsoc.nii.ac.jp/jsrm/
- The Center for Promotion of Regenerative Medicine (NPO)

http://www.rm-promot.com/ (in Japanese)

- The Japanese Society for Tissue Engineering
  http://www.jste.net/english.htm
- The Physiological Society of Japan
  http://wwwsoc.nii.ac.jp/psj/index-e.html
- The Japanese Society for Bioinformatics
  http://www.jsbi.org/welcome_E.html
- The Japanese Society for Medical Electronics and Biological Engineering
  http://www.jsmbe.or.jp/ *A study group on molecular and cell therapies is set up in this society.
- The Japanese Society for Biomaterials
  http://wwwsoc.nii.ac.jp/jsbm/ (in Japanese)
- The Society for Biotechnology, Japan
  http://wwwsoc.nii.ac.jp/sfbj/
- The Japanese Biochemical Society
  http://edpex104.bcasj.or.jp/jbs/index-e.htm

(7) Presence on the Web site

Many Japanese companies are eager to obtain useful information on technologies and corporations that their rival companies have not yet seen or noticed. For that purpose, there are many companies that are searching for such information on the Internet every day. Therefore, it should not be forgotten that disclosing the company's presence on the Web pages or that disseminating information about the company, could sometimes lead to a new business deal.

VIII. Reference

1. Trade Fairs and Exhibitions

Genome Technology Business Forum

Organizer : IDG Japan, Inc.

Date : September 18 - 19, 2003

Location : Tokyo Fashion Town Building / TFT Hall

Contact : Genome-Technology Business Forum & BioIT World Japan Management Office,
IDG Japan, Inc.
3-4-5 Hongo, Bunkyo-ku, Tokyo 113-0033
Tel : 03-5800-3734 Fax : 03-5800-3735
E-mail : gt@idg.co.jp
http://www.idg.co.jp/expo/gt/index.html（in Japanese）
http://www.idg.co.jp/expo/gt/english/index.html（in English）

Bio Forum 2003 Osaka

Organizer : NPO Kinki Bio-industry Development Organization, Osaka Scientific Instrument Association Osaka, The Japan Industrial Journal (FujiSankei Business i)

Date : October 22 - 24, 2003 (Friday)

Location : INTEX Osaka Hall 6

Contact : Scientific Instrument Association Osaka
Umeda-Tatsumi Bldg., 8-1 Kamiyama-cho, Kita-ku, Osaka 530-0026
Tel : 06-6364-7113 Fax : 06-6364-7759
E-mail : ork@sia-osaka.gr.jp
The Japan Industrial Journal
Sankei Bldg., 2-4-9 Umeda, Kita-ku, Osaka 530-0001
Tel : 06-6343-3223 Fax : 06-6341-4773
E-mail : osaka-inf@jij.co.jp
http://www.sia-osaka.gr.jp/sis/（in Japanese）

CPhI Japan

Organizer : The Chemical Daily Co., Ltd., CMP Japan Co Ltd, CMP Information

Date : April 21 - 23, 2004

Location : Tokyo "Big Sight" Exhibition Center

Contact : CMP Japan Co Ltd
Kanda 91 Bldg., 1-8-3 Kaji-cho, Chiyoda-ku, Tokyo 101-0044
Tel : 03-5296-1020 Fax : 03-5296-1018
E-mail : sales@cmpjapan.com
http://www.cphijapan.com/jp/mainflam.html（in Japanese）
http://www.cphijapan.com/en/mainflam.html（in English）

International Bio Expo Japan

Organizer : Reed Exhibitions Japan Ltd.

Date : May 19 - 21, 2004

Location : Tokyo Big Sight

Contact : Bio Expo Japan Show Management, Reed Exhibitions Japan Ltd.
Shinjuku-Nomura Bldg. 18F, 1-26-2 Nishi-Shinjuku, Shinjuku-ku, Tokyo 163-0570
Tel : 03-3349-8509 Fax : 03-3349-4900
E-mail : bioexpo@reedexpo.co.jp
http://web.reedexpo.co.jp/bio/jp/（in Japanese）
http://web.reedexpo.co.jp/bio/english/（in English）

Bio Japan 2004

Organizer : Japan Bioindustry Association (JBA)
Japan Health Sciences Foundation (JHSF)
Society for Techno-innovation of Agriculture, Forestry and Fisheries (STAFF)
Japan Biological Informatics Consortium (JBIC)
Japan Association of Bioindustries Executives (JABEX)
Japan Pharmaceutical Manufacturers Association (JPMA)
The Kinki Bioindustry Development Organization (KBDO)

Date : September 28 – 30, 2004

Location : New Takanawa Prince Hotel

Contact : BioJapan 2004 Managing Office, Nikkei Business Publications, Inc.
Shiozaki Bldg. 6F, 2-7-1 Hirakawa-cho, Chiyoda-ku, Tokyo 102-0093
Tel : 03-5210-7005 Fax : 03-5210-7014
E-mail : biojapan@nikkeibp.co.jp
http://expo.nikkeibp.co.jp/biojapan/2004/（in Japanese）
http://expo.nikkeibp.co.jp/biojapan/2004/eng/（in English）

2. Related Organizations

2-1 Governmental Ministries and Offices

Name	Address / Tel / URL
Ministry of Health, Labour and Welfare	1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-8916 Tel : 03-5253-1111 http://www.mhlw.go.jp/（in Japanese） http://www.mhlw.go.jp/english/index.html（in English）
Ministry of Education, Culture, Sports, Science and Technology	3-2-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-8959 Tel : 03-5253-4111 http://www.mext.go.jp/（in Japanese） http://www.mext.go.jp/english/index.htm（in English）
Ministry of Economy, Trade and Industry	1-3-1 Kasumigaseki, Chiyoda-ku, Tokyo 100-8901 Tel : 03-3501-1511 http://www.meti.go.jp/（in Japanese） http://www.meti.go.jp/english/index.html（in English）
Japan Patent Office	3-4-3 Kasumigaseki, Chiyoda-ku, Tokyo 100-8915 Tel : 03-3581-1101 http://www.jpo.go.jp/indexj.htm（in Japanese） http://www.jpo.go.jp/index.htm（in English）

2-2 Industry groups

Name	Address / Tel / Fax / URL
Japan Bioindustry Association (JBA)	Grande Bldg. 8F, 2-26-9 Hatchobori, Chuo-ku, Tokyo 104-0032 Tel : 03-5541-2731　Fax : 03-5541-2737 http://www.jba.or.jp/index.html（in Japanese） http://www.jba.or.jp/index_e.html（in English）
Japan Association of Bioindustries Executives (JABEX)	c/o Bio Industry Association Grande Bldg. 8F, 2-26-9 Hatchobori, Chuo-ku, Tokyo 104-0032 Tel : 03-5541-2731　Fax : 03-5541-2737 http://www.jba.or.jp/jabex/（in Japanese） http://www.jba.or.jp/jabex/english%20version/index2.htm（in English）
Japan Bio-Venture Development Association (JBDA)	Otemachi IT Bldg., 1-27-4 Kanda-Nishikicho, Chiyoda-ku, Tokyo 101-0054 Tel : 03-5280-7751　Fax : 03-5280-7756 http://www.jbda.jp/（in Japanese）
Japan Health Sciences Foundation (JHSF)	Kyodo Bldg. 4F, 13-4 Nihonbashi-Kodenmacho, Chuo-ku, Tokyo 103-0001 Tel : 03-3663-8641　Fax : 03-3663-0448 http://www.jhsf.or.jp/（in Japanese） http://www.jhsf.or.jp/English/index_e.html（in English）

Procedures for Investment in Japan

1. Summary and Procedures for Setting Up a Base in Japan

Table 1. shows the tasks, and the order in which they need to be implemented, required of a foreign company, from the Japan investment planning stage to the establishment of a base. There is particular focus on the stage of establishing a company.

For details of each procedure (such as documents to be submitted and where to submit them), please consult with experts, make inquiries to authorities concerned (including JETRO IBSC) listed in Section 2, or check JETRO publications and the JETRO web site "Invest Japan!" (http://www.jetro.go.jp/investjapan/index.html).

1-1 Setting Up a Base

(1) Start-up Types

Table 1. shows each start-up type and its requirements. When a foreign business desires to set up a base in Japan, there are generally three different choices of organization: 1) a joint-stock company (*kabushiki kaisha*), 2) a limited liability company (*yugen kaisha*), or 3) a branch (*shiten*) of the parent company overseas.

Among these three choices, establishing a joint-stock company is the most popular due to the limited liability of its investors, high social credibility, and advantages in financing. However, since a joint-stock company requires ten million yen or more as minimum capital, small- to-medium-sized enterprises sometimes choose to establish a limited liability company (*yugen kaisha*) for which the minimum capital requirement is three million yen, or even a branch, which does not have minimum capital requirements[1].

A joint-stock company can be established two ways; 1) promotive incorporation where promoters take all issued shares, and 2) subscriptive incorporation where a public offering is made to attract outside investors. Each method requires different procedures and documents to be submitted. Figure 1. only shows promotive incorporation details as it is more common when foreign businesses make direct investment in Japan.

[1] For details of an exceptional measure for minimum capital requirements, please refer to section 1-1, (2).

Table 1. Start-up Types and Requirements

Start-up type	Business activity	Registration	(Minimum capital requirements)	Directors required	Internal Auditor(s)	Remittance
Representative office	Not allowed	None	None	None	No	—
Branch (Shiten)	Allowed	Required	None	None	No	No tax is imposed
Joint-stock company (Kabushiki Kaisha: K.K.)	Allowed	Required	10 mil. Yen	At least three	Yes	Profits, dividends and royalties are taxable
Limited liability company (Yugen Kaisha)	Allowed	Required	3 mil. Yen	At least one	No	Profits, dividends and royalties are taxable

(2) An Exceptional Measure for Minimum Capital Requirements

As an exceptional measure for minimum capital requirements, the government forced "the Law for Supporting for the Challenge of SMEs *(Chusho Kigyou Chosen Sien Hou)*", revised the part of the Law for Facilitating the Creation of New Business, since Feb. 1, 2003 and practically abolished the regulations of minimum capital requirements under some conditions (http://www.meti.go.jp/english/information/data/cMinimumCapitale.html).

Both a joint-stock company and a limited liability company can be established with a capital of over 1 yen under the following conditions: 1) The company need to prepare and get the notification of articles of incorporation and after that need to get the confirmation of Bureau of Economy, Trade and Industry that sited in the local area the company will be established in advance. 2) The established organization will be changed or liquidated in the case that it cannot fulfill the minimum capital requirements already mentioned within five years from incorporation. 3) The distribution for stockholders cannot be acknowledged during the time the company does not fulfill the minimum capital requirements. 4) The company is liable to open its financial condition to the public broadly. It is necessary for the company to pay attention to fulfill the minimum capital requirements in Table.1 within five years from incorporation.

Since this law is the time-limited law until Mar. 31, 2008, the company must get the confirmation of Bureau of Economy, Trade and Industry until this limit. This law is under the jurisdiction of Office for New Business, Economic and Industrial Policy Bureau, Ministry of Economy, Trade and Industry.

(3) Important Points Concerning Incorporation

As procedures of registration of incorporation and application for the certificate of eligibility for status of residence are very complicated and require professional knowledge, foreign companies investing in Japan normally commission such tasks to Japanese qualified experts (such as lawyers and public accountants) who can do business in English[2]. In such a case, it should be noted, since in Japan there are very few joint offices of lawyers and public accountants which can provide one-stop service, and since lawyers and public accountants may re-commission some tasks to other qualified experts such as judicial scriveners and administrative scriveners, which are not present in Europe and North America.

When a registration of incorporation is filed at a registry office, it is necessary to attach a "certificate of a seal impression" of a representative director. If a promoter or a representative director of a joint-stock company is a non-Japanese person who has not obtained an alien registration certificate, since the person is not able to obtain the certificate of seal impression, the person may endorse by signature in place of affixing a seal. However, in this case, each time a signature is presented it is necessary to attach a "certificate of signature" issued by a notary public in the home country of the non-Japanese promoter or the representative director.

1-2 Investment-Related Laws and Regulations

Major investment-related laws and regulations include the Foreign Exchange and Foreign Trade Control Law, the Commercial Code (Corporate Law), and the Antimonopoly Act. In addition, regulations under the Labour Law and the Intellectual Property Rights Law should also be considered at the start of, and during operation of, a business in Japan. Depending on the type of business, it may be necessary to have a license or approval from a competent authority in accordance with applicable laws and regulations.

(1) Foreign Exchange and Foreign Trade Control Law (The Foreign Exchange Law)

The Foreign Exchange and Foreign Trade Control Law stipulates rules for proper management of foreign trade based on the principle of freedom of foreign trade. When a foreign company makes direct investment in Japan, it must follow a series of procedures based on the principle of "ex post facto notification in principle, prior permission or notification in part" under the law.

[2] Please refer to *"Directory for Setting Up Enterprises in Japan 2000"* (by JETRO, 4,000 yen) for information on contacts of major qualified experts and supportive companies.

(2) Commercial Code (Corporate Law)

The Commercial Code (Corporate Law) in Japan defines three types of companies, excluding a limited liability company (*yugen kaisha*)[3]. In recent years, many revisions and modifications of the law have been made to promote more flexible restructuring of companies. Specifically, these have included simplification and rationalization of M&A related laws and regulations, introduction of legislation on stock-swap and stock-transfer systems, establishment of legislation on company split-offs, revision of Corporate Reorganization Law, and the adoption of a system complying with internationally accepted accounting standards.

(3) Antimonopoly Act (The Act Concerning Prohibition of Private Monopolization and Maintenance of Fair Trade)

The Antimonopoly Act restricts private monopoly and unfair trade for the purpose of promoting free and fair competition. In recent years, however, deregulation is underway, which includes lifting the ban on establishing holding companies in principle, and simplifying the notification system of M&A activities.

1-3 Preferential Treatment Associated with Investment in Japan

(1) Law on Extraordinary Measures Related to the Promotion of Imports and the Facilitation of Inward Investment Activities (Import and Inward Investment Promotion Law, FAZ Law)

Foreign companies that invest in the areas designated as FAZ (Foreign Access Zones) and can also meet the requirements for specific investors in Japan can receive the following preferential treatment. The application period of this law has been extended to May 2006.

1) Although the carry forward period of operating losses is usually five years from the start of business, this law allows investors to carry forward losses up to 7 years.

2) Industrial Structure Improvement Fund (ISIF) guarantees of debt incurred to loans to buy equipment and to obtain working capital for businesses.

3) When a small- and medium-sized foreign private company obtains loans, the Japan Small and Medium Enterprise Corporation (JASMEC) guarantees the loans.

4) Development Bank of Japan (DBJ) and Japan Finance Corporation for Small Business offers low-interest, long-term loans.

As of December 2003, 22 areas are designated as FAZs. For further information on each FAZ, please refer to the JETRO web site (http://www.jetro.go.jp/ov/e/faz/index.html).

[3] Rules and regulations related to limited liability companies (yugen kaisha) are stipulated in the Limited Liability Company Law *(Yugen Kaisha Hou)*.

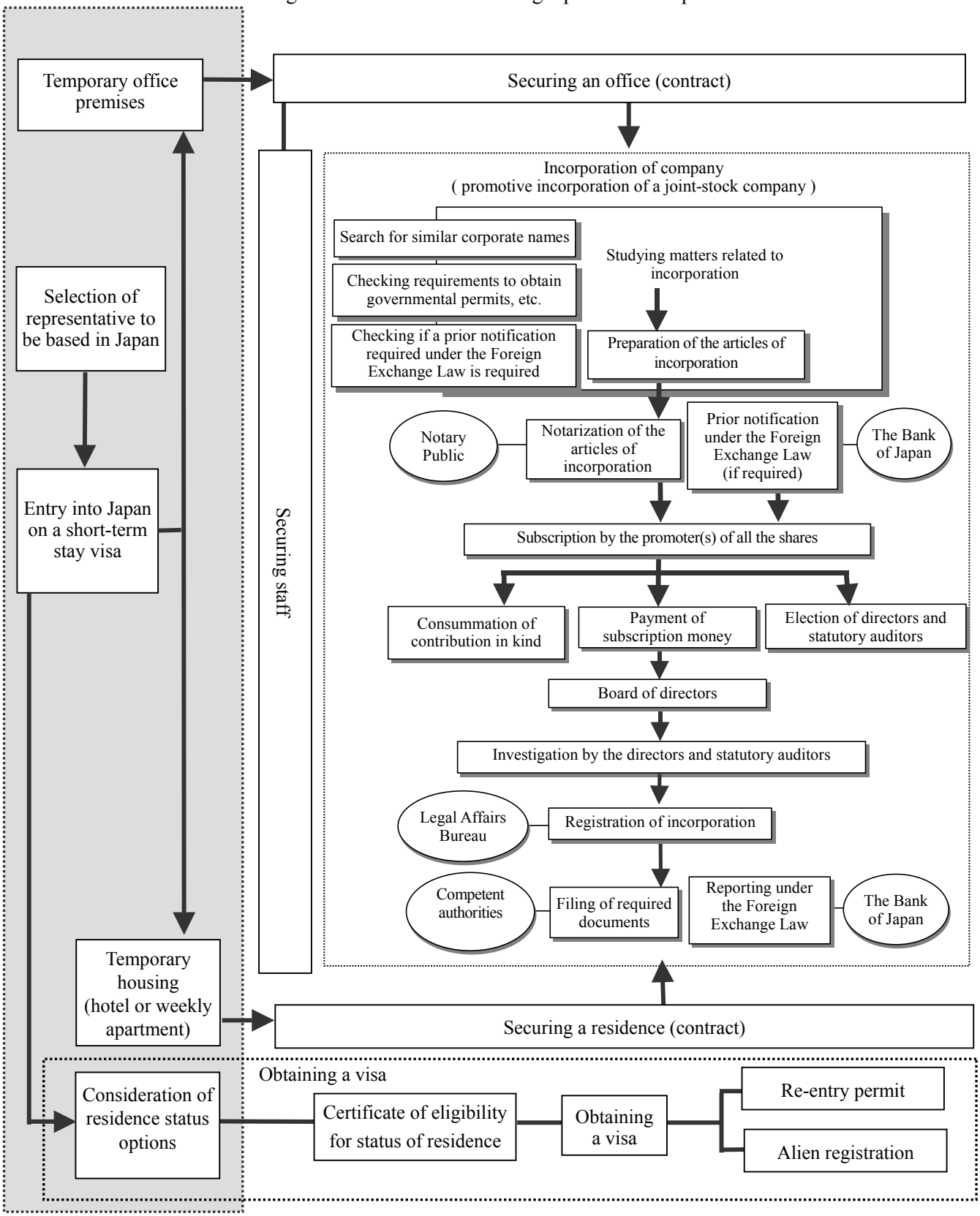
(2) Low-Interest Loans by Development Bank of Japan (DBJ)

DBJ offers low-interest, long-term loans to foreign companies that make full-scale investment in Japan for the first time or whose investment is expected to contribute to the upgrading of the Japanese industry structure, the creation of a new industry, or an increase in employment.

(3) Subsidies, Tax Exemptions, Low-Interest Loans by Prefectural Governments

Prefectural governments also offer various forms of support to foreign businesses investing in Japan. As supportive measures are different in each prefecture, please contact each prefectural government or JETRO Trade Information Center for further information on support offered in each area. Contact points for each center are given at <http://www.jetro.go.jp/ov/e/domestic_offices.html>.

Figure 1. Procedures for Setting Up a Base in Japan



Note 1: Application for certificate of eligibility for status of residence and opening of a bank account should be made after establishing an office and a residence (i.e. after signing lease contracts of an office or residence).

Note 2: For inquiries about incorporation procedures and visa applications, please refer to Section 2 of this reference.

Source: *"Setting Up Enterprises in Japan"* by JETRO (1995) and *"The Japan Start-up Handbook: Procedures and Costs for Foreign Companies Establishing a Japanese Base"* by JETRO (1999)

2. Sources of Information on Investment in Japan

2-1 Governmental Offices: "Office of INVEST JAPAN"

	Organization	Division	Contact	Web site (Invest Japan)
1	Cabinet Office	Office of Foreign Direct Investment Promotion	03-3581-8950 (direct) 03-5253-2111 ext.45207 invest-japan.be@mfs.cao.go.jp	http://www5.cao.go.jp/access/english/jic_main_e.html
2	Financial Service Agency	Planning and Coordination Bureau, International Affairs Division	03-3506-6049 (direct) 03-3506-6000 ext.3199 invest-japan@fsa.go.jp	http://www.fsa.go.jp/invest/20030603e.html
3	Ministry of Public Management, Home Affairs, Posts and Telecommunications	Minister's Secretariat, Policy Planning Division	03-5253-5156 (direct) invest-japan@soumu.go.jp	http://www.soumu.go.jp/kyoutsuu/tainiti.html (in Japanese)
4	Ministry of Justice	Minister's Secretariat, Secretarial Division	03-3592-7420 (direct) 03-3580-4111 ext.2087 invest-japan@moj.go.jp	http://www.moj.go.jp/KANBOU/TAINICHI/tainichi01.html (in Japanese)
5	Ministry of Foreign Affairs	Economic Affairs Bureau, Second International Economic Affairs Division	03-3580-3311 ext.5055 invest-japan@mofa.go.jp	http://www.mofa.go.jp/mofaj/gaiko/tn_toshi/madoguchi/ (in Japanese)
6	Ministry of Finance	International Bureau, Research Division, Legal Office	03-3581-8015 (direct) invest-japan@mof.go.jp	http://www.mof.go.jp/invest_japan/index_e.htm
7	Ministry of Education, Culture, Sports, Science and Technology	Minister's Secretariat, Policy Division	03-5253-4111 ext.3472 invest-japan@mext.go.jp	http://www.mext.go.jp/a_menu/tainichi/main.htm (in Japanese)
8	Ministry of Health, Labour and Welfare	Counsellor's Office (Labour Policy) to Director-General for Policy Planning and Evaluation	03-5253-1111 ext.7718 invest-japan@mhlw.go.jp	http://www.mhlw.go.jp/general/seido/toukatsu/tousi/ (in Japanese)
9	Ministry of Agriculture, Forestry and Fishery	General Food Policy Bureau, Food Industry Policy Division	03-3502-8111 ext.3222, 3194 invest_japan@nm.maff.go.jp	http://www.maff.go.jp/sogo_shokuryo/toushi.htm (in Japanese)
10	Ministry of Economy, Trade and Industry	Policy Bureau, International Planning Division, International Transport Policy Office	03-3501-1774 (direct) invest-japan@meti.go.jp	http://www.meti.go.jp/english/policy/index_FDI_into_Japan.html
11	Ministry of Land, Infrastructure and Transport	Policy Bureau, International Planning Division, International Transport Policy Office	03-5253-8313 (direct) invest-japan@mlit.go.jp	http://www.mlit.go.jp/sogoseisaku/invest/index_.html (in Japanese)
12	Ministry of the Environment	Environmental Policy Bureau, Environment and Economy Division	03-5521-8324 (direct) invest-japan@env.go.jp	http://www.env.go.jp/policy/invest_j/ (in Japanese)

13	Japan External Trade Organization (JETRO)	Invest Japan Business Support Center (IBSC)[*1]	03-3584-6042 (direct) invest-japan@jetro.go.jp	http://www.jetro.go.jp/ip/e/bsc/ibsc.html
14	Development Bank of Japan	International Department, Center for the Promotion of Direct Investment in Japan	03-3244-1770 (direct) dbjmail@dbj.go.jp	http://www.dbj.go.jp/english/index.html

Note 1: JETRO IBSC opens windows to the administrative procedures for foreign companies looking to invest in a business in Japan. Please refer to section 3-1.
Note 2: For further information, please refer to JMR No.70 *"Japan's Investment Environment: Facility Services,"* Chapter VIII.

2-2 Sources of Information in Investment in Japan

	Information	Organization	Division	Contact	Web site
Applicable Laws and Regulations					
1	Foreign Exchange and Foreign Trade Law	Bank of Japan	Balance of Payment Division, International Department	03-3277-2107 post.ind6@boj.or.jp (direct)	http://www.boj.or.jp/about/tame/tameindex.htm (in Japanese)
2	Commercial Code	Ministry of Justice	Commercial and Corporation Registration and Deposit Division, Civil Affairs Bureau	03-3580-4111 webmaster@moj.go.jp (main)	http://www.moj.go.jp/MINJI/index.html (in Japanese) http://www.moj.go.jp/ENGLISH/CIAB/ciab-01.html (in English, summary of Civil Affairs Bureau only)
3	Antimonopoly Act	Japan Fair Trade Commission		03-3581-1998 intnldiv@jftc.go.jp (International Affairs Division)	http://www2.jftc.go.jp/e-page/legislation/antimonopoly.html
Preferential Treatment for Investors in Japan					
4	Law for Facilitating the Creation of New Business, Law for Supporting for the Challenge of SMEs *(Chusho kigyou Chosen Sien Hou)*	Ministry of Economy, Trade and Industry	Office for New Business, Economic and Industrial Policy Bureau	03-3501-1569 (direct)	http://www.meti.go.jp/policy/mincap/index.html (in Japanese) http://www.meti.go.jp/english/information/data/cMinimumCapitale.html (in English)
	Same as above	Same as above	Regional Bureaus of Economy, Trade and Industry	webmail@meti.go.jp (main)	http://www.meti.go.jp/english/network/index_b_bureaus.html (information on each Regional Bureau)

5	Law on Extraordinary Measures for the Promotion of Import and the Facilitation of Foreign Direct Investment in Japan	Industrial Structure Improvement Fund		03-3241-6283 webmaster@isif.go.jp (main)	http://www.isif.go.jp/english/frames_e/f_yunyue.html
	Same as above	Japan Small and Medium Enterprise Corporation	Credit Guarantee Corporations (CGCs) in the relevant area	03-3270-2371 (direct)	http://www.cig.jasmec.go.jp/top.html (information on CGCs, in Japanese)
	Same as above	Ministry of Economy, Trade and Industry	Regional Bureaus of Economy, Trade and Industry	webmail@meti.go.jp (main)	http://www.meti.go.jp/english/network/index_b_bureaus.html (information on each Regional Bureau)
6	Special loan program for the promotion of direct investment in Japan	Development Bank of Japan	International Department	03-3244-1990 (General Affairs Department)	http://www.dbj.go.jp/english/index.html
Procedures for Incorporation					
7	Procedures for Incorporation - Registration of joint-stock company - Acquisition of a certified copy of company registration - Certificate of a seal certificate of a representative director	Regional Legal Affairs Bureau and Registry Office in the relevant area			http://www.moj.go.jp/MINJI/minji10.html (a list of Legal Affairs Bureaus in each area is available, in Japanese)
	- Notification of articles of incorporation	Notary Office in the relevant area			http://www.koshonin.gr.jp/address.htm (a list of notary offices in each area is available, in Japanese)
Procedures after Incorporation					
8	Procedures after incorporation - Notification of establishment of corporation - Notification of consumption tax payer etc.	Taxation Office in the relevant area*[1]			http://www.nta.go.jp/category/syoukai/syozaiti.htm (a list of taxation offices in each area is available, in Japanese)
9	Filing of notifications related to the corporation (inside of Tokyo 23 ward)	Local Taxation Office in Tokyo			http://www.tax.metro.tokyo.jp/jimusho/tozei.htm (a list of counsel offices in each area is available, in Japanese)
	Filing of notifications related to the corporation (outside of Tokyo 23 ward)	Local Taxation Office and Commune Office in the relevant area			http://www.soumu.go.jp/czaisei/czaisei_seido/ichiran07.html (a list of local taxation offices in each area is available, in Japanese) - Information on each commune office is provided by web page of each prefecture.
10	Distribution of a guidebook of metropolitan tax in English, Chinese, and Korean, free of charge (postage should be paid)	Bureau of Taxation, Tokyo Metropolitan Government	General Affairs Division, General Affairs Department	03-5388-2927 tax@section.metro.tokyo.jp (direct)	http://www.tax.metro.tokyo.jp/oshirase/2003/200309a.htm (guidebook distribution information in 2003, in Japanese)

Procedures of Social Insurance					
11	Procedures related to industrial insurance - Business report - Employment policy - Labor insurance- related notifications	Labor Standards Bureau in the relevant area			http://www.mhlw.go.jp/general/sosiki/chihou/ (a list of Labor Standards Bureaus in each area is available, in Japanese)
12	Notification of establishment of relationship between an insurer and the insured under the industrial and employment insurance system - Notification of establishment of relationship between an insurer and the insured under the employment insurance	Public Employment Security Office in the relevant area			Same as above
13	Procedures related to health insurance and social security pension	Social Insurance Office in the relevant area			http://www.sia.go.jp/outline/index.htm (information web page on health insurance and social security pension provided by Social Insurance Agency, in Japanese)
Other Useful Sources of Information					
14	Search for telephone numbers and addresses	Town Page - Japan telephone directory -			http://english.itp.ne.jp/
15	Information on investment in Japan	Japan External Trade Organization		03-3582-5511 webmaster@jetro.go.jp (main)	http://www.jetro.go.jp/

Note 1: Only the Tokyo Taxation Bureau has set up a dedicated counter for non-Japanese people. The telephone number is: 03-3821-9070

3. JETRO Services

3-1 JETRO Invest Japan Business Support Center (IBSC)

JETRO IBSC provides foreign companies with information necessary for investment in Japan. IBSC has a wide range of services and facilities to help foreigners who would like to start or invest in a business in Japan. IBSC provides office space free of charge to foreign companies. Advisors and JETRO staff supplies you with useful information and consultation (http://www.jetro.go.jp/ip/e/bsc/ibsc.html).

For further information or application, please contact the nearest JETRO offices (http://www.jetro.go.jp/it/e/profile_network/worldmap.html).

(1) Providing Well-Equipped Facilities for Temporary Offices

IBSC has office space free of charge for foreigners hoping to enter the Japanese market or develop business operations in Japan. The Center's office space is equipped with all the tools necessary to immediately launch business activities in Japan.

(2) Consultation Services by Investment Advisors

IBSC has highly specialized resident advisors (market advisors and corporate management advisors) who can help you with offering market information and conducting individual consulting. Also, at some JETRO overseas offices, investment advisors provide information and consultation regarding direct investment in Japan to potential investors.

(3) Providing the Administrative Information

Backed by the Japanese government, the IBSC opens windows to the administrative procedures necessary for foreign companies looking to do business in Japan.

(4) Introducing Supportive Companies and Arranging a Visit to Potential Properties

IBSC introduces agents who can perform various procedures for setting up a base in Japan, recruiting companies, property companies, and other companies that can help foreign companies investing in Japan. Through a network with local governments, IBSC also gathers information on real estate property in specific regions, arranges visits to candidate properties, and sets up meetings with staff members of local governments.

3-2 Providing Information on Investment in Japan

(1) "Invest Japan!"

The JETRO web site "Invest Japan!" (http://www.jetro.go.jp/investjapan/index.html) provides comprehensive information and data on the investment environment in Japan to foreign businesses that are interested in investing in Japan. This includes Japanese macro economic data, related laws and regulations, and examples of foreign companies that have been successful in establishing their business in Japan.

(2) Publications

JETRO publishes many books that summarize laws and procedures concerning investment in Japan.

For example:

- Setting Up Enterprises in Japan
- Human Resource Management Guidebook: Q&As for Managers of Foreign Affiliates
- Directory for Setting Up Enterprises in Japan

etc.

For further information, please visit the following JETRO web site. (http://www.jetro.go.jp/it/e/pub/index.html).

(3) Seminars for Investment in Japan

JETRO organizes seminars and individual consultations in various countries in order to provide information on a variety of themes, such as trends in the Japanese market, investment climate, and laws and procedures concerning investment in Japan.

(4) Library

You can browse various materials on trade and investment in many countries and JETRO publications on the JETRO Library site (http://www.jetro.go.jp/li/e/index.html).