OECD/TIP Project on Biopharmaceutical National Innovation Systems

National Report: Japan

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By Kazuyuki Motohashi[1]

[1] Associate Professor, Reseach Center for Advanced Science and Technology, University of Tokyo. Views expressed in this paper are those of the author and not of his organizations. Correspondence: motohashi@rcast.u-tokyo.ac.jp

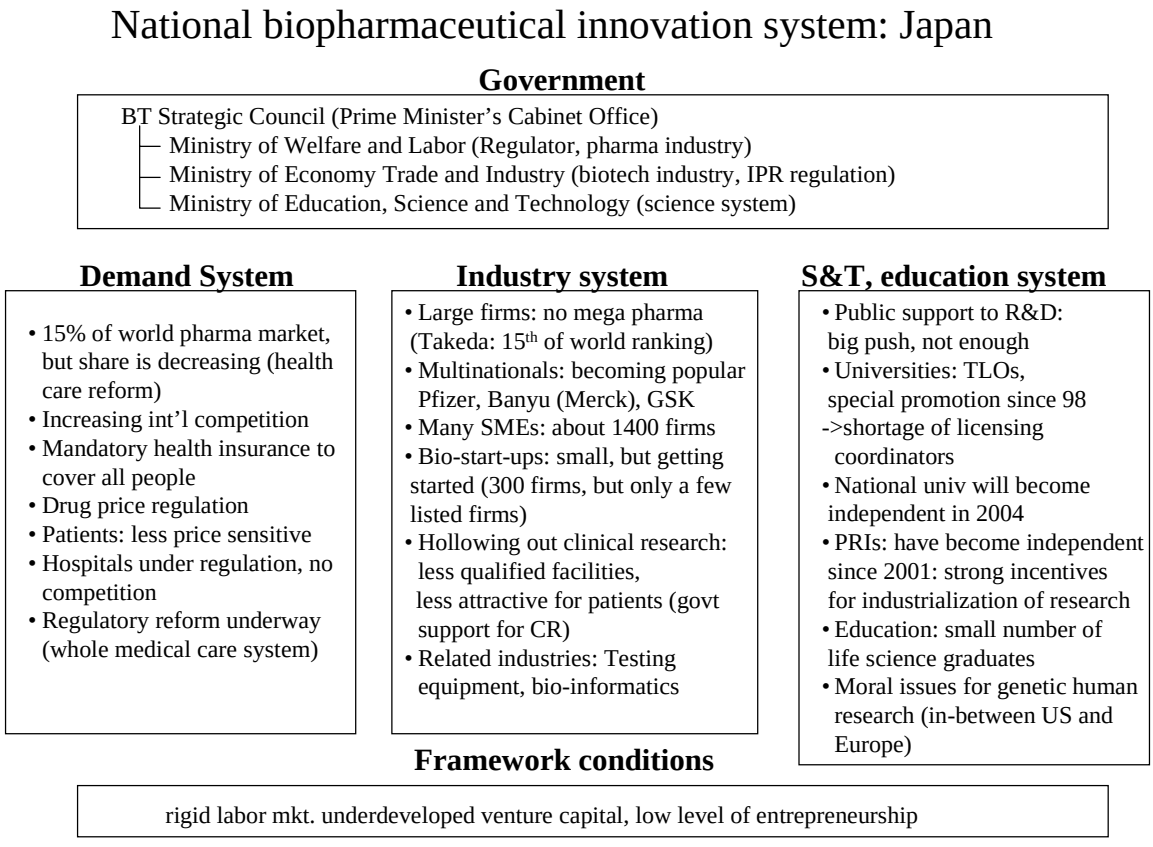
1. Introduction

1.1. Goals

In this report, we present the Japanese innovation system of biotechnological medicines, as a national report to the OECD/TIP research project on biopharmaceutical national innovation systems. This report addresses innovation activities and the interaction of pharmaceutical companies, biotechnology firms, public research institutes and universities. We conducted research on present governmental support to promote innovation, the biopharmaceutical market and the framework conditions of innovation, in order to identify problems of Japanese biotech medicine, and policy implications.

1.2. Approach

This report takes a systemic approach to identify various factors in the national innovation system and their interactions. The following chart shows the framework for analysis in later chapters.

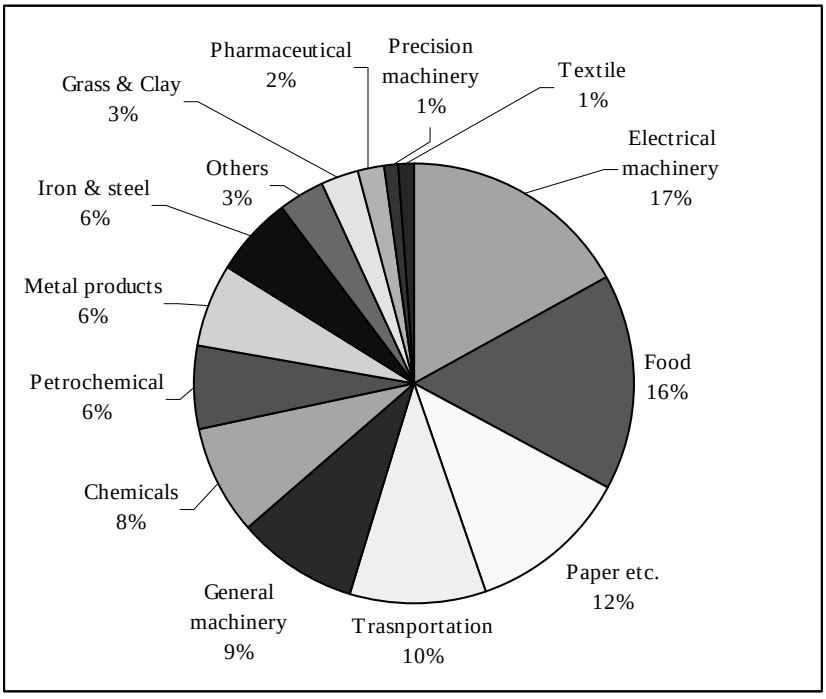


1.3. National characteristics

In 2001, Japan's Gross Domestic Product (GDP) was 504.4 trillion yen and its GERD was 16.5 trillion yen, and thus the ratio of R&D expenditures to GDP was 3.29%. In value-added-based figures, the ratios of primary, secondary and tertiary industries were 1.5%, 21.0% and 77.5%, respectively. These figures indicate that Japan's manufacturing industry share is relatively high among OECD countries.

As shown in Figure 1-1 *Breakdown of manufacturing industry in Japan*, the electrical machinery industry had the largest share of value added, followed by food, pulp/paper/publishing and transportation machinery, in that order. The pharmaceutical industry accounted for 0.5% in terms of value added, 0.3% in terms of number of employees (210,000 out of a total workforce of 64,460,000 in Japan), and 4.8% in terms of R&D expenditures. About 720 out of a total of 1,400 pharmaceutical firms in Japan produce ethical drugs. The degree of industrial concentration has tended to move upward recently.

Figure 1-1 Share of value added in manufacturing, 2001, Japan



2. Overview of National R&D, Technology and Innovation Policies

2.1. Main actors involved in policymaking and policy program management

Since biotechnology can be applied in various fields, such as pharmaceuticals, industrial goods, agriculture and environmental protection, policymaking for biotech R&D and the biotech innovation system is spread across various authorities, including the Ministry of Health, Labour and Welfare (medicine), the Ministry of Economy, Trade and Industry (industrial goods), and the Ministry of Agriculture, Forestry and Fisheries (agricultural products). In addition, the Ministry of Education, Culture, Sports, Science and Technologies (MEXT) is in charge of the higher education sector and public research organizations. These four Ministries have been working together to formulate Japan's biotech policies. To further promote biotechnology in Japan, the Biotechnology Strategy Council (BTSC) was recently established in the Cabinet Office as a body for coordinating the biotechnology promotion policymaking spread across various related bodies (see Annex for BTSC's purpose and members). BTSC members include the Prime Minister, the Ministers of the four ministries mentioned above and nongovernmental experts.

The BTSC's Biotechnology Strategy Guidelines contain three strategies vital for the future development of biotechnology in Japan: "overwhelming enhancement of R&D," "fundamental strengthening of the industrialization process" and "thorough understanding of the people." The Guidelines outlines a vision in which the fulfillment of these plans will substantially improve Japan's standard of living and enhance Japan's global competitiveness. The Guideline's three key strategies list specific action plans, according to which the concerned Ministries are to set up biotech policies. As we will mention in the next paragraph, the scope of these action plans ranges widely, from the reinforcement of major research areas, such as protein and genome analysis, to the establishment of ethical standards to promote citizens' understanding about biotechnologies, as well as the formulation of access-to-information guidelines.

The Council for Science and Technology Policy (CSTP), headed by the Prime Minister, coordinates a range of science and technology policies adopted by several ministries.[2] The CSTP has substantially increased its influence since the government's ministries and agencies were drastically reorganized in April 2001. The main mission of the CSTP is to release a

Science and Technology Basic Plan every five years to set the course of the government's overall science and technology policy.

In the second Science and Technology Basic Plan (2001-2006), the government will spend a substantial amount of its science and technology promotion budget on biotechnology and three other key projects. The Basic Plan also states the targeted amount for the total science and technology budget, which was boosted from 17 trillion yen in the first Basic Plan (1996-2000) to 24 trillion yen in the second Basic Plan (2001-2006), representing an outlay of 5 trillion yen per year or about 1% of the GDP. While the overall budget is expanded, biotechnology is designated as one of the main fields to benefit from the budget, indicating the government's firm commitment to domestic development of biotechnology.

The CSTP was established to coordinate the activities of the relevant ministries and agencies (including MEXT, and other concerned authorities; the Ministry of Economy, Trade and Industry; the Ministry of Agriculture, Forestry and Fisheries; the Ministry of Land Infrastructure and Transport; and the Ministry of Public Management, Home Affairs, Posts and Telecommunications) and its secretariat consists of 100 staff members sent by these ministries and from private organizations.

2.2. Main vertical (= specifically dedicated to biotech) policies and principal horizontal (generic- considering all fields) programs and instruments

2.2.1 Policies for knowledge base support

One of the keys for a policy to expand the basic knowledge about biotechnology is increasing the biotechnology R&D budget.

The biotechnology-related budget in fiscal 2003 is about 500 billion yen. The main part of the budget is a R&D budget for four ministries: the Ministry of Economy, Trade and Industry, the Ministry of Agriculture, Forestry, and Fisheries, the Ministry of Health, Labor and Welfare, and MEXT.

[2] See Motohishi (2003a) for further information about the Council for Science and Technology Policy and other recent developments in Japan's innovation policy.

Figure 2-1: Main biotechnology related R&D projects financed by government

	million yen
Ministry of Economy, Trade and Industry	**16,000**
Biotechnology and IT fusion apparatus developmet project	4,000
Protein functional analysis and practical use project	4,500
Oligosaccharide engineering project	3,000
Nano capsule model artificial oxygen conveyance object manufacturing project	900
Nanoparticle nano biotechnology device project	900
Advanced model nano biotechnology device project	900
Protein interaction analysis nano biochip project	700
Ultra-fine-processing-technology-based cellular tissue manufacturing project	1,100
Ministry of Agriculture, Forestry and Fisheries	**26,875**
Rice genome research	10,268
"Insect technology" research	3,112
General research about the safety and functionality of food	2,965
Development of management technology of detrmental chemistry substance in agricultural, forestry and fishery ecosystem	1,400
Agriculture, forestry and fishery biotechnology recycling research	1,464
Fresh and delicious "Nippon Brand"	3,922
General research for agricultural product provision	2,949
Technical development for controling over Bovine spongiform encepphalopathy (BSE) and other human and animal common infections	795
Ministry of Heath, Labor and Welfare	**12,000**
Disease-related protein analysis project	4,000
Apparatus development project for body functional analysis, assistance and substutition	3,000
Activation project of unreleased medicine trials on patients	3,500
Research over secure safety of food	1,500
Ministry of Education, Culture, Sports, Science and Technology	**22,899**
Tailor maid medical realization project	8,113
Human organs reproduction realization project	4,509
Life molecule (protei, sugar, etc.) production project	4,509
Cell and living body simulation project	3,768
Research and development of living body functional measurement technology with opto-electronics	2,000

The budget is for the following projects: the Ministry of Economy, Trade and Industry's "biotechnology and IT apparatus fusion project" and "protein functional analysis/practical-use project"; the Ministry of Agriculture, Forestry, and Fisheries' "Rice genome project"; the Ministry of Health, Labour and Welfare's "disease-related protein analysis project" and "body functional assistance/substitution apparatus development project"; and MEXT's "tailor-made medical realization project" and "life molecule (protein, sugar, etc.) production project." The total of these budgets is 341,700 million yen, and Figure 2-1 shows the budget for each project.

Besides the budget for such major government-sponsored projects, there is budgeting for competitive research funding, open to application by researchers in universities or public research organizations. This funding represented a total of 266 billion yen in fiscal 2002, and 47% of that amount (about 124 billion yen) was for life science-related research projects. Furthermore, the competitive project funding has been increased to about 300 billion yen in fiscal year of 2003, and the amount for life science-related research projects will be, if the same ratio of 47% is used, a total of 140 billion yen.

In addition, it is estimated that a biotechnology-related budget of about 10 billion yen is to be spent for the independent administrative agencies under the jurisdiction of the Ministry of Economy, Trade and Industry or the Ministry of Agriculture, Forestry, and Fisheries. The total of the entire biotech budget amount will be about 500 billion yen. It should be noted that the budget of 500 billion yen includes biotechnology-related R&D budgeting for various purposes, such as agricultural products, industrial products, and environmental measures.

Data on budgeting for biopharmaceutical R&D does not exist. The amount of the biotechnology-related budget of the Ministry of Health, Labour and Welfare, nearly all of which is supposed to be for medical and heath care projects, is about 160 billion yen. Substantial portions of the budgets of MEXT and the Ministry of Economy, Trade and Industry are earmarked for basic research, such as gene and protein analysis, so biopharmaceutical R&D funding is expected to be quite larger than about 160 billion yen.

In addition to fiscal appropriation, tax incentives for R&D is also important for pharmaceutical innovation. The system for R&D tax credits was revised this year, with stronger incentives added. Formerly, the tax credits were applied only to R&D spending in excess of the threshold amount, using a formula[3]. However, under the new system, the tax credit is a certain percentage (8% to 12% of an experimental-and-research-expense sales ratio) of the total amount of R&D expenditures. The total amount of incentive by this system is expected to be about 600 billion yen, which should have a substantial impact on R&D of large pharmaceutical companies, which substantially invest in R&D.

[3] A: R&D expense in this year. B: The average amount of the largest expenditures of three of the last five years. A-B: “amount in excess,” which was used as the base for this tax reduction.

2.2.2 Policies for commercialization support

Commercialization of research findings from public research institutes (PRIs), including universities has been strongly promoted by various kinds of policy initiatives under the guidelines of the Science and Technology Basic Plans. The mechanism of the commercialization can take various forms. It could be the licensing of PRI patents or the "spinning out" of researchers to set up new companies. In addition, research collaboration between PRIs and industry is also encouraged in order to increase the potential for commercialization of research results. Furthermore, such collaboration will also induce knowledge spillover from PRIs to industry, which eventually enhances industrial innovation.

At the institutional level, the Law for Promotion of University-Industry Technology Transfer plays an important role. This law was enacted in 1998 to support technology-licensing offices (TLOs) at PRIs. Under this law, the registered TLOs can receive financial support for their activities, and other special treatment, such as reduced patent application fees. The number of patent applications made through registered TLOs between the end of 1998 and the end of 2000 exceeded 700. (There were 26 TLOs as of January 2002).

In addition, since fiscal 1987 joint research centers have been established at universities as footholds for the promotion of industry-academia cooperation. These centers provide space for the conducting of collaborative research projects between university and private firms, as well as an inside-university focal point of interaction with industry representatives. There were 61 centers as of the end of March 2002. At national universities, the number of joint research projects has increased 4.4-fold, and the number of researchers for those projects has increased 2.7-fold during the last 10 years. As for national research institutes, most of which are now operating as independent administrative institutes (IAIs), commercialization of research and collaboration with industry are at the top of the agenda for their mid-term plans. Each institute's evaluation committee evaluates the overall activities of IAIs, and the national guidelines on research evaluation states that the evaluations should be based on quantitative criteria as far as possible. Therefore, the quantitative indicators for research output, such as the quantity of patents and papers, become important for PRIs. In addition, IAIs are encouraged to attract external research funding, including not only project-based grants from the government, but also research funds from private firms for contracted research and joint research projects. These policy initiatives for commercialization of the research findings of PRIs and collaboration with industry have started to work. According to a survey conducted by MEXT in 2000, the share of firms that reported an increase their joint research with

universities during the five years preceding the survey was 21.8%, while the share of those reporting a decrease was 9.2%. As for national research institutes, the share of firms with increases in joint research was 13.7%, while the share of those with decreases was 11.5%. In addition, there are other signs of the success of the policy initiatives, such as increases in the number of joint papers published by PRIs and industry, and in the number of patent applications and the amount of licensing revenues of universities.

However, the policy push for commercialization of the research findings of PRIs has only started recently, and there are many things to be developed on the PRI side. Other statistics show that R&D expenses for joint research with domestic PRIs are not increasing, in contrast to the upward trend of R&D expenses with foreign PRIs. According to an opinion survey of managers of Japanese firms, it is difficult to gain attractive research output in PRIs. In addition, compared with international PRIs, Japanese PRIs lack experienced staff in charge of dealing with contracts.

As for researchers at PRIs, incentives for commercializing their research output are not so strong. However, involvement in research projects with industry is encouraged. Under the new management style of IAIs, each researcher has stronger incentives to collect external funding and to work together with industry as well as with other research institutes. In addition, the government has prepared R&D program funding, granted only to joint research teams consisting of researchers from both PRIs and private firms, to promote collaboration between PRIs and private firms. The turnover of researchers among institutions is important in order to facilitate the collaboration of industry and science, and it enhances knowledge spillover embodied in human capital. In connection with the human interchange at public research institutes, during off-duty hours, part-time work to conduct R&D or give technical guidance at businesses has been allowed since 1996 for national research institutes, and since 1997 for national universities. Also, in 2000, dual assignment of university educators to the TLOs and to the directorship of businesses that use research output was approved.

In addition, introducing the system of IAI to national research institute gives more flexibility to human resource management. Originally, national research institutes had to comply with regulations for government employees, such as seniority-based promotion and wage systems. However, after being converted to an IAI, an institute introduces its own human resource strategy, and sometimes mid-career university professors are hired as a directors or team leaders in PRIs.

The system of intellectual property rights is also important for facilitating discussions about researcher incentives for commercializing research results. MEXT has a guideline on the IPR ownership for intramural research at national universities. It states that the ownership of a right is attributed to the Japanese government when the research concerned is for the specific development of an application, but otherwise the ownership of a right is attributed to the individual researcher. In the case of research projects conducted at national universities, the majority is curiosity-driven basic research, for which rights are attributed to researchers. However, actual patent application has occurred only rarely, due to the heavy financial burden of applying for and maintaining the right. For national research institutes there has been no such guideline, but IPRs are attributed to either an individual researcher or the government. University research faces the same problem, as does individual holding of IPRs, and in the case of a government holding, effective utilization of the IPRs is not possible, due to the complex procedures for the disposition of national property. The treatment of IPRs in PRIs is now in the process of reform, and the general policy direction is that they should be attributed to IPRs, instead of to individual researchers. In the case of IAIs, there is no problem associated with national property, since IAIs are no longer part of the Japanese government. In addition, a TLO attached to each PRI can effectively conduct the maintaining and licensing of IPRs. National universities will be converted to IAI-type independent institutes in 2004. Then each institute can conduct effective management of IPRs. As for researcher incentives, it is important to set rules for remuneration to inventors. Under the patent law in Japan, ownership of a patent in the course of work in private firms belongs to the employee, but the firm can obtain the right according to the employer-employee contract by paying a "reasonable amount of remuneration." Since this language of the patent law is too vague, currently there is heated discussion on this clause. The question of whether a different clause for patents registered by PRIs is needed is also under debate. A Revision of existing clause for inventions for employee is still under discussion.

2.2.3 Policies with a socio-economic and/or ethical dimension

It is expected that rapid development of life science in recent years will bring innovation to a number of fields, such as medical treatment. On the other hand, it also will bring about bioethical problems with respect to human dignity and human rights. To discuss those problems appropriately, the bioethics special board of inquiry of the comprehensive Council for Science and Technology investigates and examines statements of principles or important

matters of bioethics. MEXT is improving related statutes and guidance, and is appropriately reviewing their content.

As for human cloning technology, MEXT seeks to prohibit human cloning and ensure proper handling of human embryos through its "Guidance on the Handling of Designated Embryos[4]," based on "Law on Regulation of Human Cloning and Related Technologies." The Council for Science and Technology's bioethics special board of inquiry is investigating and examining "the state of handling of fertilized embryos as the origin of human life."

In the United Nations, efforts are underway to work out an international treaty forbidding the generation of human clones, and Japan is proactively responding to this challenge. At the September 2002 meeting of the task force for creating the treaty, Japan supported the proposal of Germany and France that only generation of cloned human individuals be prohibited, a proposal that was aimed at the early establishment of the treaty since most countries were already in support of this limitation. However, some countries persisted to prohibit all human cloning-related studies, so further ironing out of these differences is required.

MEXT reviews whether plans for generating or using human embryonic stem cells in research are in conformity with its "Guidance on Creation and Use of Human Embryonic Stem Cells."

In epidemiological research, a lot of personal information is collected and used, and the information is saved over a comparatively long period of time, so it is necessary to provide for protection of research candidates' human rights, appropriate information management, and other such concerns. Consequently, MEXT and the Ministry of Health, Labor and Welfare jointly established "The Ethics Indicator for Epidemiological Research" in June 2002. Recombinant DNA technology, which is applied in not only basic biological research but also a broad spectrum of fields, is also able to give new attributes to living things. MEXT seeks to ensure the safety of recombinant DNA experiments through its "Guidelines for Recombinant DNA Experiments." These guidelines also provide a new framework for the "educational use recombinant DNA experimentation" so that institutions of higher education can also carry out elementary recombinant DNA experiments.

With regard to industrial application of this technology, the Ministry of Health, Labor and Welfare, the Ministry of Agriculture, Forestry and Fisheries, and the Ministry of Economy,

Trade and Industry separately establish safety guidelines according to the purpose of use of genetically modified organisms. Recognizing citizens' understanding as an essential element to the realization of practical genetic combination technologies, the Ministry of Agriculture, Forestry and Fisheries distributes pamphlets, holds study sessions, and engages in other educational activities. Also, it has held a "Citizen Meeting for Examining the Subject of Genetically Modified Agricultural Products," and conducts research in response to the proposals gathered from the meeting.

Furthermore, concerned Ministries are working together toward an early conclusion of "Cartagena Protocol on Biosafety," an international framework for "protecting biological diversity from the potential risks posed by living modified organisms," by formulating legislative bills that provide for the domestic implementations needed to support the protocol.

Clinical research aimed at realizing gene therapies is checked for conformity with the "Guidance on Gene Therapy-related Clinical Trials," jointly established by MEXT and the Ministry of Health, Labor and Welfare, in order to maintain the scientific validity and ethical correctness of such research.

3. Structure, dynamics and performance of the biopharmaceutical/biomedical system

3.1. National public R&D system

R&D expenditure on biotechnology research was about 2 trillion yen in fiscal 2001, accounting for about 12% of the total 16.5 trillion yen spent on all research fields. The breakdown of biotechnology-related research expenditure is as follows: spending by private enterprises, 950 billion yen; by public research organizations, 330 billion yen; and by universities, 700 billion yen. The biotech R&D expenditures of public research organizations and universities are almost completely funded by governmental sources, and more than half of all biotech R&D expenditures are covered by governmental support. Spending on biotech R&D has been increasing steadily and its ratio to the total expenditure on all R&D is also growing.

[4] "Designated embryos" refers to the following nine types: human divided embryos, nuclei transplanted human embryos, cloned human embryos, united human embryos, human-nonhuman fused embryos, hybrid human

Figure 3-1: Biotechnology R&D (billion Yen)

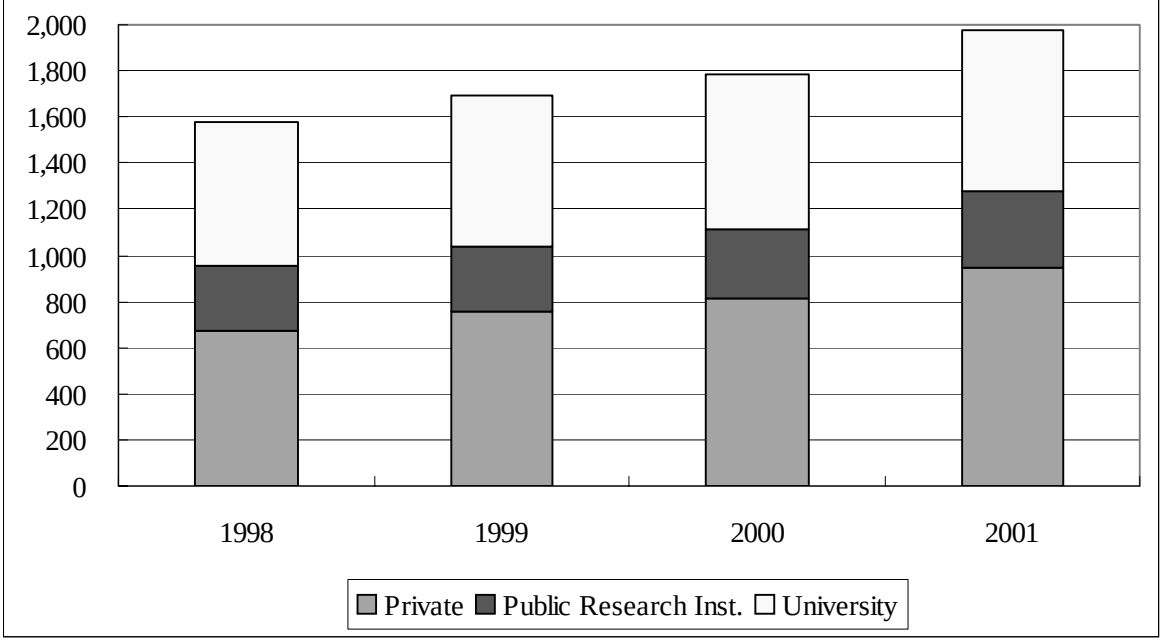
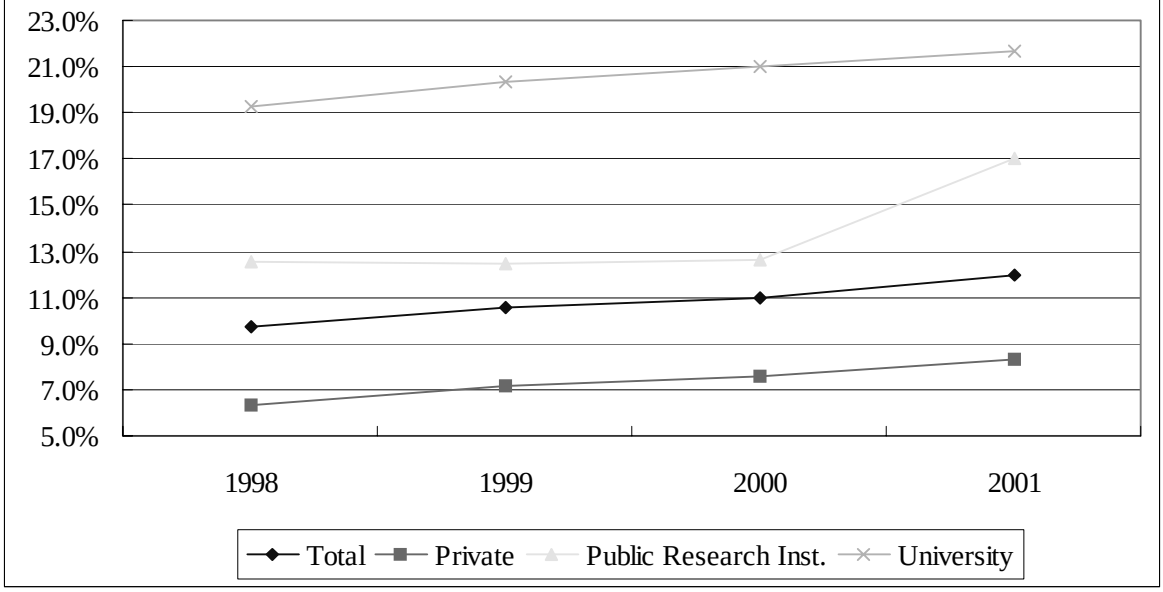


Figure 3-2: Share of Biotechnology R&D



These figures include biotech R&D for applications in not only biomedicine, but also agriculture, industrially, and other sectors (life science-related R&D in the "Science & Technology Research Survey" conducted by the Ministry of Public Management, Home Affairs, Posts and Telecommunications).

embryos, united human origin embryos, animal origin fused embryos and animal origin united embryos.

As is shown in Figure 3-3, of the 945 billion yen spent on life science R&D by the private sector, 698 billion yen (more than 70 percent) was spent by the pharmaceutical industry. In addition, it is found that more than 80 percent of life science R&D by universities (700 billion yen) went spent to healthcare-related projects. Although data on the breakdown of biotech-related R&D budgets at public research organizations does not exist, we estimate from the universities' circumstances that a considerable portion is spent for pharmaceuticals and health care related projects.

Figure 3-3: R&D for life science in 2001

(billion yen)

Industry	945	57.4%	
Pharmaceuticals	698	73.8%	Share in industry
Chimicals	84	8.9%	
Food manufacturin	64	6.8%	
Electronics	15	1.5%	
Universities	700	42.5%	
Public Research Inst.	329	20.0%	
Total	1,645		

A large-scale public biotechnology research institution like NIH does not exist in Japan, but there are a few PRIs in certain fields of applied research. The most important institution in the biopharmaceutical field in Japan is the National Cancer Research Center, under the supervision of the Ministry of Health, Labor and Welfare. Important roles in biotech research are also played by the Ministry of Economy, Trade and Industry's AIST (Agency for Industrial Science and Technology) and MEXT's RIKEN (Institute of Physical and Chemical Research), as well as university hospitals, such as the University of Tokyo Hospital.

3.2. Business system

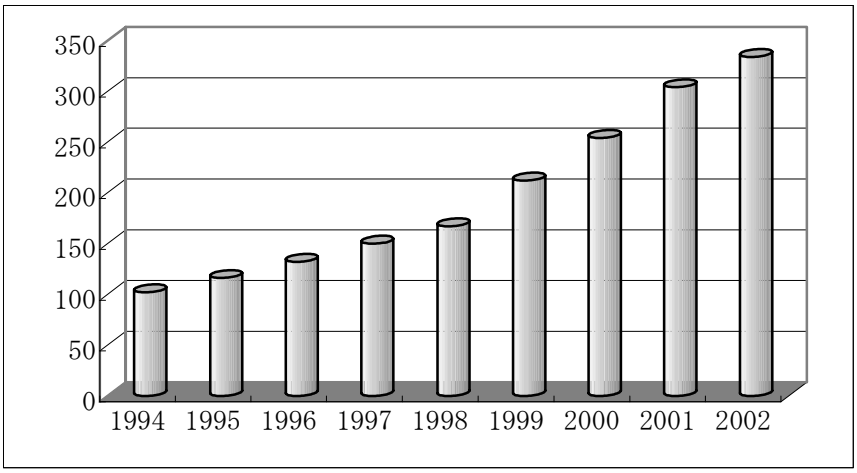
3.2.1. Business entry and exit, including mergers and acquisitions

The number of biotech companies in Japan is 334 as of February 2003 (source: Japan Bio-industry Association) and has been growing rapidly in this year (see Figure 3-4). However, the number is still considerably small when compared with some 2,000 firms in the U.S.A. and roughly 2,500 firms in the Europe. The size of Japanese biotech firms is also small. According to the survey of Japan Bio-industry Association, the average number of employees is 20, and the average amount of sales is about 400 million yen. (JBA, 2003)

Consequently, few biotechs have made Initial Public Offerings (IPO). AnGes MG, founded

by Professor Morishita at Osaka University, was listed on the Mothers section of Tokyo Stock Exchange in September 2002, marking the first case of a university spin-off to make an IPO in Japan. In the following December, Trans Genic Inc., which utilizes innovative technologies developed by Kumamoto University, was also listed. Some biotechs involved in development of new medicines, DNA chip techniques, and other such technologies are prepared to be listed in the near future.

Figure 3-4: Growing number of biotech companies



Source: Japan Bio-industry Association

3.2.2. R&D cooperation, including the system's international dimension

According to the Survey of Research and Development (Ministry of Public Management, Home Affairs, Posts and Telecommunications), the pharmaceutical industry's ratio of R&D expenditures to gross sales in 2001 was 8.6%, significantly higher than the overall average for all industries, 3.0%. Development of new drugs is said to take a period of more than 10 years and R&D outlays of several to tens of billions of yen. Accordingly, the pharmaceutical industry is an R&D-intensive industry with a high ratio of R&D expenses to production and sales expenses. Collaborations with external organizations are crucial for efficient R&D on new drugs. Figure 3-4 summarizes the R&D expenditures of the pharmaceutical industry, for both research outsourced to and contracted by external organizations, according to the Survey of Research and Development.

Figure 3-5: External R&D partnerships in the pharmaceutical industry (2001)

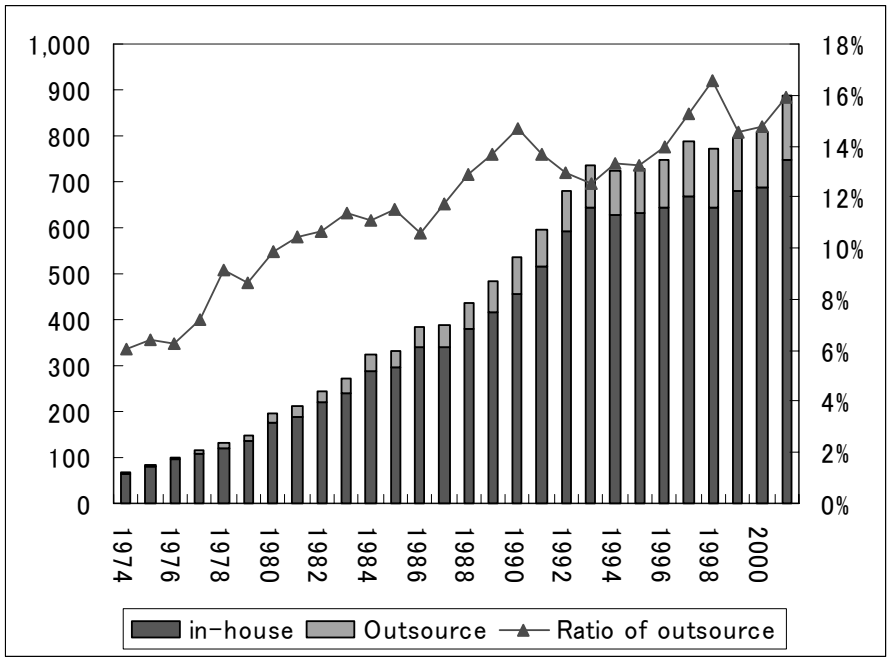
		R&D (100 million yen)	Ratio to in-house R&D	Average of entire industry
R&D total		8,875	(100%)	(100%)
R&D outsourced		1,413	15.9%	11.1%
	to government org.	176	2.0%	0.3%
	to other public	7	0.1%	0.2%
	to private	636	7.2%	9.4%
	to foreign org.	593	6.7%	1.3%
R&D contract-in		132	1.5%	4.9%
	from government org.	10	0.1%	1.2%
	from other public	5	0.1%	0.6%
	from private	13	0.1%	2.6%
	from foreign org.	103	1.2%	0.5%

Source: “Survey of Research and Development” (Ministry of Public Management, Home Affairs, Posts and Telecommunications

The total R&D expenditure of the pharmaceutical industry was 887.5 billion yen, 15.9% of which was paid to external organizations. On the other hand, the ratio of recompensed expenditures (on R&D contracted by external organizations) to the total R&D budget was a small 1.5%. A significant amount of the recompensed expenditure appears to be the result of intra-company remuneration from foreign organizations to affiliates in Japan, indicating that the R&D expenditure recompensed purely by external organizations is extremely small. Because the proportion of the expenditures paid to external organizations is larger than the average for all industries while that of the expenditure recompensed is smaller, the collaboration of the pharmaceutical industry with external organizations may be regarded as a virtually unilateral use of external organizations. A closer examination of the items making up the R&D expenditures paid to outside organizations reveals the significant scale of those paid to private companies and foreign organizations.

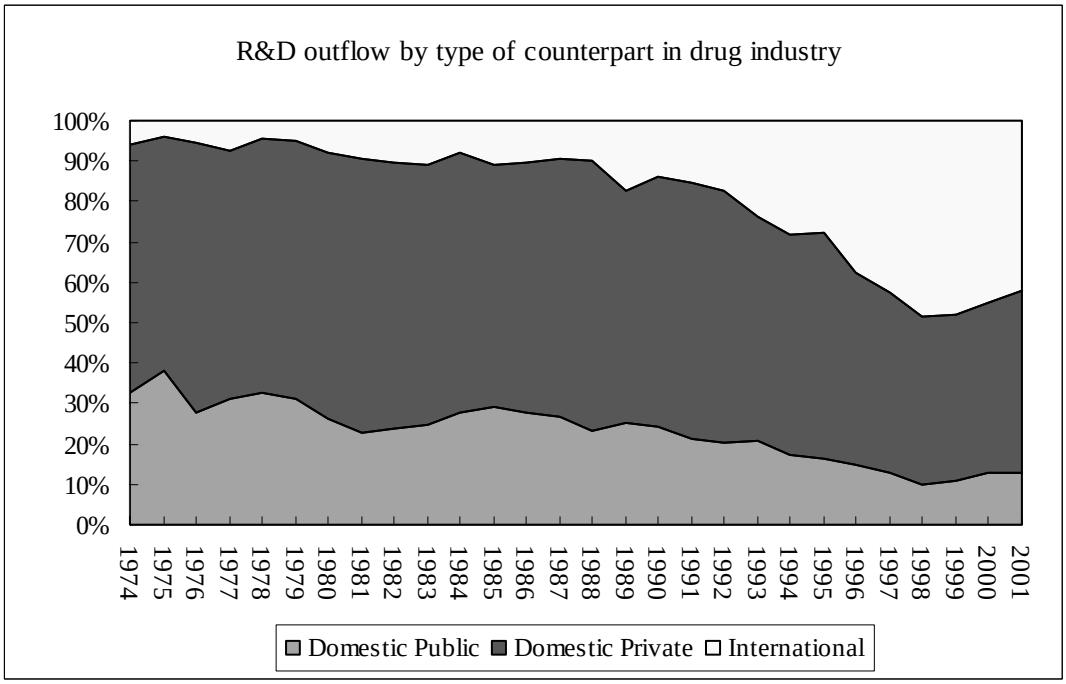
Figure 3-6 shows the annual changes as a proportion in internal R&D expenses and externally paid R&D expenses against total R&D expenses, while Figure 3-7 shows the change in shares of respective partners in externally paid R&D expenses. As Figure 3-6 makes clear, the growth rate of overall R&D expenses of the pharmaceutical industry has declined from the early 90s, while the ratio of externally paid R&D expenses has consistently expanded. Figure 3-7 also shows that collaborations with partners such as foreign companies and research institutes has increased dramatically. Despite an apparent recent decline in the share of these foreign organizations, almost half of externally paid expenses still go to organizations overseas.

Figure 3-6: Changes in internal and externally R&D expenses of the pharmaceutical industry



Source: "Survey of Research and Development" (Ministry of Public Management, Home Affairs, Posts and Telecommunications)

Figure 3-7: Share of partners in outsourced R&D expenditures of pharmaceutical industry



Source: "Survey of Research and Development" (Ministry of Public Management, Home Affairs, Posts and Telecommunications)

Hirai (2002) conducted a detailed analysis of external collaborations in R&D and other areas at Japanese pharmaceutical companies, using a database on inter-corporate alliances. Based on data on inter-corporate R&D alliances, including data submitted to the SEC from companies, he thoroughly analyzed these collaborations from various viewpoints: the identity of contracting partners, the subject of the projects, and R&D stages. According to the results, the most common type of partner for Japanese pharmaceutical companies, and the one for which the rate of collaboration is growing fastest, is bio-venture companies, most of which are located in the U.S. As shown by the Survey of Research and Development, as biotechnology progresses, the outflow of R&D expenditures in such overseas collaborations dwarfs the inflow, presumably due to increasing numbers of collaborations with overseas venture companies, mainly in the U.S., whose purpose is to acquire state-of-the-art bio-technologies. Hirai (2002) also discussed changes in the number of alliances for each R&D stage. The general flow of pharmaceutical R&D programs is identification of a target compound for development, synthesis of a lead compound, screening, preclinical tests (e.g., animal tests), and human clinical trials. Approximately one-third of alliances formed in the late 90s involved collaborations at the target identification stage, a ratio that has grown year after year, indicating the desire of pharmaceutical companies to import state-of-the-art technologies. This is part of a trend toward the spread of new drug development methods based on genetic information, which is exerting enormous influence on the upstream stages of pharmaceutical R&D programs.

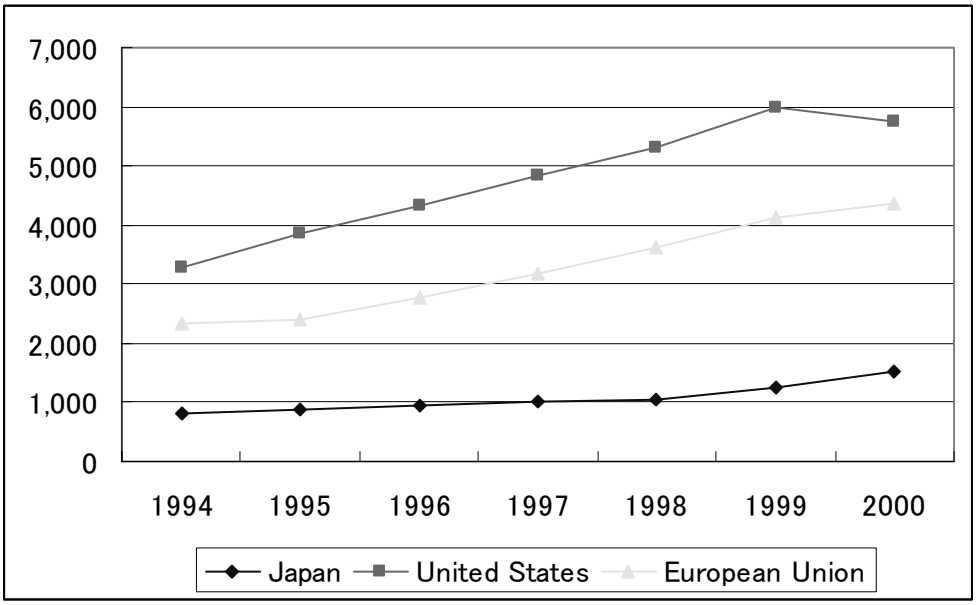
Odagiri (2002) investigated the number of collaborations involving pharmaceutical research based on data described in "World Bio-Companies," an article in *Nikkei Biotechnology* that reported that the number of R&D alliances for ten major Japanese pharmaceutical companies increased in each case from 1989 to 1999.

3.3. Performance

As the biomedicine innovation system's core output, we focused on the number of pharmaceutical and biopharmaceutical patent applications defined by IPC code[5]. Firstly, the numbers of pharmaceutical patents and the share of biopharmaceutical patents are compared between Japan, United States and EU countries by using looking at EPO patent database.

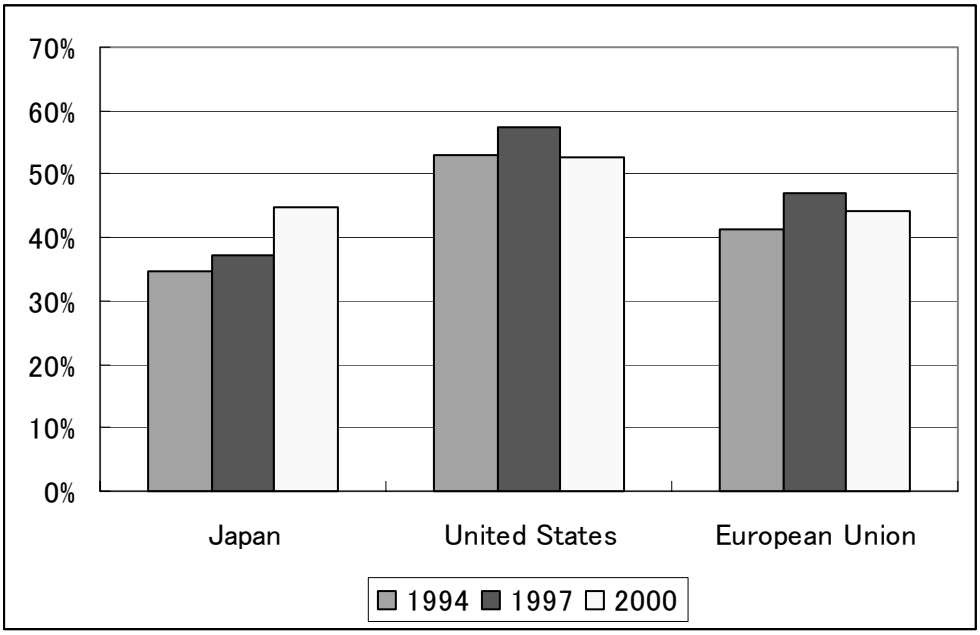
[5] Pharmaceutical patents: A61 and subgroups of C12 and C07. Biopharmaceutical patents: intersection of pharmaceutical and biotechnology, where biotechnology's codes are C12 and subgroups of C07, G01, A61 and A01

Figure 3-8: The number of pharmaceutical pantet applications at EPO



Source: EPO patent database, compiled by OECD biopharmaceutical project

Figure 3-9: The share of biopharmaceutical patents in pharmaceutical patents

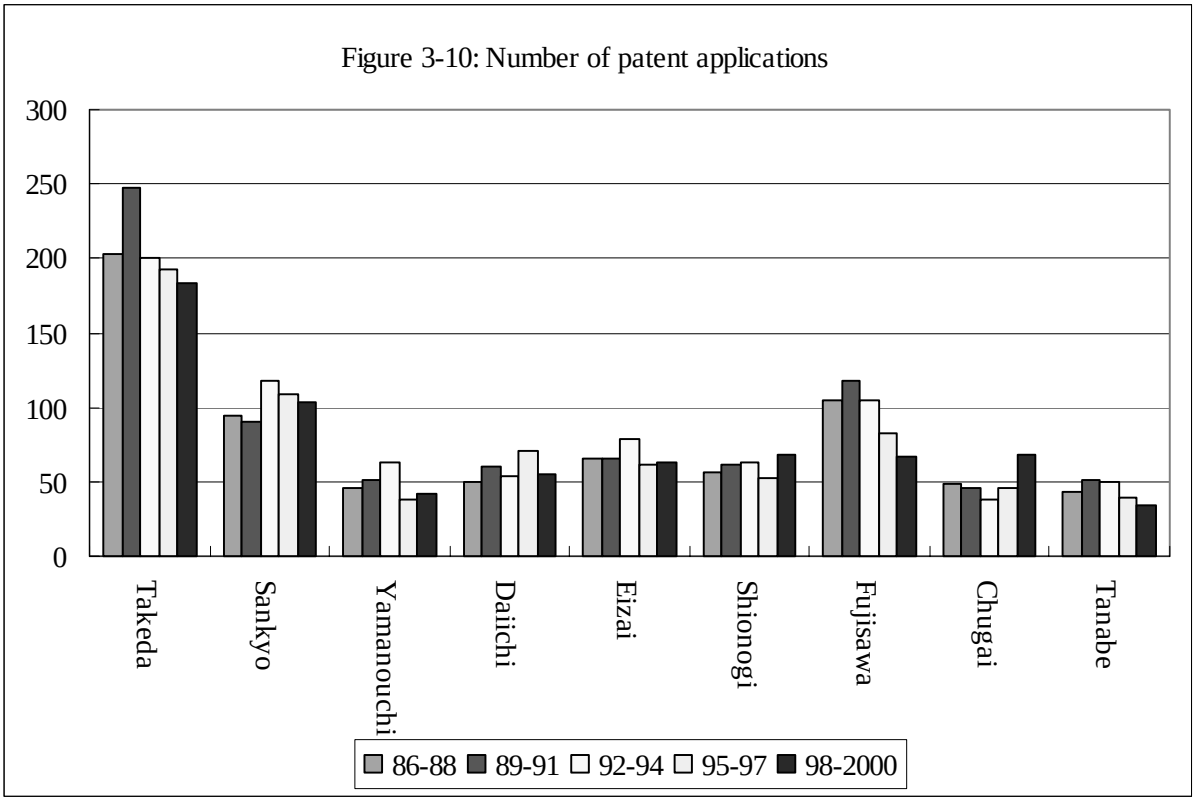


Source: EPO patent database, compiled by OECD biopharmaceutical project

For each of the triad, the number of pharmaceutical patents is growing, and the number of patents nearly doubled from 1994 to 2000. In terms of the share of biopharmaceutical patents, that of the U.S. is the highest and Japan and EU follow. Japan used to be the lowest in 1994, but caught up with Europe in 2000, by rapid adaptation of biotechnology in a process of pharmaceutical innovation.

The increasing share of biotechnology pharmaceutical patents can be also observed by looking at JPO patent database. Here, we look at the number of patent applications made by Japan's nine major pharmaceutical firms. (Figure 3-10)

Figure 3-10: Number of patent applications



Source: Data Book 2002, JPMA

Judged by the number of pharmaceutical-related patents, the innovation performance appears to be in a downward trend recently, but we emphasize that each patent has became more effective because the number of claims per patent has significantly increased since the Japan Patent Office started allowing multiple claims on a single patent in 1988. Although we do not know the specific average number of claims per pharmaceutical-related patent, the average number of claims for all patents in Japan has increased from 2.8 in 1989 to 7.6 in 2001, which shows the quality of each patent has improved. And the results of interviews of pharmaceutical firms also support this hypothesis, since most firms now apply stringent selection criteria to patent applications. (Motohashi, 2003c) Therefore, we cannot conclude that the innovation performance of Japanese pharmaceutical firms has gone down.

The ratio of biotech-related patents to all patents of the nine major pharmaceutical firms has been growing since the late 90s[6] (see Figures 3-11 and 3-12), which shows that these companies have shifted R&D resources to biopharmaceutical technology with some innovative output.

Figure 3-11: Share of biotech patent applications (broad definition)

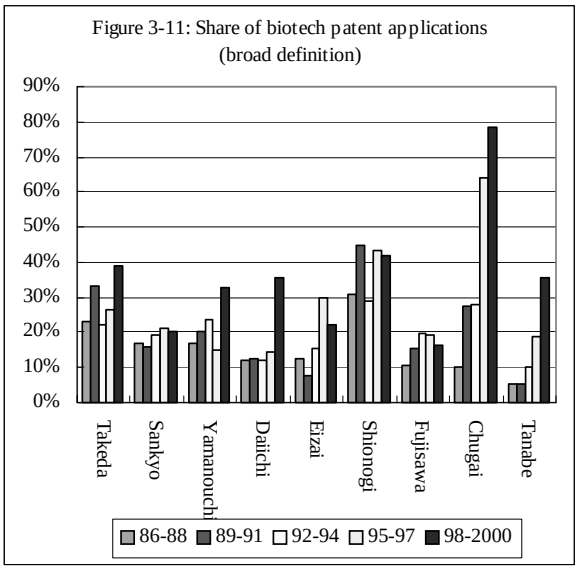
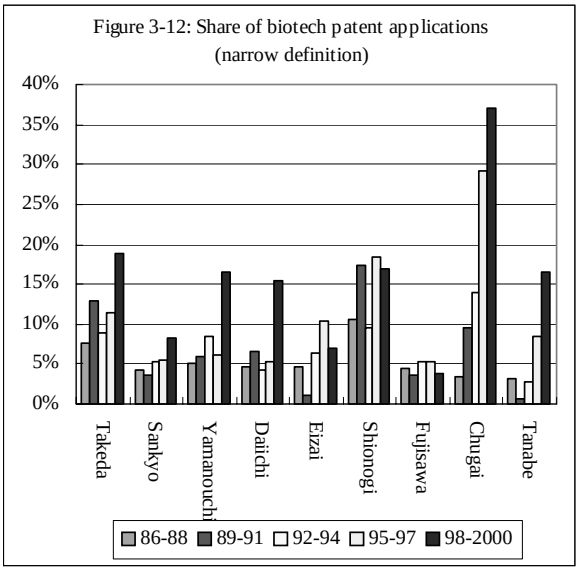


Figure 3-12: Share of biotech patent applications (narrow definition)

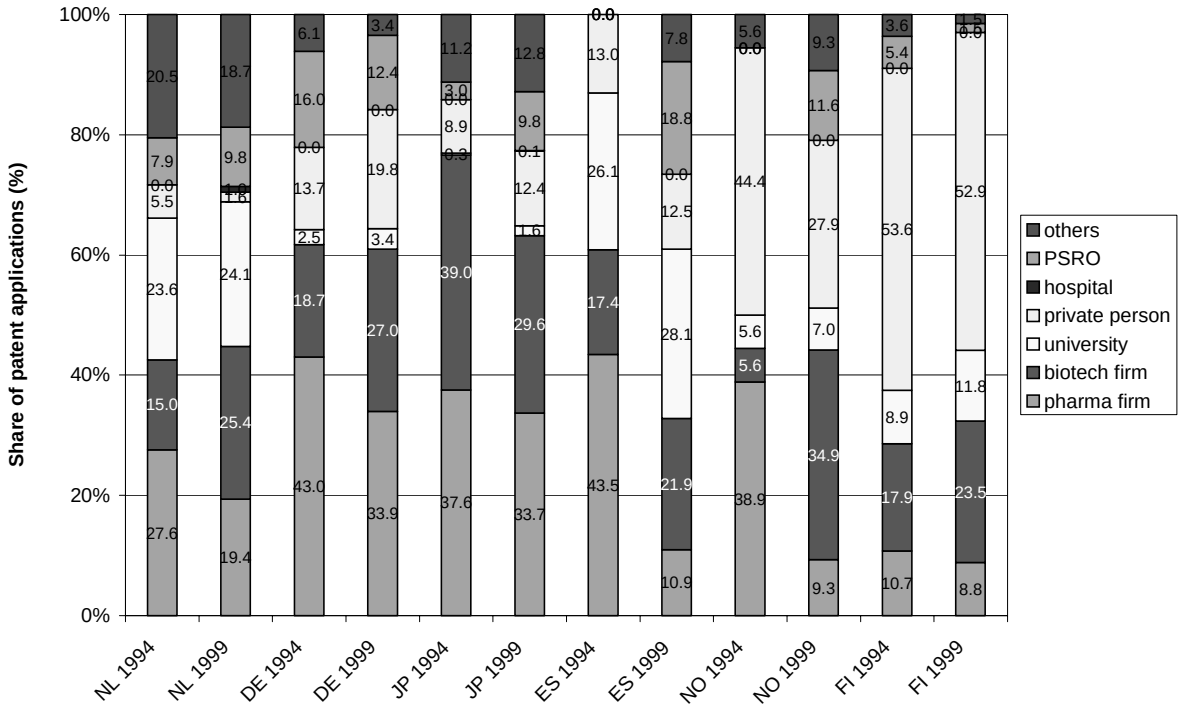


Source: PATOLIS database

As compared to other OECD countries, the role of large pharmaceutical firms in biopharmaceutical innovation is relatively important. Figure 3-13 shows the share of biopharmaceutical patenting at EPO by actor of innovation. It is found that the share of pharmaceutical firms is larger than other countries, although it decreased from 1994 to 1999. In contrast, the share of university is very small in Japan. As is described in section 2.2.2, inventions at national university are mainly attributed to professors instead of university. In addition, in many cases, university professors do not apply patent due to the cost associated with patent application and examination. Therefore, this kind of institutional difference in IPR system should be taken into account when one looks at Figure 3-13. In addition, a large share of biotech firms may come from the fact that non pharmaceutical private companies, diversifying into pharmaceuticals, are active in biopharmaceutical innovation in Japan.

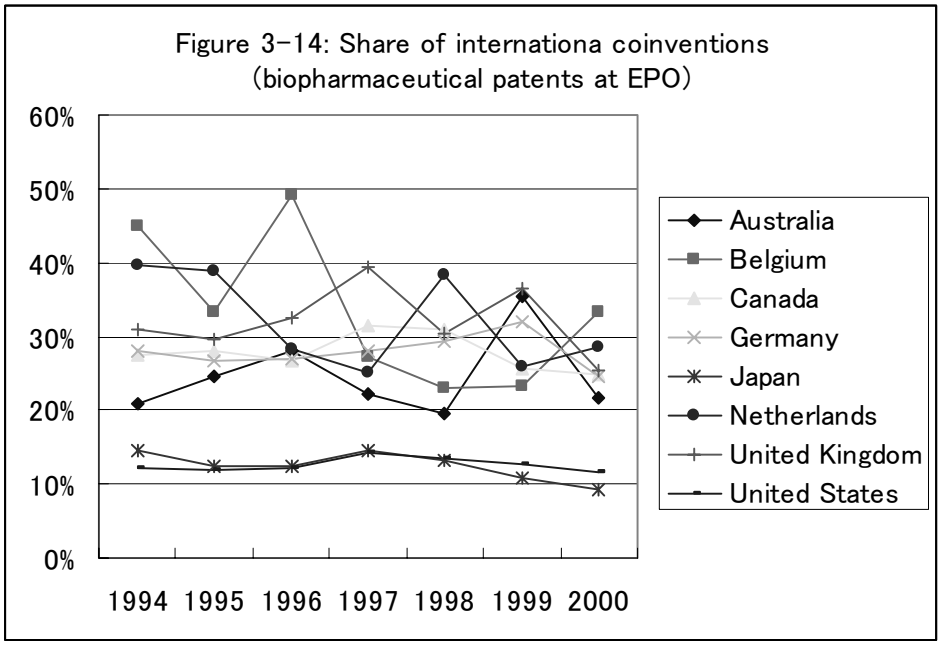
[6] The ratio is based the biotech-related patents under both the broad and narrow definitions of "biotechnology" given by OECD (2002). The broad definition of biotechnology is A01/06+A61K48/+C12N1/+C12N9/+C12N15+C12P21/C12Q1/68 +G01N333/50-98, and the narrow definition is C12N15/.

Figure 3-13: Share of biopharmaceuticals by innovation actor

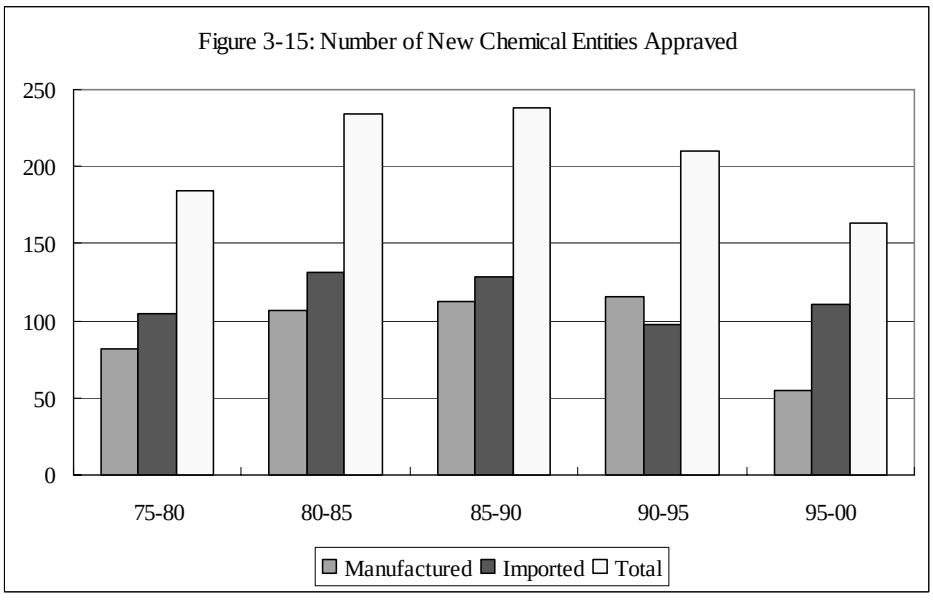


Source: EPO patent database, compiled by OECD biopharmaceutical project

Figure 3-14 shows the share of international coinvensions for biopharmaceutical pantents at EPO. It is natural to see that the shares in European countries are higher than those of Japan and the United States. It is interesting to see that there is no clear pattern of inceasing international coinvensions. In case for Japan, the share seems to be decreasing. International knowledge spillover has an positive impact on innovation performance in home country in general. However, growing technological capabilities at domestic players may push down the share of international coinvensions. The trend in Figure 3-14 contains both of these factors against each other.



It is possible to look at the innovation performance of the pharmaceutical industry in terms of the number of new drugs approved. However, it should be noted that under the Pharmaceutical Affairs Law, the total number of new drug approvals includes existing drugs whose ingredients remain the same but needed re-approval due to the development of new methods for administering or manufacturing them. In this sense, it would be better to use the number of new chemical entities as an innovation performance indicator. Figure 3-11 shows this number, broken down into domestically manufactured (developed) drugs and imported drugs.



Source: Data Book 2002, JPMA

Both the number of domestic new chemical entities (NCEs) and the number of imported NCEs grew steadily in 1980s, but the former started to decrease after the early 1990s.

In the 1990s, Japanese pharmaceutical firms expanded alliances with their overseas counterparts, so it is thought that a substantial number of domestic NCEs are licensed by overseas firms. In this sense, innovation performance seems to be declining in this decade. However, it should also be noted that the quality of NCEs will improve due to the recent revision of the Pharmaceutical Affairs Law. The Ministry of Health, Labor and Welfare stringently screens new drugs whose ingredients are similar to those of existing drugs, and thus pushes pharmaceutical firms to develop innovative drugs. The details of this legislative change will be provided in Chapter 5. Developing an innovative new drug which functions in the human body through a new mechanism involves considerable risk and requires substantial spending on R&D. Therefore, instead of seeking to increase the number of new drugs they develop, Japanese pharmaceutical firms are concentrating their R&D budgets on developing a smaller number of target entities, but with higher quality. As a result, the number of new drug approvals is decreasing.

Pharmaceutical companies are reinforcing their new drug development potential by using biotechnology, which offers higher probability for the development of innovative drugs. Biopharmaceuticals can be largely divided into first-generation biopharmaceuticals, which include human growth hormone, erythropoietin, G-CSF and other human proteins that are mass produced through genetic recombination technology, and second-generation biopharmaceuticals, the so-called “genome base pharmaceutical development,” which are developed from genome information or gene functional analysis. The market scale of biopharmaceuticals in 2002 was about 1 trillion yen (out of the 7 trillion yen market of prescription drugs), and most of them are first-generation biopharmaceuticals. Monoclonal antibodies and other second-generation products are under development and the ratio of biopharmaceuticals to all prescription drugs is gradually increasing. (Hayakawa and Ishii, 2002)

4. Innovation barriers/drivers – Framework conditions

4.1. Knowledge sources

Many factors encourage Japanese pharmaceutical companies to engage in R&D partnerships with external organizations. We conducted a questionnaire survey of 21 major pharmaceutical

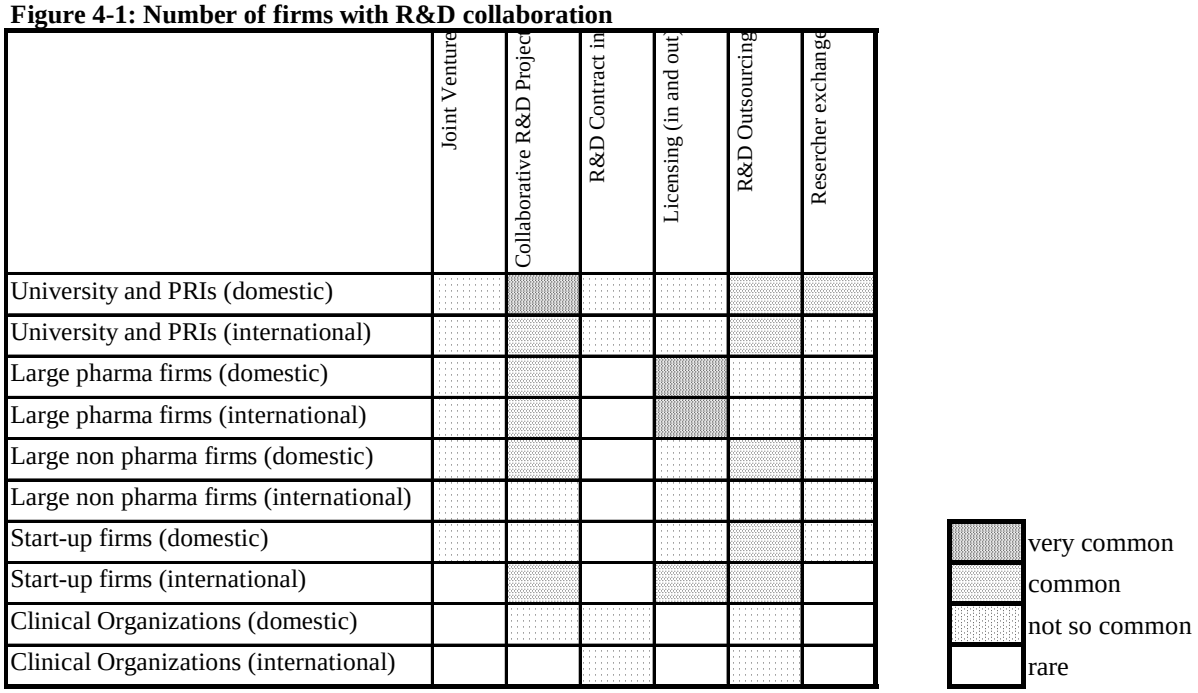
companies and an interview survey of 10 companies to analyze these factors in detail. As described above, external collaborations differ, depending on whether the partner organization is a company or a research organization, such as a university, and also depending on the stage of R&D at which the collaboration occurs. We must first gain a detailed understanding of the actual status and recent trends in these partnerships. We also undertook a survey of factors essential for entering such partnerships (including such aspects as technology, demand, regulation, and political measures promoting innovation.[7] A brief summary of the survey is provided below.

(1) Actual conditions of partnerships with external organizations

Figure 4-1 and 4-2 show the results of the questionnaire survey on the current status of external collaborations and the change in their numbers from the latter half of the 1990s. With respect to the type of collaboration, joint research projects are now both more numerous and their rate of growth more rapid, with licensing arrangements and consigned research (outsourcing) just behind. Joint ventures, externally funded research, and exchange of researchers are less common. With respect to collaboration partners, instances of joint research with domestic universities and public research organizations are now both more numerous and their rate of growth more rapid. In addition, the number of mutual licensing agreements with major drug makers, particularly with overseas companies, is increasing. For venture companies, licensing agreements with overseas companies are increasing in number and growing at a more rapid rate. Described below are the results of in-depth interviews regarding the nature of these partnerships.

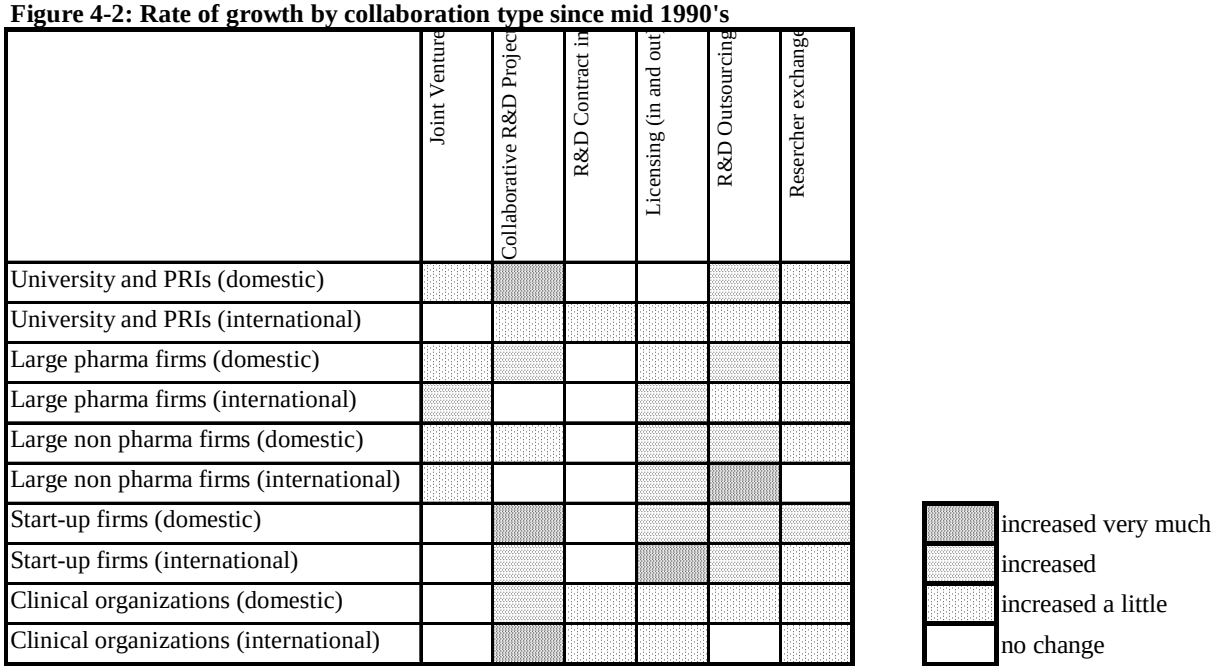
[7] For details of survey, refer to Motohashi (2003b)

Figure 4-1: Number of firms with R&D collaboration



PRIs:Public Research Institutes

Figure 4-2: Rate of growth by collaboration type since mid 1990's



(Joint research projects with domestic universities and public research organizations)

- Pharmaceutical companies have worked closely with universities, primarily with university medical schools, and the number of such collaborations is growing.

- Previously implemented in such a way that left ownership of research results ambiguous, these partnerships are now much more often delineated in research contracts, presumably due to the establishment of guidelines for joint research and of TLOs in universities.

- However, pharmaceutical companies rarely accept patent licenses directly from universities, preferring instead to take research concepts generated in universities and further develop them in joint research.

- According to the evaluations of Japanese universities, despite the establishment of TLOs and recent measures for promoting university-industry partnerships, which will undoubtedly lead to collaboration of university members with private companies, the business sense of university members is unlikely to reach maturity any time soon.

(Joint research projects with and licensing from overseas venture companies)

- Japanese pharmaceutical companies collaborate with overseas venture companies in restricted, focused areas. In many cases, partnerships are conducted under a set of license agreements for a patent granted to the venture company and a co-R&D contract for patent development.

- Major joint efforts include (1) use of databases on gene function and (2) screening systems based on gene-related patents.

- Many foreign venture companies are companies spun off from universities.

(Partnerships with major drug makers)

- Partnerships with large companies primarily focus on downstream processes in pharmaceutical R&D. Examples of such partnerships include clinical trials with overseas pharmaceutical companies and CROs.

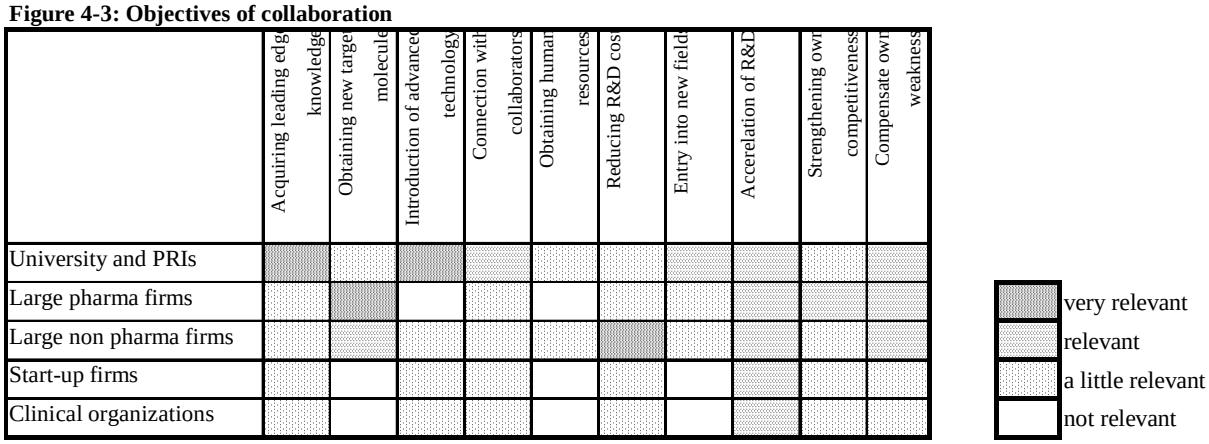
- Sometimes, pharmaceutical companies will license or sell to other companies in the pharmaceutical sector candidate drugs for which they have ceased sustained development.

(2) Purpose of external partnerships and changes in their importance

Figure 4-3 and Figure 4-4 summarize the results of the questionnaire survey on the reasons for external partnerships and the changes in their importance. The reasons for external partnerships marked as “greatly relevant” in the responses include “acquisition of leading-edge technology and information” and “introduction of a state-of-art technology” in partnerships with universities and public research organizations; “acquisition of new drug candidate compounds” in partnerships with major drug makers; and “reduced research costs” in partnerships with large companies (in other business sectors). The reasons currently

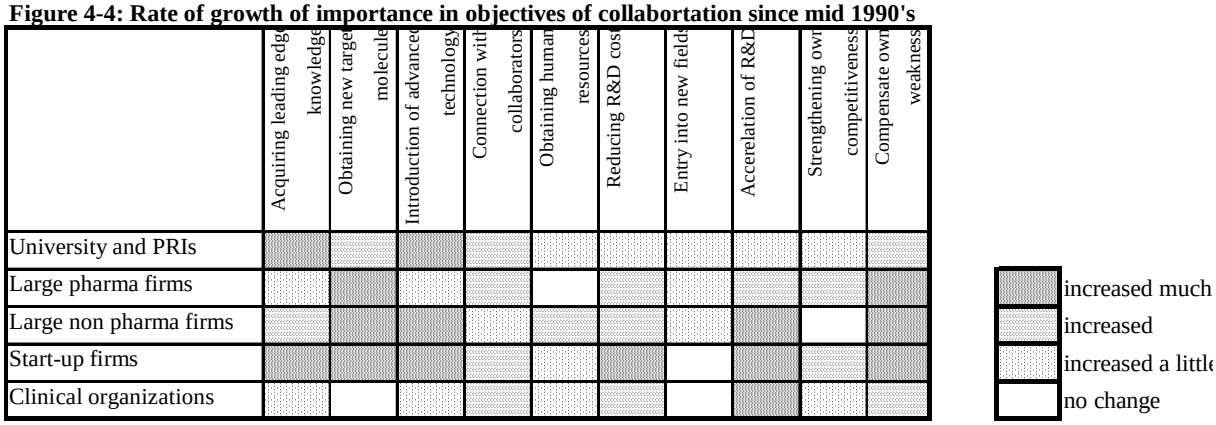
gaining importance include, in addition to the reasons given above, “faster, more efficient research” and “overcoming the company’s disadvantages.” Amid biotechnological advances, Japanese pharmaceutical companies are apparently pursuing partnerships in order to acquire state-of-the-art biotechnologies, and at the same time, improving R&D efficiency to retain their hold in an increasingly competitive market.

Figure 4-3: Objectives of collaboration



PRIs:Public Research Institutes

Figure 4-4: Rate of growth of importance in objectives of collabortation since mid 1990's



PRIs:Public Research Institutes

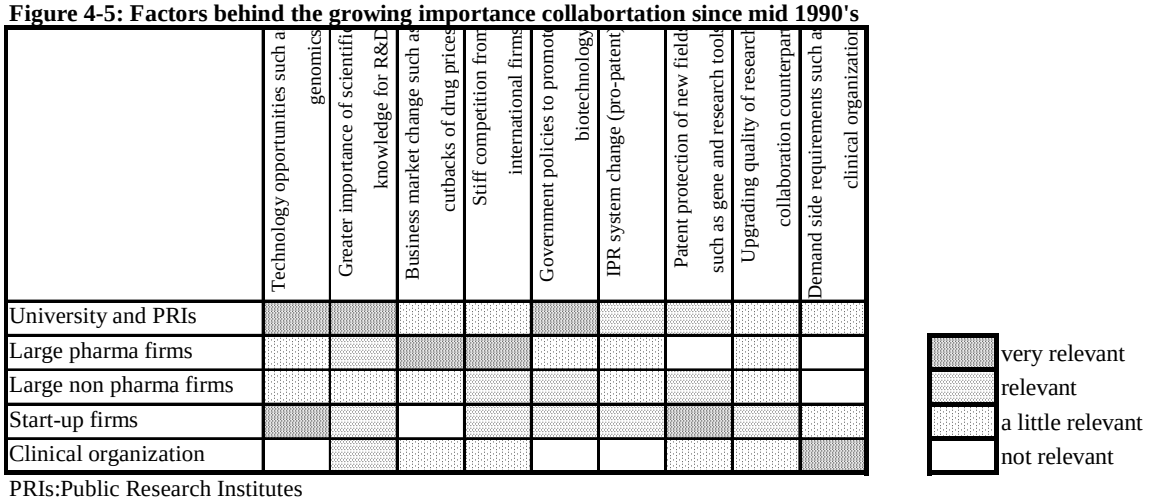
However, the results of interviews with companies revealed that most regard some recent biotechnological methods, e.g., high throughput screening, to be rather restrictive with respect to improvements in the speed and efficiency of R&D (manual procedures by trial and error are more effective). Furthermore, despite the broadening of the repertoire of methods for finding new candidate drug compounds brought about by genomic drug development, it is not generally acknowledged to have directly led to any improvements in the speed and efficiency of R&D. While companies are keenly aware of and are in fact currently tackling issues related to improved R&D efficiency, they do not believe that the new genomic methods have led to improved efficiency thus far. Many companies cite the increasing importance of reduced research costs promised by partnerships with venture companies. According to some, this

applies to partnerships involving R&D efforts that cannot be tackled internally, not R&D efforts that can be performed in-house, particularly high-risk projects for which internal resources are insufficient. This reflects the same trends that led more companies to acknowledge the increased importance of "overcoming the company's disadvantages" over "strengthening the company's advantages."

(3) Factors pushing the industry into external partnerships

Finally, according to the results of the questionnaire survey on factors underlying the increasing importance of external partnerships (Figure 4-5), the factors pushing companies to rush into external partnerships vary depending on the specific partner in question. Factors associated with technological progress, such as an "expansion of research fields, including discovery of genomic drugs" and "importance of scientific knowledge in product development" are important factors for strengthening partnerships with universities and public research organizations. Additionally, factors associated with regulatory and market environments, such as "changes in the regulatory environment such as suppression of the drug price standard (DPS)" and "intensified competition due to the penetration of foreign-affiliated companies into the domestic market," affect partnerships with other companies in the pharmaceuticals sector. Government measures for promoting biotechnology significantly influence partnerships with universities and public research organizations, while measures granting patents for gene fragments and research tools affect partnerships with venture companies.

Figure 4-5: Factors behind the growing importance collabortation since mid 1990's



PRIs:Public Research Institutes

According to the results of the interview survey above, the author wishes to add that it will take some time for universities and public research organizations to become equal partners in

industry-university collaborations, despite their enthusiasm for those collaborations, and that governmental prodding is still needed in the short term to encourage participation in industry-university joint efforts. Regarding the patent system, patents in new fields, such as gene fragment patents, have a greater effect on partnerships than the general pro-patent policy. This appears to reflect the fact that the partnerships involve license agreements based on patents owned by overseas biotech companies. Finally, the demands of end users (e.g., hospitals) have wrought changes in partnerships with clinical organizations, indicating a growing need for R&D projects, including translational research involving clinical organizations.

(4) Licensing of the patents in the medical supplies industry

The interviews mentioned above show that domestic pharmaceutical firms actively pursue alliances with foreign firms as biotechnology advances. The extent of overseas alliances as compared with in-house developments can be examined by using licensing statistics collected by the Japan Patent Office in a general survey of corporate intellectual property-related activities that the JPO has been conducting since 2002. The survey focuses on licensing activities of firms by type of counterparts, as well as by type of IPR, e.g., patent, utility model, trademark and design.

Figure 4-6 is a summary of patent licensing activities of pharmaceutical firms in 2001. The firms' income from licensing was about 100 billion yen while their expenditure on licensing was about 40 billion yen. The biggest licensing counterparts are firms and research organizations in the U.S., and their share far exceeded that of domestic counterparts. The ratios of licensing income and expenditure to in-house R&D were 13.8% and 5.3%, respectively.

Figure 4-6: Licenses in and out for pharmaceutical firms in 2001

(million yen)

	Income	Expense
To/From Japan	19,953	10,540
To/From US	73,823	19,513
To/From Europe	13,095	10,937
To/From Asia	142	0
To/From Others	576	183
Total	107,589	41,173
Ratio to R&D	13.8%	5.3%

Source: Intellectual Property Activity Survey in 2002, Japan Patent Office

4.2. Human resources

Japan lacks sufficient human resources in biotechnology. In 1998, the number of bachelor degrees awarded in biology and pharmacy was 10,914, as small as one-sixth of that in the U.S. The number of master degrees and doctorates conferred in the same fields were 2,607 and 476, respectively. Adding medical, agricultural and chemical degrees, the totals increase to 20,987, 3,154 and 3,373, respectively. These numbers have not significantly changed since the mid-1990s. In contrast, 67,112 bachelor degrees, 6,368 master degrees and 5,854 doctorates were awarded in biotech-related fields in the U.S. While differences in the academic systems of both countries make it difficult to make a solid comparison, judging from the size of their economies, it can be said that the number biotech-related degree holders in Japan is rather small.

4.3. Financing

Managed funds are gradually growing in Japan, but the fund scale for venture companies is still considerably small. There are seven times more venture capitals in the U.S. than in Japan, and American venture companies can easily raise funds from venture capitals or the money market.

In order to vitalize the biotech venture market, it is necessary to also stimulate the industries that support start-ups, such as venture capitals, financial institutions, audit corporations and other such enterprises. Currently, the number and quality of these companies is not sufficient to meet the needs of all bioventures, and Japanese government needs to quickly resolve this problem. The following is a list of major venture capitals in Japan. No figures on the funding amount to bioventures are currently available.

Figure 4-7: List of major venture capital for biotech firms in Japan

CSK Venture Capital (CSK-VC bio-incubation fund)	Established in Oct, 1999
MBL Venture Capital (Life Science Venture Fund Network)	Life Science Venture Fund Network was jointly established by MBL Venture Capital, (affiliated by Medical & Biological Laboratories) and consulting company ReqMed
Sumitomo Corp. (Summit Biotechnology Fund)	Sumitomo Corp. funded 5 billion yen of total 10 billion yen capital
Biotech Healthcare Partners	Established in January 2001, with support of Japan Development Bank.
Biotech Frontier Global Investment Fund	Venture capital investment only to biotech. Established in March 1999
Bio Vision Capital	Investment fund affiliated with Softbank Investment. In addition to funding, it also provides start-ups with a variety of supports, including R&D facility

4.4. Regulations

Guidelines for regulation of biopharmaceuticals were enacted in 1999 under the Good Manufacturing Practice (GMP) rules of the Pharmaceutical Affairs Law. In addition, the Pharmaceutical Affairs Law was drastically reformed in 2002. Under the new legislation, biophamaceuticals are treated as a separate category from chemical synthesis-oriented medicines. Special regulations for bio-medical drugs are applied at the beginning and middle stages of production, including donor selection, securing of safe materials and prevention of contamination. In addition, once a bio-drug is marketed, proper indications, information accessibility, donor tracing and regular reports on infections are required. Moreover, strict rules on handling of biopharmaceuticals in clinical testing, production and sales were established.

These regulations will help to ensure the reliability of bio pharmaceutical for better public acceptance. Keen competition brought about by revision of the Pharmaceutical Affairs Law and the Health Insurance Law gives pharmaceutical firms incentives for biotech development of innovative drugs.

4.5. Entrepreneurship

As we mentioned in 3.2.1, “Business entry and exit, including mergers and acquisitions,” the number of biotech firms is increasing in recent years. Figure 3-1 shows the number of biotech firms existing in each year. The number of newly established firms (the number of openings less the number of closings) in the past two or three years is estimated to be around 50. In

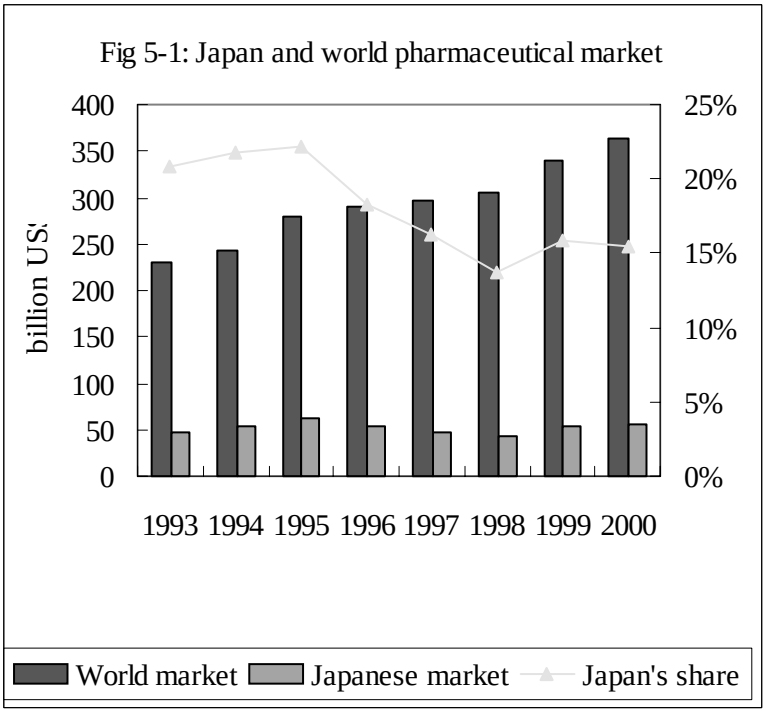
September 2002, a biotech took its stock public for the first time ever, and was followed by another biotech later that year. The number of biotech IPO is still small.

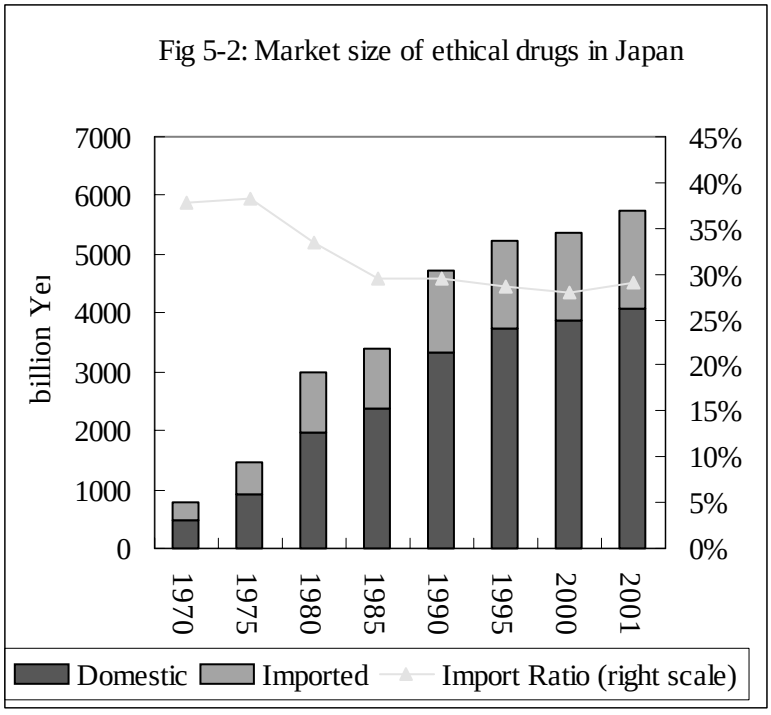
5. Markets

For an analysis of external R&D collaborations and their relationship to the Japanese innovation system, we must take into account the factor of demand. Strict regulations provide for drug safety during development. This report analyzes demand factors, changes in the corresponding regulatory environment, and their relationship to external collaborations. According to the Survey of Pharmaceutical and Medical Device Industry conducted by the Ministry of Health, Labor, and Welfare, the size of the pharmaceutical market in Japan was approximately 8.1 trillion yen in 2000, about 85% of which was accounted for by ethical pharmaceuticals, which require a physician's prescription or approval for administration. Because drug makers normally compete head-to-head in R&D for ethical pharmaceuticals, this report will focus on ethical pharmaceuticals.

First, the domestic market for ethical pharmaceuticals expanded consistently until about 1990, and since then has remained steady at about 7 trillion yen, with no significant expansion in size. In contrast, the worldwide market for ethical pharmaceuticals has continually expanded, in part due to the booming American market. This is about to reduce the share of Japanese companies in the world market. In addition, the ratio of imported products in the domestic market has grown. More recently, the share of foreign-affiliated pharmaceutical companies has also expanded, increasing competition in the domestic market. Because the worldwide market, primarily the American market, continues to grow in contrast to sluggish growth in the domestic market, Japanese major drug makers are implementing new drug R&D efforts from a global viewpoint, targeting not just the domestic market, but overseas markets.[8]

[8] However, pharmaceutical companies in the U.S. and Europe have developed drugs distributable all over the world, while a significant proportion of new drugs developed by Japanese companies are only distributed within the domestic market.





(Source: “Data Book 2003,” Japan Pharmaceutical Manufacturers Association)

Important background elements of the changes in the pharmaceutical market environment include a reform of the medical administration system and a revision of regulations governing standards for clinical trials and the approval of new drugs under the Medicine Act. The price of each ethical pharmaceutical is specified by the drug price standard (DPS) stipulated in the Health Insurance Act, and the price determination method, often referred to as the “price

determination by comparable drug," determines the price of a drug based on the price of similar drugs and by adding a certain allowance based on originality, usefulness, and marketability of the drug. All drug prices have gradually declined since the mid-1980s due to revisions of this DPS. In particular, drug prices have declined every one or two years since 1992, when a new method was established for determining the price of a drug, based on the weighted average of the drug in the market within a fairly broad range.[9] This reflects the government's goal of suppressing ethical drug expenses resulting from inadequate health care insurance accounting, in the face of a growing tide of national medical expenses. As a result, the percentage of ethical drug expenses within overall national medical expenses has steadily declined since the 1990s.[10]

In the sluggish domestic market for ethical drugs, an increase in the number of imported products and the entry of foreign companies into the Japanese market have rendered an already competitive environment even more competitive. Despite a gradual decline in its position in the world market, the Japanese market still retains a significant share, more than 15%, and remains an attractive market for foreign companies. In addition, it is important to point out that further progress in the international harmonization of clinical trials, as stipulated by the Medicine Act, would erode barriers that keep foreign companies from entering the Japanese market. Pharmaceutical companies are obliged to conduct clinical tests (clinical trials) of a drug to confirm its effectiveness and safety before obtaining approval for the drug in any country. The clinical tests are regulated by the Medicine Act in Japan. The International Conference on Harmonization (ICH)[11], which was established here in Japan in 1991, sought to promote the harmonization of technical regulations for pharmaceuticals among Japan, Europe, and the U.S. Guidelines issued by the ICH describe a gradual transition toward a system in which a company can submit an application for drug approval with clinical trial data obtained abroad if the company conducts domestic clinical tests for ethnic differences (bridging tests). Good Clinical Practice (GCP), a standard for clinical trial

[9] A method in which the price of a drug is determined on the basis of the weighted average of the market price of the drug obtained by a drug-price survey conducted every other year within a fairly broad range (R zone). The method employed previously was the so-called "bulk line method," in which a drug price is determined by multiplying a certain coefficient (e.g., 90% in the case of 90% bulk line) by the lowest transaction price for the drug (Jiho, 2003).

[10] However, Japan's national health care insurance system reimburses ambulatory pharmaceutical costs at a level almost identical to costs for other medical practices, reducing the patient burden for drugs but dramatically increasing the demand for pharmaceuticals. Accordingly, the percentage of ethical drug expenses within overall national medical expenses is already high (Endo, 2001). In contrast, ambulatory pharmaceutical costs are not reimbursed by health insurance organizations in the U.S., and ambulatory pharmaceuticals are reimbursed at low levels in France.

[11] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

procedures for drugs established in 1990, had been used as the standard for clinical trials in Japan. In 1997, a revised GCP came into force that is consistent with the ICH guidelines. The revised GCP, which specifies thorough implementation of informed consent from test subjects, detailed definitions of the protocol of clinical tests, management of the test process by documentation as well as bridging tests, offers a more objective standard for new drug approval. These amendments pulled down barriers that had impeded foreign companies from entering the Japanese market. At the same time, it is important to note that the amendments also resulted in forcing Japanese pharmaceutical companies to strengthen their capabilities domestically in a manner that helped prepare them to conduct similar clinical tests abroad for their entry into overseas markets. The intensified competition and globalization of the domestic market have led to various effects on the pharmaceutical R&D process. First, Japanese pharmaceutical companies, conducting R&D to enter the global market, are shifting the emphasis of drug development programs from the improvement of conventional products to the development of completely innovative products. A scheme for an "innovation supplement" to a drug price in the determination of the drug price standard (DPS) was introduced as an incentive for innovative drug development in 1991, and the scale of the price supplement was further increased in 2000 and 2002.[12]

Additionally, the globalization of the domestic market has led to increasing numbers of alliances between Japanese companies and foreign pharmaceutical companies, clinical organizations, and clinical research organizations (CRO). While many of these alliances with overseas pharmaceutical companies are intended primarily to strengthen the marketing potential of Japanese companies that do not have sales bases overseas and have no direct bearing on R&D, they may eventually lead to collaborations in R&D. In addition, it is often difficult for Japanese companies to conduct clinical tests and submit applications for approval of new drugs abroad, resulting in an increase in the number of cases in which they contract clinical tests to CROs.

6. Synthesis and conclusions on research questions

The Japanese innovation system is seemingly characterized by the "in-house development principle" mainly adopted for innovations in larger companies, and differs distinctly from the network-type innovation system found in the U.S., which tends to involve venture companies and universities as well. This is due to several background factors applicable to Japanese

[12] The rate of this supplement was originally 10%, but was later raised to 40% in 2000 and to 100% in 2002.

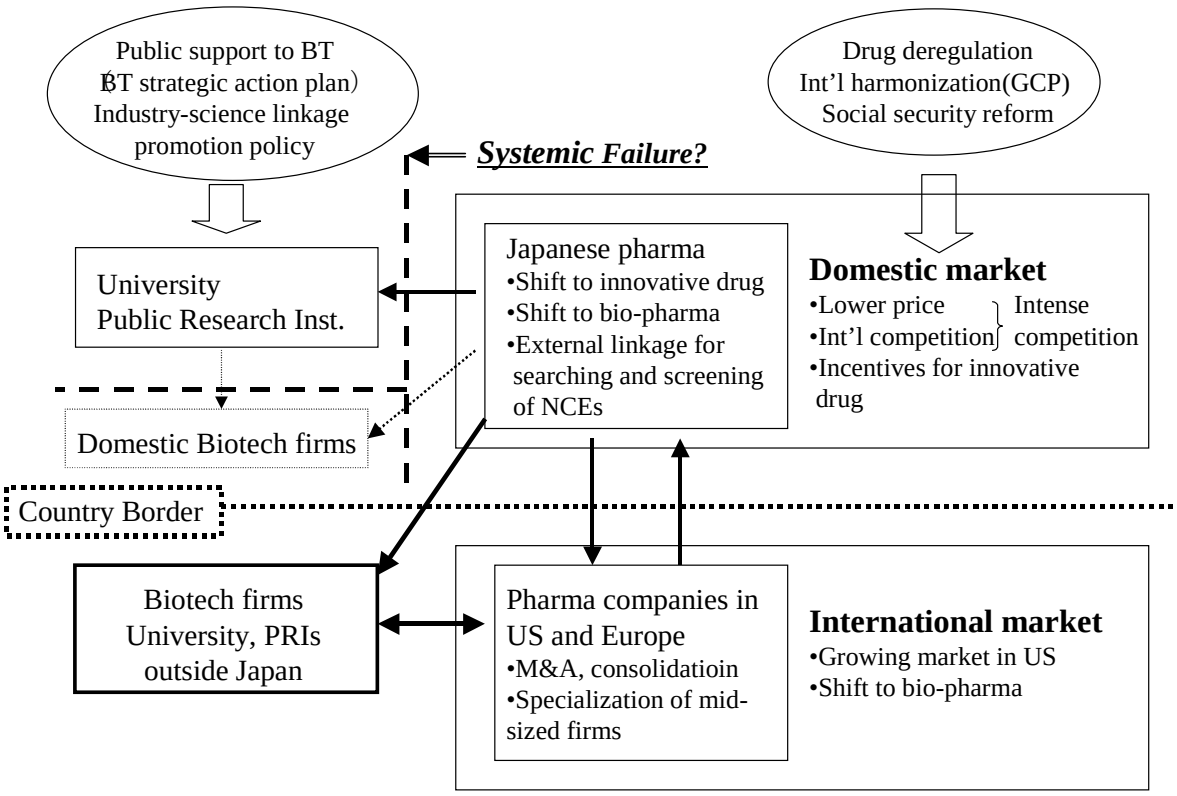
companies, including various interconnected factors such as the low mobility of researchers in companies and universities, the short supply of venture capital for start-up companies, the tendency of universities to focus on basic research and to be unenthusiastic about industry-university cooperation, and a corporate climate in which in-house development is highly valued and strategies of alliance disregarded. In the case of the pharmaceutical industry, it is also important to note that drug prices under the current national health care insurance scheme are determined not by competition but by the drug price standard (DPS), impeding fair market competition, and to note that the historical absence of incentives for clinical organizations--users of ethical pharmaceuticals--to make daring applications of innovative drugs, weakening the drug makers' motivation to seek innovative drugs in the first place.

Amid changes in R&D processes for new drugs and progress in biotechnology, various innovations in the development of new pharmaceuticals took place, mainly in biotech companies in the U.S., while Japan was left behind, presumably because its innovation system had mainly been dominated by large companies, hindering innovation. This is due to the generally low level of basic research in fields such as molecular biology in Japanese universities (Cockburn and Henderson, 2001). However, even though trailing slightly, Japanese drug makers are progressively entering into external R&D partnerships and producing results in the biopharmaceutical field. It is also interesting to note that new entrants from other business sectors, such as Japan Tobacco Inc. and Kirin Brewery Co, Ltd., are taking active roles. Such new entries of companies from other sectors into the pharmaceutical industry may be an effective model for maintaining a company's superior competitiveness, generating non-continuous innovation while maintaining healthy competition in Japan, where a start-up innovation model is not feasible. However, it is also natural to consider that a dynamic and flexible system, in which university-industry partnerships and venture companies are generated one after another, would be more effective in a field characterized by non-continuous innovations. Additionally, it is important to link universities closely to public research organizations in fields such as biopharmaceuticals, in which scientific knowledge has a more important role. From this viewpoint, we must continue to seek to make the Japanese innovation system more open and more flexible. At the same time, we must seek changes in a number of factors, including finance, human resources, the environment of competition among companies, and incentives for researchers in universities as described above. Only establishment of venture capital does not necessarily lead to a massive flow of researchers to biotech companies. Nor does a reform of the incentive system in universities always lead to

increased cooperation between universities and industry, due to problems on the company side. All factors are complementary; the overall system must be revised.

What specific systemic problems do we face, from the viewpoint of the innovation system of a pharmaceutical industry greatly influenced by progress in biotechnology? Figure 6-1 summarizes factors capable of influencing the biopharmaceutical innovation system. As described above, the pharmaceutical R&D process has been changing dramatically as biotechnology progresses. Japanese drug makers, recognizing an expansion of the research fields that they cannot handle with their own human resources and technologies, have strengthened partnerships with external organizations. The survey of drug makers indicates that companies are strengthening partnerships, especially with domestic universities and public research organizations and with overseas venture companies. However, detailed examination of the partnerships reveals that the purpose of most alliances with domestic universities and public research organizations is non-specific – for example, for obtaining general knowledge – while licenses and joint research focused on the development of specific new pharmaceuticals mainly involve partnerships with overseas venture companies (most of which are university spin-offs). In other words, as is apparent in Figure 6-1, companies acquire technical seeds from overseas biotech companies, and then develop them into products that are to be brought into increasingly competitive domestic and overseas markets.

Figure 6-1: Dynamics of pharmaceutical innovation system in Japan



Japanese drug makers, making the most of the global innovation system, are attempting to keep pace with changes in pharmaceutical R&D processes associated with progress in biotechnology. However, this move is believed to lag significantly behind those of pharmaceutical companies in the U.S., the U.K., and Switzerland (Cockburn et al., 1999).[13] Perhaps geographic distance affects technology spillover (Jaffe et al., 1993). External R&D collaboration demands information on the partner and an evaluation of the content and the level of development of its technologies. Companies must be able to assess potential partners and to obtain the comprehensive information needed to make such a judgment. Geographic distance is, of course, a critical factor in such determinations. Furthermore, spillover of technology from one country to another faces obstacles due to linguistic barriers. Although Japanese drug makers have already established many research bases abroad, the scale of these operations is far below that of giant pharmaceutical companies abroad.

In considering the Japanese innovation system in light of these problems, it is critically important to analyze the reasons that collaborations between pharmaceutical industry and Japanese universities or public research organizations are inadequate, as shown in Chart 3-4 (in other words, why Japanese drug makers regard biotech companies spun-off from universities in the U.S. and Europe as more important partners), and to determine why these companies spun off from universities are less common in Japan than in the U.S. In the biotechnology strategy guidelines and the Science and Technology Basic Plan, the government expressed its intention to preferentially allocate public research funds to the life sciences. In order for these governmental measures to produce innovations in the Japanese pharmaceutical industry, efficient university-industry partnerships are essential. To this end, many problems remain to be overcome, including problems of human resources, financing, and incentives both for universities and for the company. Of these problems, the most important is the issue of the mobility of human resources.

Zucker and Darby (1997) describe American pharmaceutical companies as employing a vast number of specialists in the life sciences to cope with changes in R&D processes associated with progress in biotechnology. Furthermore, according to Zucker et al. (1998), bio-company-university clusters in the U.S. are usually formed by a star scientist at a university, who conveys, through research cooperation in the university-industry partnership, knowledge and technology to companies in the area. In this way, scientific knowledge capable of improving

[13] This report indicates that Germany, France, Italy, and Japan were left behind in the development of biopharmaceuticals.

the efficiency of pharmaceutical innovations moves with a scientist. The labor market of scientists in Japan is rigid, thus possibly impeding the flow of scientists and knowledge. Many bio-venture companies spun off from universities (e.g., Genentech Inc. established by Boyer, one of the inventors of DNA recombination technology) have contributed to the industrialization of basic research in the U.S. In Japan, university professors are less likely to sacrifice their almost perpetual posts to face new challenges. Although the problems of incentives for universities and delays in the establishment of organizations for university-industry partnerships in universities are likely to be gradually resolved by the incorporation of national universities and various public measures for promoting university-industry partnerships, the structural problem of mobility of researcher resources may not be solved merely by changing individual incentives. It is important to build a mechanism that encourages star scientists at universities to contribute more to innovations at private companies – for example, a job assignment system for sending university members to corporate research laboratories. Measures for improving the mobility of researchers in university and public research organizations, such as the “Program for Supporting 10,000 Postdoctorals and Others” are also important. Additionally, venture companies spun off from universities, in which scientific knowledge leads directly to innovations, are expected to grow more common over time.

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Annex 1

Concerning the Biotechnology Strategy Council

July 5, 2002

Prime Minister's Decision

1. Purpose

   It is increasingly important to apply the remarkable achievements of biotechnology (BT) to practical use and industrialization, thus leading to the improvement of people's lives and the enhancement of industrial competitiveness. To this end, the Biotechnology Strategy Council (hereinafter referred to as “the Council”) shall be convened in order to quickly establish and advance a BT strategy for Japan.

2. Composition

   (1) The Council consists of the Prime Minister, the Chief Cabinet Secretary, the Minister of State for Science and Technology Policy, the Minister of Education, Culture, Sports, Science and Technology, the Minister of Health, Labor and Welfare, the Minister of Agriculture, Forestry and Fisheries, the Minister of Economy, Trade and Industry and the Minister of the Environment as well as the experts noted in the attachment, and the Prime Minister shall convene its meetings.

   (2) The Prime Minister shall request a chairperson from among the experts.

   (3) The Council, when necessary, may request the attendance of concerned parties.

3. Other

   The administrative affairs of the Council will be handled by the Cabinet Secretariat with the cooperation of the Cabinet Office and relevant administrative organizations.

Members of the Biotechnology Strategy Council

Kenichi Arai	Dean, Institute of Medical Science, the University of Tokyo
Hiroyuki Itami	Professor, Graduate School of Commerce and Management, Hitotsubashi University
Hiroo Imura	Member, Council for Science and Technology
Katsuhiro Utada	Chairman, Japan Association of Bioindustries Executives (JABEX) Senior Advisor to the Board, Ajinomoto Co., Inc.
Michio Oishi	Director, Kazusa DNA Research Institute
Tadamitsu Kishimoto	President, Osaka University
Etsuhiko Shoyama	Co-Chairman, Committee on Industrial Technology, Japan Business Federation President and Representative Director, Hitachi Ltd.
Tatsuo Sugiyama	Director, RIKEN Plant Science Center
Masaaki Terada	President Emeritus, National Cancer Center
Tadashi Hirata	President and Chief Executive Officer, Kyowa Hakko Kogyo Co., Ltd.
Akira Fujiyama	President, Federation of Pharmaceutical Manufacturers' Association of Japan (FPMAJ) Chairman, Fujisawa Pharmaceutical Co., Ltd.
Tomoko Mihoya	Chief Editor of Nutrition and Cookery, Kagawa Nutrition University Publishing Division