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Paradox of Japanese Biotechnology: Can the Regional Cluster Development Approach be a Solution? *

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December 1, 2008

Abstract

Japan lags behind the U.S. and Europe in the commercialization of biotechnology research despite Japan's exemplary reputation in life science research. This paper investigates what is missing and what could be a good solution to the problem. The author argues that although the creation of the new network- type innovation model or the clustering of biotech companies could be increasingly necessary at least in the bio-pharmaceutical sector, the geographical proximity may not be always important. Besides, Japan may demonstrate alternative development model different from that of either the U.S. or Europe.

JEL Classification Numbers: O3; O5
Keywords: Biotechnology, Network, Clusters, Innovation, Japan

* This research is partly supported from a Grant-in-Aid for Scientific Research of the Japan Society for the Promotion of Science (JSPS).
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I. Introduction

For the last couple of decades biotechnology has attracted an enormous interest not only from natural scientists but also from social scientists and policy makers for a couple of reasons. First of all, although biotechnology appears a rather narrow field, its applications are so wide in health, agro-food, energy and environmental sectors that it is becoming a core competence across a substantial portion of our modern economic activities (Cooke 2004: 915). Second, biotech industry differs from conventional one since not the engineering but scientific knowledge constitutes an important base of the industry (Henderson et al. 1999: 268). [i] Thus, the detailed mechanisms of not only the industrial transformation but also the interaction between scientific knowledge and organizational capabilities, industry structure and institutional context began to be studied very carefully.[ii]

Japanese biotechnology seems to demonstrate a very interesting case. Although Japan has a relatively good, world-wide reputation in life science research, the presence of its biotech industry is said to be rather small. OECD (2006) concludes that Japan is performing poorly both in ''science'' and in ''innovation" and "industrial development" in the most recent study related to biotechnology. OECD's interpretation of the result does not, however, seem to be accurate. As Zucker and Darby (2001) and Lynskey (2001) argue, Japan's problem is not so much the lack of input (scientific knowledge creation) but its low rate of commercialization particularly in biopharmaceuticals. [iii]

Since the end of the 1990s the Japanese Government has introduced various reforms and policies including the corporatization of national universities and the formation of regional clusters so as to enhance the development of science-based industries such as the biotech one. This policy is modeled after the open and network innovation system that appeared to be so successful first in the United States. That involves a large number of spin-off venture companies located near a core university. The question is whether the regional cluster development approach will be a solution to Japan's paradox or not. This purpose of this paper is, therefore, to understand the causes of the paradox of Japanese biotechnology, and to examine how effective the promotion of university-based regional clusters will be to solve the paradox.

The outline of the paper is as follows. Section II empirically examines the performance of

Japanese biotech industries both in terms of research output and its industrial application. Section III discusses the major causes of the lag of Japan behind the US and Europe in the commercialization of the fruits of bioscience and biotechnology particularly in the field of biopharmaceuticals. A hypothesis different from that of OECD (2006) is provided. Section IV summarizes both advantages and disadvantages of the Japanese mode of innovation. A fundamental weakness that remains in the emerging Japanese new innovation system is pointed out especially in the biopharmaceutical sector. In the section V, the applicability of regional cluster development approach is discussed. Although the 'Cluster Plan' has been the most comprehensive industrial plan since the 1960s, it remains to fulfill people's expectation. Section VI concludes the paper and provides policy implication.

2. Paradox of Japanese Biotechnology

2.1 Active scientific research production

Currently, US, Japan, Germany, UK and France are the top five countries in the world with respect to the production of scientific knowledge. Japan has an exemplary reputation in life science research as well. Shares of science world article by field and by country in 1996 and 2003 are shown in Table 1. Clinical medicine, biomedical research and biology are chosen as life science and life science-related fields.

<Table 1>

Despite the declining relative contribution of the above top five countries as a whole to the world total production of scientific knowledge from 62.2 to 56.3 percent between 1996 and 2003, only Japan managed to increase its share. It increased from 8.5 to 8.6 percent during this period. This is particularly true to the field of biomedical research, a core of life science. Japan's share increased from 8.0 to 8.3 percent in biomedical research in spite of the decline of the share in all other major countries. Although the gap between Japan and the US is still large and the dominance of the latter is still significant in biomedical research, Japan seems to be performing at least better than other major European countries such as Germany, UK and France. Zucker and Darby (2001: 38) also note that Japanese bioscientists are second only to the U.S. in their genetic sequence discoveries, the crucial driving force behind the latest major wave of technology transfer from basic science.

The same is true to the development of biotechnology. Figure 1 shows the number of patents granted by the US Patent Office in the 1990s in the filed of biotechnology. It also demonstrates that the performance of Japan is at least better than that of major European countries in the technological development activities of the biotech sector.

<Figure 1>

2.2 Low presence of the Japanese biotech industry in the world

Notwithstanding the variety of possible industrial applications, the pharmaceutical industry has attracted the greatest amount of attention among many industries because the drug industry is the most affected by the biotechnology (Chiesa and Chiaroni 2005:19). In early 1990s biotech drugs, or the drugs developed through the application of biotechnology, occupied only 12.6 percent of the total number of new drugs approved in the world. Within a decade the share almost doubled (Takatori 2007: 12). Obviously, the future success of the pharmaceutical companies increasingly depends on their ability to develop and/or sell biotech drugs in the world.

Despite an exemplary reputation of Japan in life science research described above, its presence seems to be low in the biopharmaceuticals sector Figure 2 shows the total number of biotech drugs in pipeline by country in 2006. According to the figure, the U.S. dominates the biopharmaceutical industry. The number of drugs under development by US companies is substantially large relative to other major industrialized countries (269). Figure 2 also demonstrates that Japan is substantially low in terms of the number of biotech drugs in pipeline not only relative to the U.S. but also relative to other major European countries such as the U.K., France, and Germany.

<Figure 2>

3. OECD Hypothesis and Alternative Explanation

3.1 OECD hypothesis and its underlying assumptions

Regardless of the existence of its relatively large domestic market and scientific and technical expertise, Japan lagged considerably behind not only the U.S. and but also other major European countries in the commercialization of biopharmaceutical biotechnology for the past two decades. OECD argues this results primarily because Japan's innovation system had been dominated by large companies in which in-house development is still highly valued and alliance strategies are disregarded (OECD 2006: 75).

In the U.S. and more recently in Europe, indeed, the national innovation system shifted away from in-house development principle that had prevailed mainly in large companies to the network-type innovation system where a large number of similar and inter-related venture firms are concentrated geographically surrounding universities/ research institutes, and cooperate as well as compete each other in research and industrial activities. The biotech cluster in California (Bay Area and San Diego) is one of the most prominent ones in the U.S. Cambridge biotech cluster grew to be the biggest and the strongest one in Europe. A large number of biotech clusters started to emerge both in other parts of the US and Europe thereafter. [iv]

Although not explicitly stated, the above OECD hypothesis seems to be based on three lines of study, such as Malerba and Orsenigo (1997) , Audretsch (1997) , Jaffe (1986, 1989) as its intellectual basis. First of all, Malerba and Orsenigo (1997: 93-94) empirically found that the patterns of innovation tend to differ significantly across sectors, but converge across countries for a specific technology. In other words, examining the patterns of innovative activities across sectors and countries, they hypothesize that technological regimes implied by the nature of technology and knowledge influence the rate and the structure of innovative activities. If their observation is correct, Japan may need to introduce more quickly the network- type innovation system that became so dominant in the US to enhance the development of the biotech industry.

In the meanwhile, Audretsch (1997) emphasizes the importance of newly established firms in an economy especially when an economy is going through radical technological changes. When new information such as biotechnology created outside the incumbent firms cannot be easily transferred to those incumbent enterprises, the holder of such knowledge must enter the industry by starting a new firm in order to exploit the expected value of his knowledge (Audretsch 1997: 58-59). Combining with the bureaucratic organization of incumbent firms involved in making a decision, the asymmetry of new knowledge and information often makes it hard for incumbent firms to acquire it and to enter a new business (Audretsch 1997: 56).

A stream of recent research on innovation in the U.S. has also emphasized geographically localized knowledge spillovers occurring around major universities (Jaffe 1986, 1989). This effect is also often cited as one of the major merits of forming a regional cluster surrounding universities especially when a radical technological change is progressing.

3.2 Alternative explanation

The above OECD hypothesis does not, however, seem to address the fundamental issue lying at the heart of the Japanese science-based industries. In fact, both government and business have been making substantial efforts to transform the country's innovation system into the one more suitable for science-based industries during the first decade of the 21st century in Japan. The Japanese Government increased budget for research related to high-tech industries, and the adoption of the legal and policy framework to the need for university-industry collaboration, effective use of intellectual property rights, and the formation of start-up companies (Odagiri 2006b: 143). Following the establishment of the Second Science and Technology Basic Plan by a Cabinet Decision in March 2001, the Japanese Government [v] has also endeavored to form regional clusters surrounding major universities and public R&D institutes since 2002.

Industries have also been adapting in order to survive in the changing environment. Contrary to the assessment of OECD (2006), the Japanese innovation system became much more open than ever before during the past two decades. For instance, the R&D outsourcing ratio in the entire business sector almost doubled from 7 to 14 percent between 1990 and 2006. [vi] The R&D outsourcing ratio of the pharmaceutical industry alone is even higher: the ratio had reached almost 20 percent by 2006. Obviously, a much more outward-oriented innovation system emerged in Japan as well during the past decade.

What seems to be a real issue in Japan is, instead, the coexistence of the new innovation system with traditional business and industrial practices.[vii] Chesbrough (2003) argues that the increasing mobility of high-skilled workers and the increasing availability of venture capital funds were two of the vital factors for the erosion of the closed innovation paradigm in the U.S. high-tech industries. As highly trained workers became more and more mobile and available in the labor market, the knowledge they possessed from the fortified towers of internal R&D organizations and universities started to diffuse widely to suppliers, customers, partners, start-ups, etc. in the U.S. In addition, although demonstrating a causal relationship between the presence of venture capital investment and innovation is a challenging empirical problem (Gompers and Lerner 2001: 164), venture capitalists indeed backed many of the most successful high-tech firms during the 1980s and 1990s in the U.S., including Apple Computer, Cisco Systems, Genentech, etc.

In contrast, the low mobility of high-skilled workers and a paucity of financial resources to back highly risky investment projects still characterizes the Japanese economic institution. The lifetime employment is robust to changes despite the emergent diversity of corporate governance and organization architecture in Japan. Employment stability still remains very high in Japan compared not only with the US and the UK but also with Germany (Aoki and Jackson 2008: 17).

The low availability of risk money for start-up, high-tech companies is another characteristics of the Japanese financial system. Both venture capital investment as a percentage of GDP and the share of high-technology sectors in total venture capital are extremely low in Japan compared with the majority of OECD countries (OECD 2007: 39). Gompers and Lerner (2001:163) argue that the existence of a robust market for initial public offerings is a key to stimulate the venture capital activity. If their argument is correct, the external private funds for high-tech industries may not become available so easily in an economy like Japan, which is still dominated by bank financing.

Even though the exact nature of the new innovation and business system is sill unclear, it seems that the Japanese new innovation model will not go all the way to an American or an European model. How to promote innovation activities with some of the traditional business and industrial practices is an interesting, but challenging task for Japan.

4. Comparative Advantages and Disadvantages of the Japanese New Innovation Model

4.1 Industrial evolution of the Japanese biotech sector

Malerba and Orsenigo (1997) empirically found that the pattern of innovation tends to be similar across countries for a given technology. The case of the Japanese biotech industry, however, seems to suggest that the modes of innovation and organizational architecture cannot be considered as purely technologically determined prior to corporate governance (Aoki and Jackson 2008: 10) .

Several previous studies [viii]observes the characteristics of the Japanese biotech industry. Almost all of them tend to focus on the later part of the biotech industrial development of Japan, such as the industry-university collaboration, the creation of new biotech start-up companies, etc. The history of the Japanese modern biotech industry, however, goes back to as early as the late 1970s or the early part of the 1980s. In fact, the initial stimulus of the biotech industrial development came neither from academic institutes nor from biotech start-up companies. It came from non-pharmaceutical companies, such as Suntory, Ajinomoto, Takara Shuzo, Kyowa Hakko, Kirin, Teijin, AsahiKASEI.[ix] They are all large and established companies, but the main lines of their businesses are food, beverage, or chemical products rather than the pharmaceuticals, though.

Table 2 illustrates the characteristics of the early days of the Japanese biotech industry. It shows the shares of biopharmaceuticals patents applied in Japan between 1977 and 1999 by nationality and by type of institution. While both nonprofit organizations such as universities and public institutions and biotech start-up companies began to emerge as an important player of biopharmaceutical biotechnology development in the U.S., large-scale established companies dominated the invention activities in the biopharmaceutical sector in Japan at least up until the end of the 1990s. This does not mean, however, there were no new entries into the pharmaceutical industry in Japan. On the contrary, the entrants from other business sectors such as food, beverage, and chemicals rather than start- up companies spun off from universities or pharmaceutical companies were taking active roles in the technological development of the biopharmaceuticals field. Europe seems to stand between Japan and the U.S.

<Table 2>

Table 3 provides basic facts of some of the new entrants from other business sectors into the pharmaceutical/biomedical industry and their subsequent evolution including their economic performance in the year of 2007. In fact, there were a lot more new entries. [x] The table only lists firms that had succeeded in launching biotech drugs or have them in pipeline now.

<Table 3>

Firms on the table 3 have many commonalities. First of all, they entered the pharmaceutical industry either in the 1970s or in the early 1980s. Obviously, many of Japanese firms were stimulated by the rapid development of biotechnology.

Second, all of the companies show an inter-industry innovation model that seems to be found often in the new environment and energy markets of Europe. In-house evolution of innovation capabilities from food, beverage and chemicals corporates entering and selling products and services in new biotech markets was a characteristic of the development of the early days of the Japan's biotech sector. [xi] By 2007, all of the divisions got independent from their parent organizations at least operationally except Kyowa Hakko and became a company. [xii] They are still under tight control of parent firms in terms of ownership, though. [xiii]

Third, all of the in-house corporate ventures grew up to become companies that are highly R&D- intensive and profitable although their scale of operation is not substantially large compared with incumbent pharmaceutical companies. This implies that instead of pursuing scale expansion, the new entrants from other business sectors tend to make focused investments into business areas where they can make the most of their strengths. That includes their innovation activities in the biopharmaceutical sector.[xiv]

4.2 Coexistence of two modes of innovation

What distinguishes Japan from other countries is that two different modes of innovation not only exist but also tend to persist instead of converging into one even in the biopharmaceutical sector. Figure 3 shows the number of biotech drugs in pipeline by type of company. The drugs are classified depending on which company originally develops those biotech drugs.[xv] The figure illustrates three important points.

<Figure 3>

First, the new entrants from other business sectors instead of biotech start-up companies have been playing a significant role in originating biotech drugs in Japan since the beginning of the development of the biopharmaceutical industry. This is very consistent with the data of patent acquisition shown in Table 2. Both food and beverage and chemical companies have been engaged substantially in research and development of biotech drugs in Japan since as early as the late 1970s.

Second, dedicated biotech companies (DBCs) began to play a significant role in the R&D activities of biotech drugs in parallel with the new entrants from other business sectors during the first decade of the 21st century. In 2002, AnGes MG became the first university start-up company to have made an initial public offering (IPO) in Japan. Subsequently, around 17 DBCs made an IPO until the mid-2007. [xvi] Only three out of 17 companies are engaged in the drug discovery and development and have biotech drugs in pipeline, though.

Third, the role of pharmaceutical companies as an original developer of drugs has lessened since the mid-1990s. This is also confirmed in Table 4, which shows the number of both biotech and non-biotech drugs in pipeline as of the end of 2007 by four largest Japanese pharmaceutical companies (Takeda, Astellas, Daiichi-Sankyo, and Eisai). The number of drugs is shown depending on whether they are originally developed by a pharmaceutical company or are in licensed from other companies.

<Table 4>

Kneller (2003) once wondered whether Japanese pharmaceutical companies can be globally competitive even if their drug discovery systems remain autarkic. It seems the question is no longer relevant. The alliance strategy has nowadays become a norm of Japanese big pharmaceutical companies. This is especially true to the development of biotech drugs. Almost all of the four largest Japanese pharmaceutical companies do not possess any biotech drug originally developed by themselves (see Table 4).

The above analysis indicates that the Japanese innovation system is becoming more open and closer to that of the US or Europe than before. What distinguishes Japan from other countries is the new entrants from other business sectors continue to play an important role in the development of the biotech industry. For instance, in 2005 both Sumitomo Chemical and Mitsubishi Chemical Holdings Companies came to put Dainippon Sumitomo Pharma Co., Ltd. and Mitsubushi Tanabe Pharma Corporation respectively under their control. Both big-scale chemical companies do so because they now consider the pharmaceutical sector as a core of their business.

Moreover, in February 2008, FUJIFILM announced to enter into a business and capital alliance with Toyama Chemical Co., Ltd. and Taisho Pharmaceutical Co., Ltd. Now, FUJIFILM intends to cover all fields of "prevention", "diagnosis" and "treatment" as a comprehensive healthcare company. As part of its intention, FUJIFILM made such a business alliance with pharmaceutical companies. [xvii] The expansion of synergies in research and development is stated as one of the most important merits resulting from business alliance across the sectors.

4.3 Comparative advantages and disadvantages of the Japanese new innovation system

4.3.1 Comparative advantage

The entry into a new business from other sectors through the establishment of a kind of corporate venture is, in a sense, very suitable for such a country as Japan mainly because Japan still maintains many of the traditional business and industrial practices. For example, as discussed in Section III, despite the exhibition of substantial change in the Japanese business system, the norm of lifetime employment has remained remarkably robust in many Japanese firms. Long-term worker-employer relationship was considered conducive to accumulation of firm-specific human skills and close intra-firm and intra-group information sharing, which made cumulative technological innovation easier (Odagiri 2006a, Odagiri 2006b).

The traditional Japanese system is considered to have some merits even in science-based industries such as the biotech one for several reasons. First, the application of the accumulated skills and know-how on fermentation to the mass production process of biotech drugs gave several Japanese companies such as Kyowa Hakko, Kirin Pharna, a competitive advantage over their rivals. Both Kyowa Hakko and Kirin Pharma are very active in developing therapeutics monoclonal antibodies (see table 3) primarily because those biotech drugs in particular require high accumulated skills and know how for their mass production.

Second, intra-firm and intra-group information sharing related to biotechnology may have expanded the synergies in research and development of the new entrants from other business sectors. The wide applicability of biotechnology to different industries and sectors is well noted. The diversification of the business activities of incumbent companies such as food, beverage, and chemicals into the pharmaceutical sector (especially the biopharmaceutical one) through the establishment of a kind of in-house corporate venture may have been only natural under the persistent business practice such as lifetime employment and the immaturity of equity finance. Bartholomew (1997: 253) argues that the strengths of the US innovation system in the present may weaken in the future partly because the US system has been highly geared towards innovation in biopharmaceuticals only. Her statement implies that there may be some merits in the Japanese mode of innovation.

4.3.2 Comparative disadvantages

The Japanese new innovation system also contains a weakness. That is, Japanese companies tend to fall behind the US and European counterparts especially in the highest-tech, highest-value area of human therapeutics and vaccines despite the emergence of a large number of DBCs during the first decade of the 21st century.

Figure 4 shows the number of Japanese DBCs between 1994 and 2006. It illustrates that a large number of DBCs have been born in Japan especially since the beginning of the 21st century. This resulted partly because both business and government have been making various efforts to transform the country's innovation system into one more suitable for science-based industries including biotech one. One of the most important efforts was the Law of Promoting Technology Transfer from University to Industry adopted by the Japanese Diet in April 1998. Through this law, the Japanese government started to support academia-industry collaborative R&D and the establishment of Technology Licensing Offices at universities in Japan. Since then, the number of academic biotech start-up companies increased sharply. [xviii]

<Figure 4>

The major difference between Japan and the U.S. or Europe is, though, the low share of DBCs engaging in most high-tech, high-value activities such as the drug discovery and development process in Japan. According to the same survey, only around 32 percent of the Japanese DBCs are engaged in such activity. The rest of the DBCs range widely including the suppliers of enabling technologies for core biotech drug companies to environmental and agricultural biotech companies (See figure 5). In other words, Japanese biotech companies tend to operate in the business model characterized by the low risk/reword profile. This presents a sharp contrast to the U.S. where around 84 percent of biotech start-up companies listed on the NASDAQ stock market are indeed engaged in the drug discovery and development including diagnostic agents (Ohtaki 2003: 22).

<Figure 5>

This is also confirmed by the number of drugs that Japanese DBCs possess in pipeline. Currently, in Japan only around 30 DBCs have drugs in pipeline and the total number of drugs in pipeline is as low as 56 (Kohno 2007: 3). Besides, only 31 percent of the drugs in pipeline are biopharmaceuticals. The rest are still conventional low-molecular compounds.

4.4 What constrains the development of the DBS in biopharmaceuticals in Japan?

Research and development on biopharmaceuticals has advanced rapidly ever since recombinant DNA technology was successfully developed in the 1970s.[xix] A succession of technologies has been rolled out in past decades, including gene cloning and recombinant protein production. Those advances opened up the possibility of steadily supplying a variety of therapeutic proteins using biotechnology in the 1980s (the 1st generation biopharmaceuticals). As Table 5 shows, almost half of the total global biotech drugs in pipeline were occupied by those of the first generation in 1996. Their share subsequently declined, however, between 1996 and 2006.

<Table 5>

With technology continuing to evolve, antibodies and others that generate therapeutic effects by binding to specific molecules began to be aggressively researched and developed (the 2nd generation biopharmaceuticals) in the 1990s. The share of the biotech drugs of the 2nd generation is still the biggest (28 percent) in 2006 although it also declined from 32 percent in 1996 (Table 5).

Entering the 21st century some of the biotech companies even advanced to research and develop new medicines and therapies such as gene therapy, nucleic acid medicine, vaccine, cellular therapy, etc (the 3rd generation biopharmaceuticals). In spite of the small number of Japanese DBCs in biopharmaceuticals, more than half of the biotech drugs they originally developed are already those of the type of the 3rd generation in 2007 (Table 5). This indicates some of the Japanese DBCs already reached the highest level of science and technology in biopharmaceuticals.

Then, what really constrains the development of Japanese DBCs in biopharmaceuticals despite their advancement in science and technology? Table 6 compares five Japanese DBCs with the average of the ten largest US biotech start-up companies in terms of financial and development performances. [xx] Four Japanese companies are selected based on whether they have biotech drugs in pipeline and whether they went on an IPO. The striking difference between Japan and the U.S. is the amount of the R&D expenses spent on the drug discovery and development. The most successful DBC in Japan is AnGes MG as mentioned before. R&D expenses of even this most successful one run up to only 38 percent of those of the U.S. counterparts despite its comparable performance in terms of the number of biotech drugs in pipeline.

The amount of the R&D expenditures is extremely low in the case of other three Japanese companies (OncoTherapy Science, J-TEC, and IBL) in spite of their accumulated knowledge of science and technology as shown in the relatively large number of biotech-related patents acquired and their success in recruiting professional business managers on board. [xxi] According to a report of Value Management (2007), the biggest obstacle to starting up a biotech company is the difficulty in recruiting people with a wide variety of business experience. This is partly due to the low mobility of labor market in Japan. The cases of companies listed on Table 6 seem to suggest that the development of DBCs in biopharmaceuticals is not so much affected by the low mobility of labor, but by a severe financial constraint they face in their mid- stage of research and development.

<Table 6>

The case of such company as IBL in table 6 seems to show an interesting example. IBL was established in as early as 1982, but it was only last year (2007) that IBL succeeded in its IPO. A part of their success in IPO seems to lie in their success in entering into an alliance with Astellas pharmaceutical company one year earlier (in 2006). The alliance with a big pharmaceutical company seems to have sent an important signaling to the financial community that IBL is worth investing. As Mishkin (2000) emphasizes, asymmetric information is very severe in financial markets because one party does not know enough about the other party. This is especially so in the case of biopharmaceuticals because their R&D activities are increasingly becoming more expensive, more lengthy and riskier. [xxii] The licensing activities of Japanese pharmaceutical companies have come to play an important role as a signaling device to the investors.

An increasing number of Japanese DBCs started to possess their biotech drugs in pipeline entering the 21st century (Table 7). Moreover, the majority of the drugs in pipeline now belong to the 2nd and the 3rd generation types of medicine. How to tackle the problem of severe asymmetric information in the financial sector remains to be an important policy issue in Japan.

<Table 7>

5. The Applicability of the Regional Cluster Development Approach

5.1 The "Cluster Plan"

In parallel with substantial efforts to change the Japanese innovation system more suitable for the science-based industries, the Japanese Government, especially the Ministry of Economy, Trade and Industry (METI) and the Ministry of Education, Culture, Sports, Science and Technology (MEXT) has endeavored to form regional clusters surrounding major universities and public R&D institutes since 2002, following the establishment of the Second Science and Technology Basic Plan by a Cabinet Decision in March 2001. The "Cluster Plan" has become the most ambitious and comprehensive governmental plan since its 1960s bet on heavy industry (Ibata-Arens 2005: 92).

More specifically, METI and MEXT launched the Industrial Cluster Project and the Knowledge Cluster Initiative respectively. Their intention was to introduce a new, network-type innovation system into Japan so that its productivity will improve, innovation will be spurred, and new business creation will be fostered in Japan (Inoue 2003). In fact, as many as eighteen clusters were expected to be developed with regional universities as a core under the Knowledge Cluster Initiative of MEXT. Life science was regarded as an important part of the cluster development in as many as eleven clusters.

5.2 Geographical distribution of Japanese DBCs

Although it is too early to evaluate the full effects of the “Cluster Plan” since only five years or so have passed since its initiation, to observe the geographical distribution of Japanese DBCs may reveal some effect.

Tables 6 and 7 introduced in the section IV list the location of Japanese DBCs having biotech drugs in pipeline. It is to my surprise that those Japanese DBCs tend to scatter across the region from Akita city in the northern part of Japan through Gumma, Tochigi, Tokyo, Kanagawa, Nagoya, Mie, Shiga, Osaka, Kobe, till Okayama in the west. Scientific seeds seem to be abundant across the country. This implies that the formation of the biotech clusters is very different from the conventional regional cluster theory where a large anchor company already exists and “supply chains” have been very important as drivers of new company formation (Chiesa and Chiaroni 2005:4, Nelsen 2005).

The birth of a large number of start-up companies across the region does not, however, seem to lead to local biotech industrial development as expected under the Knowledge Cluster Plan. Table 8 shows the number of Japanese DBCs by prefecture in 2002 and 2006, and the changes both in their absolute numbers and in their percentage shares between two years.

Table 8 reveals two points. First, at least one biotech company was born in almost all of the prefectures in Japan except Fukui, Saga, and Ehime between 2002 and 2006. This also implies that scientific seeds can be sourced out across the region for the development of the biotech industry.

<Table 8>

Second, the geographically localized impacts are not, however, very strong in Japan contrary to the expectation of the Cluster Plan. As many as eleven biotech clusters were designated as biotech clusters under the Knowledge Cluster Plan. Only the Kansai area (Hyogo, Kyoto and Osaka), and Hiroshima to some extent, showed some expected result. In all other prefectures (Gifu, Shizuoka, Tokushima, Kochi, Yamaguchi, Toyama and Ishikawa) the governmental initiative did not generate a strong driving and developmental force of forming clusters.

Two reasons may account for the lack of the strong localized knowledge spillovers. The first one is a point raised by Zucker and Darby (2001:43). In Japan the industry-academia collaboration often entails one of the company's scientists working in the academic star's university laboratory and serving as liaison to the firm.[xxiii] Since any firm can reasonably move one of their scientists to the star's laboratory, [xxiv]extra-regional linkages between firms and universities are common in Japan.

The second reason may be the lack of an easy access to the managerial and financial resources necessary to sustain DBCs. The availability of expertise in such areas as law, finance and management is essential for the development of high-tech industries such as biotech one. The combination of the low mobility in the labor market and the severe problem of asymmetric information in the financial market in Japan seems to make it very hard especially for the local areas to sustain the growth momentum of the biotech industry.

6. Conclusion and Policy Implication

In the 1980s there was concern among some US observers that biotechnology would be the next industry in which Japanese firms overtook overseas competitors. But, to date this has not occurred yet. The paradox is that the global presence of the Japanese biotechnology industry is still low especially in biopharmaceuticals in spite of Japan's exemplary reputation worldwide in life science research.

OECD (2006) hypothesized that this is primarily because Japan's innovation system had been dominated by large companies in which in-house development is still highly valued and alliance strategies are disregarded. The paper argued that this is no longer applicable because both business and government has adopted various measures to introduce the new innovation system more suitable for science-based industries such as the biotech one since the late 1990s. The paper instead suggested that a more important issue may be whether Japan could succeed in the high-tech industries such as the biotech one under the coexistence of the new innovation system with traditional business and industrial practices.

The paper concluded the Japanese mode of innovation has both advantages and disadvantages. It has an advantage over the counterparts in the U.S. and in Europe in the ease in which a new and radical technology such as biotechnology is applied widely across the industries while their accumulated and incremental knowledge and technology is fully utilized in the new field of business as well.

It also has a disadvantage. That is, the Japanese mode of innovation is weak in developing very high tech, high value sectors such as biopharmaceuticals because it lacks an effective mechanism of identifying and financing biotech companies with a high risk/return profile. The severity of the problem of asymmetric information and the lack of an effective screening device seems to be hampering the development of the biopharmaceutical sector.

Entering the 21st century, the government of Japan introduced the 'Cluster Plan', which is the most ambitious and comprehensive plan since the 1960s. It was very much modeled after the success of the U.S. in forming regional high-tech clusters surrounding universities and public research institutes. The paper concluded that a cluster development approach may not be suitable for a country such as Japan where the underlying business and industrial practices are very different. The government should address the fundamental weaknesses of the Japanese new innovation system in promoting biotech industries instead of linking it too much to the Cluster Plan.

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Table 1 Share of Science World Article Output by Field and by Country in 1996 and in 2003

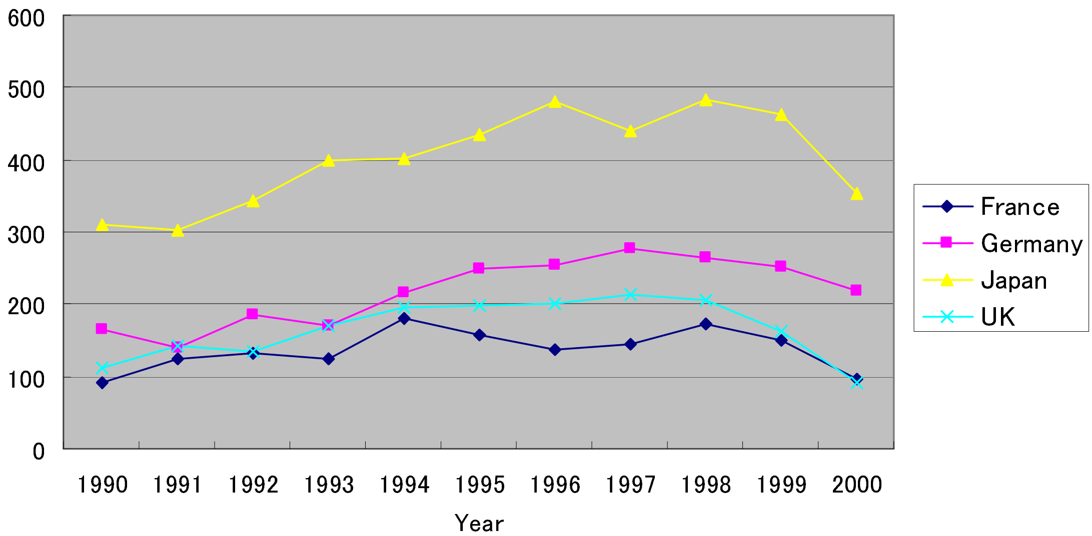
	All Fields [2]		Clinical Medicine		Biomedical Research		Biology	
	1996	2003	1996	2003	1996	2003	1996	2003
US	34.0	30.2	36.5	33.8	38.3	36.0	30.5	28.1
Japan	8.5	8.6	8.7	8.4	8.0	8.3	7.9	7.6
France	5.0	4.6	4.9	4.3	5.6	4.8	4.1	3.8
Germany	6.6	6.3	6.4	7.1	6.7	6.3	5.1	4.7
UK	8.1	6.9	9.3	8.0	8.1	7.2	7.5	6.0
Top 5 total	62.2	56.7	65.7	61.6	66.7	62.6	55.1	50.3
ROW [1]	37.8	43.3	34.3	38.4	33.3	37.4	44.9	49.7
World Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Source: the author's construction based on National Science Foundation, *Science and Engineering Indicators 2006*.

Note (1): ROW stands for the rest of the world.

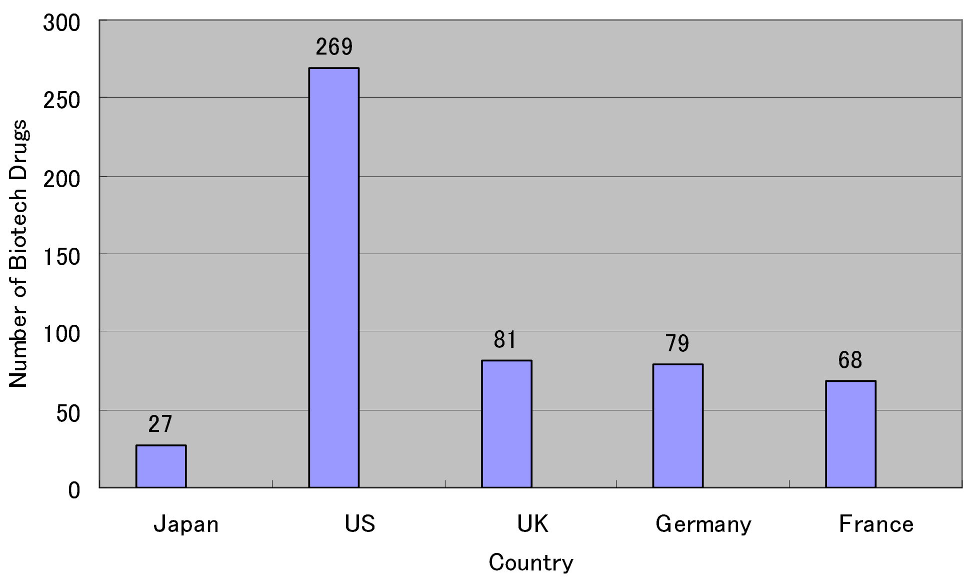
(2): Chemistry, physics, earth/space science, engineering/ technology, mathematics, psychology, social science, health science are included beside clinical medicine, biomedical research and biology.

Figure 1 Number of Patents Granted by the US Patent Office (USPTO) in the Biotechnology Sector



Source: Source OECD, *Science and Technology Statistics*

Figure 2 Number of Biotech Drugs in Pipeline [1] by Country



Source: Takatori (2007), Figure 2.

Note: [1] It includes biotech drugs in pipeline since the stage of the Clinical Phase II.

Table 2 Shares of Biopharmaceutical Patents Applied in Japan between 1977 and 1999 by Nationality and by Type of Institutions (%)

	Japan	US	Europe
Pharmaceuticals	40	38	56
Chemical products	30	0	17
Food, beverage, agronomy	22	0	3
Nonprofit organizations	9	27	15
DBCs	0	35	10
Total	100	100	100

Source: Author's construction based on the data of patents downloaded from *www.jpo.go.jp/shiryou/s.sonota/map/kagaku11/1/1-7-3.htm*.

Note: Nonprofit organizations include universities, hospitals, public research institutes.

Table 3 Major Entries from Other Business Sectors into the Pharmaceuticals/Biomedical Industry

Name	Original main business	Year of entry into new business	Original core technology	Subsequent evolution	Sales revenue in ¥ billion	Sales profits in ¥ billion A	R&D expenses in ¥ billion B	Biotech drugs launched	Biotech drugs in pipeline
Suntory	Beverage Food	1979	Fermentation	Started as a part of the diversification plan. In 2006, Suntory withdrew from the drug business. Now, the business is carried over by **Asubio Pharma Co., LTD**. under the ownership of Daiichi-Sankyo	NA	NA	NA	1	4
Ajinomoto	Food Beverage	1981	Amino acid technology	In 1999, **Ajinomoto Pharma Co., Ltd** is inaugurated. The pharmaceuticals business specializing in amino acid drug creation turned out to be successful. The development of a biotech drug was also tried in the 1990s.	83.3	15.8 (19.0%)	9.54 (11.5%)	1	0
Kyowa Hakko	Food Chemicals Drugs	1956 (drug) 1981 (bio business)	Fermentation	Kyowa aspires to be a leading biotechnology company by combining new biotechnologies with chemical synthesis technologies. The antibody business including its therapeutic antibody development has become a core business of the pharmaceuticals sector.	132.0	15.7 (11.9%)	28.5 (21.6)%	0	9
Kirin	Beverage Food	1982	Biotechnology acquired through beer brewing	Started as a part of the diversification plan. In July 2007, **Kirin Pharma Company, Ltd**. was established. It will be integrated into Kyowa Hakko within the year of 2008.	69.9	13.0 (18.6%)	18.2 (26.0%)	3 (2 with Amgen)	3
Teijin	Chemicals	1972	Technology in chemical synthesis, polymer chemistry and life sciences such as biomedical engineering	**Teijin Pharma** was established as an independent entity in 2003. It aspires to be a unique, R&D-oriented global company in the field of pharmaceuticals and healthcare services.	113.0	21 (18.6)%	NA	3	1
Asahi KASEI	Fibers Chemicals	1970	Biotechnology Technology in chemical synthesis	In 2003 **Asahi Kasei Pharma** was established to be the core operating company for all operations of the Asahi Kasei Group which serve the health care industries	104.5	13.9 (13.3%)	10.5 (10.1%)	1	0
Takara Shuzo	Beverage	1979	Fermentation	In 2002 **Takara Bio Inc**. was established to carry on the biomedical business of Takara Shuzo Co., Ltd. It consists of genetic engineering research, Arabia, and gene medicine. It went on an IPO in 2004.	20.9	0.3 (1.4%)	3.2 (15.3%)	0	9

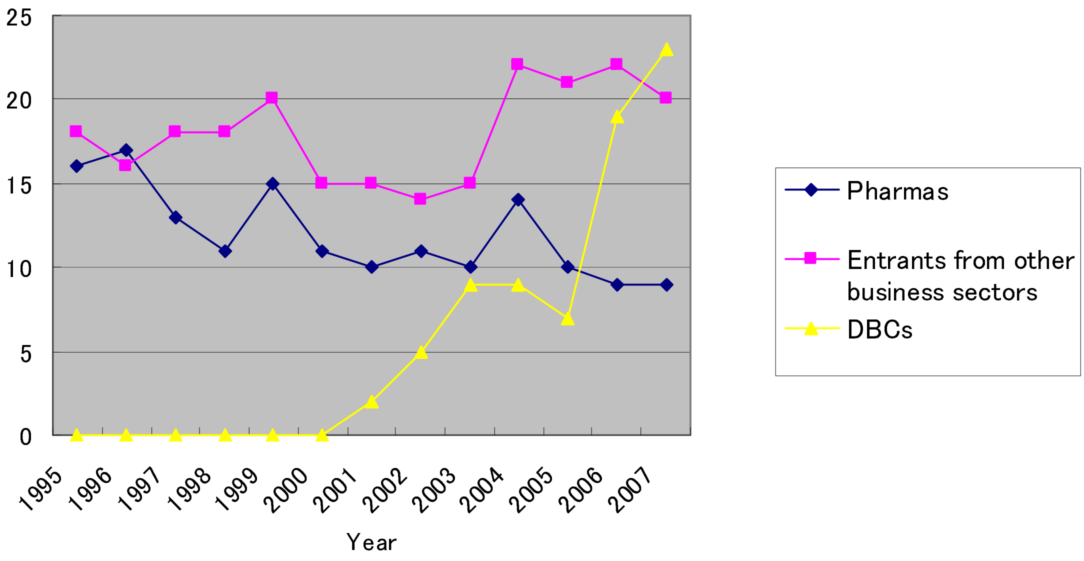
Source: the author's construction based on various reports of each company.

Notes: (1) Numbers of R&D researchers, sales revenue, sales profits, R&D expenses are the 2007 figures except Ajinomoto. Data of Ajinomoto are 2006.

(2) Figures in the parentheses of column A represent sales profits as a percentage of sales revenues.

(3) Figures in the parentheses of column B represent R&D expenditures as a percentage of sales revenues.

Figure 3 Numbers of Biotech Drugs Launched or in Pipeline[1]
by Type of Companies



Source: the Author's construction based on the *Pharmaprojects v5.2 on the Web* (March 28, 20008).

Note:[1] From the registration stage through the clinical phase

Table 4 Number of Drugs in Pipeline[1] as of March, 2008

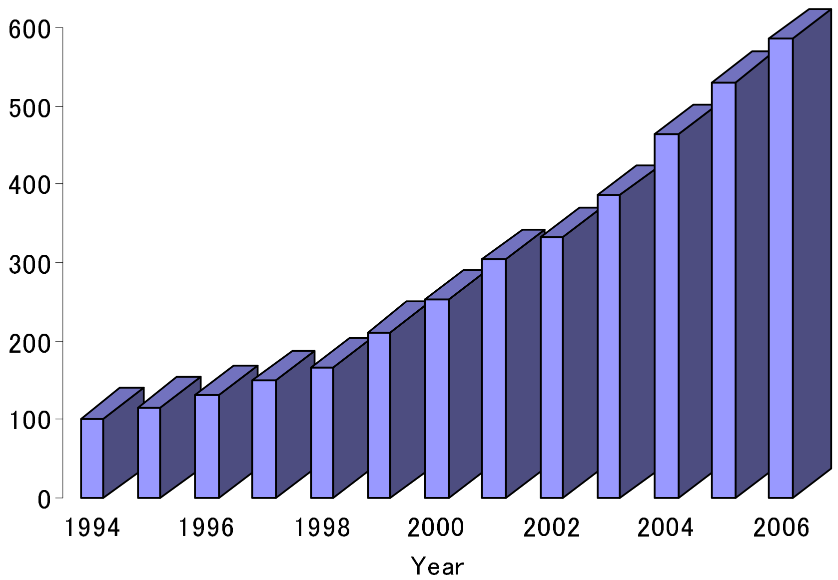
Japanese Pharmas	Biotech Drugs		
	Originate & Develop or Out License	In License & Develop	Openness Ratio[2]
Takeda	0	7	100.0%
Astellas	0	12	100.0%
Daiichi-Sankyo	2	5	71.4%
Eisai	0	11	100.0%
Japanese Pharmas	**Non-biotech Drugs**		
	Originate & Develop or Out License	In License & Develop	Openness Ratio[2]
Takeda	32	19	37.3%
Astellas	27	14	34.1%
Daiichi-Sankyo	25	11	30.6%
Eisai	25	12	32.4%

Source: See Figure 3.

Notes:[1] See Figure 3

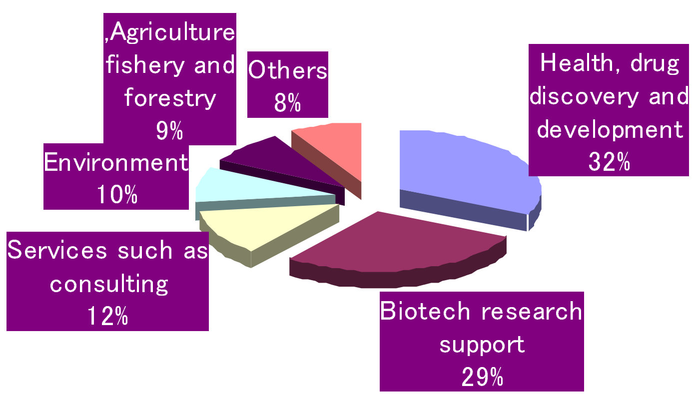
[2] The openness ratio is defined as the number of biotech drugs in licensed from other companies. as a percentage of total

Figure 4 The Number of Japanese DBCs by Year



Source: Japan Biotechnology Association (2007).

Figure 5
Percentage Shares of Japanse DBCs
by Type of their Main Activities



Source: The Japan Biotechnology Association (2007)

Table 5 Percentage Shares of Biotech Drugs in Pipeline by Category

Stages of development	Biopharmaceuticals	1996 World	2006 World	March, 2008 Japan		
				P	NP	DBCs
1st Generation	Recombinant protein production, etc.	47%	24%	78%	40%	24%
2nd Generation	Monoclonal antibodies, etc.	32%	28%	11%	55%	20%
3rd Generation	(1) Gene therapy, nucleic acid medicine	11%	23%	11%	5%	48%
	(2) Vaccine	8%	16%	0%	0%	0%
	(3) Stem cell therapy, cellular therapy	2%	9%	0%	0%	8%

Source: (1) Data of both 1996 and 2006 of the world are taken from Takatori (2007).
(2) Data of Japan are the author's construction based on *the PharmaProjects v5.2 on the Web* (March 28, 2008) and Kohno (2007).

Note: P: Pharmaceutical companies
NP: New entrants from other business sectors
DBCs: Dedicated biotech companies

Table 6 Comparison between the US. and Japanese DBCs

Name	Type of venture	Year of establish-ment	Place	Main business	IPO year	Market capitalization (March,2008)	Number of Employees	Sales value (¥ Billion)	Net income (¥ Billion)	R&D expenses (¥ Billion)	Biotech Drugs		Patents (2002-08)
											on sale (March, 2008)	in pipeline (March, 2008)	
Top Ten US DBCs						62.7	NA	1.3	-10.8	8.1	0.3	11.8	
AngesMG	Academic (Osaka Univ.)	1999	Osaka	Genetic therapy	2002	49.6	91 (2006)	1.7 (2006)	-1.7 (2006)	3.1 (2006)	2	14	30
J-TEC	Corporate venture	1999	Nagoya	Cellular therapy	2007	12.1	56 (2006)	0.1 (2006)	-0.9 (2006)	0.3 (2006)	1	2	74
OncoTherapy Science	Academic (Tokyo Univ)	2001	Kanagawa	Cancer therapy (Virus vaccine)	2003	28.1	50 (2006)	0.8 (2006)	-1.3 (2006)	1.9 (2006)	0	1	44
IBL	Independent	1982	Gunma	Monoclonal antibody	2007	1.2	66 (2006)	1.5 (2006)	0.03 (2006)	0.4 (2006)	1	1	23

Source: Chiesa and Chiaroni (2005) for the US Top DBCs in terms of market capitalization.
Japanese DBCs are based on the data obtained from companies' reports.

Note: Data of the US DBCs are for the year of 2001.

Table 7 The Emergence of Academic DBCs

Name of DBCs	Year of establish-ment	Place of main office	Number of employees	Source of seeds	Biotech drugs in pipeline
Oncolys BioPharma	2004	Tokyo	NA	Okayama University	Lytic Virus (3) RNAi (1)
ImmunoFrontier	2004	Tokyo	NA	Mie University	Gene therapy (1)
DNAVEC	2003	Tsukuba	35	Public institute	Lytic Virus (1) Gene therapy (1) Gene delivery vector (1)
Kringle Pharma	2001	Osaka	NA	Osaka University	Recombinant growth factor (1)
M's science	2000	Kobe	NA	Santen pharma	Lytic Virus (1)
UMN Pharma	2004	Akita	NA	Tokyo Univ Akita Univ Shikoku TLO	Recombinant vaccine (1) Recombinant other (1)
Y's Therapeutics	2003	Tokyo	40	Tokyo Univ	Humanized monoclonal antibody (1) Immunoconjugate (1)

Source: See figure 3.

Table 8 Number of Japanese DBCs in 2002 and in 2006 by Prefecture, and the Changes both in the Absolute Number and the Percentage Share

Prefecture	2002	2006	Changes in absolute number	Changes in percentage share
Tokyo	112	149	37	−8.2
Kanagawa	26	61	35	2.6
Hokkaido	31	52	21	−0.4
Ibaragi	17	37	20	1.2
Hyogo	9	28	19	2.1
Osaka	21	40	19	0.5
Fukuoka	11	25	14	1.0
Kyoto	20	32	12	−0.5
Hiroshima	3	12	9	1.1
Aichi	7	16	9	0.6
Okinawa	1	9	8	1.2
Mie	2	9	7	0.9
Chiba	15	21	6	−0.9
Shiga	2	7	5	0.6
Gunma	1	5	4	0.6
Okayama	2	6	4	0.4
Saitama	6	10	4	−0.1
Miyagi	4	7	3	0.0
Toyama	1	3	2	0.2
Tokushima	1	3	2	0.2
Nagasaki	1	3	2	0.2
Akita	2	4	2	0.1
Iwate	0	1	1	0.2
Nara	0	1	1	0.2
Tottori	0	1	1	0.2
Oita	0	1	1	0.2
Aomori	1	2	1	0.0
Yamagata	1	2	1	0.0
Fukushima	1	2	1	0.0
Nagano	1	2	1	0.0
Wakayama	1	2	1	0.0
Shimane	1	2	1	0.0
Miyagi	2	3	1	−0.1
Kumamoto	5	6	1	−0.5
Fukui	0	0	0	0.0
Saga	0	0	0	0.0
Niigata	1	1	0	−0.1
Yamanashi	1	1	0	−0.1
Yamaguchi	1	1	0	−0.1
Kochi	1	1	0	−0.1
Kagoshima	1	1	0	−0.1
Ishikawa	2	2	0	−0.3
Kagawa	3	3	0	−0.4
Shizuoka	8	8	0	−1.0
Ehime	1	0	−1	−0.3
Tochigi	3	2	−1	−0.6
Gifu	3	2	−1	−0.6

Source: the author's construction based on the data of Japan Biotechnology Association (2007).

[i] Biotech industry is often referred to as a science-based industry because of the importance of science as an input.

[ii] See McKelvey and Orsenigo eds. (2006).

[iii] This point is also raised by Lynskey (2006).

[iv] See Chiesa and Chiaroni (2006) for the details of the development of biotech clusters in Europe.

[v] Especially, the Ministry of Economy, Trade and Industry (METI) and the Ministry of Education, Culture, Sports, Science and Technology (MEXT)

[vi] The R&D outsourcing ratio is defined as R&D fund paid outside as percentage shares of self-financed R&D fund. Figures of both 1990 and 2006 are based on the data of the Ministry of Internal Affairs and Communications (1991, 2007).

[vii] Odagiri (2006b) also addresses the same issue.

[viii] For instance, Zucker and Darby (2001), Kneller (2003), and Lynskey (2006).

[ix] A lot of other companies such as Toray, Toyobo, Mitsubishi Chemical Corporation, Japan Tobacco, Asahi Breweries, Ltd., Snow Brand, Meiji Seika Kaisha also entered or tried to enter the biotech industry. Their analyses are not made in the paper because they have not been successful in the biopharmaceutical sector.

[x] See endnote 9.

[xi] Cooke argues that three patterns of innovation are found in biotechnology at least in Europe (Cooke 2004: 917). The first one is open innovation among universities (or research institutes), pharmaceuticals companies and small biotech firms. The second pattern of innovation is a direct basic knowledge transfer between large public research institutes and large biotechnology firms with little or no involvement of biotech start-ups. The second pattern is often found in the agro-food sector in the case of Europe. The third model of innovation is inter-industry trade by direct spinout, divisional divestiture, or in-house evolution of innovation capabilities from other business corporates entering and selling products and services in new biotech markets. Although the third model seems to be found most in new environmental or energy markets in the case of Europe, it was a dominant pattern of innovation in Japanese biopharmaceutical sectors at least until the end of the 1990s.

[xii] Around 34 percent of the total revenue of Kyowa Hakko is produced by the pharmaceutical sector alone according to the 2007 annual report of Kyowa Hakko (17 percent by fine chemicals, 26 percent by other chemical products, and 11 percent by food).

[xiii] Takara Bio is slightly more independent from its parent company relative to other firms on the table 3 because it made an IPO in 2004. Now, Takara Bio can seek the private funds externally through the stock market to finance their R&D and/or investment activities. It is also important to note, though, that even Takara Bio still maintains a close relationship with its parent company (now Takara Holding Company). First of all, more than 70 percent of the stocks of Takara Bio are still held by Takara Holding Company. Besides, almost all of the directors on board originate from the parent company except the scientific director. See the *Financial Information* (Yukashoken Hokokusho) of Takara Bio for the details.

[xiv] One of the most successful Japanese dedicated biotech companies is Takara Bio, which evolved in-house from Takara Shuzo, a 160-year old Japanese wine producer. Takara shuzo started off its biomedical business in 1979 within a corporate division. First, it succeeded in establishing a stable revenue bases in the fields of genetic engineering research and AgriBio. Then, in the 1990s the company advanced its biomedical business into the gene medicine, which requires one of the highest levels of scientific knowledge and technology in the field of contemporary life science. The biotech business expanded so much so that Takara Bio got independent in 2002 and went on an IPO in 2004. See *Annual Report 2007* of Takara Bio Inc. for the details.

[xv] Figure 3 includes biotech drugs in pipeline since as early as the registration stage in order to capture

the R&D activities of newly established companies (DBCs).

[xvi] See *Nikkei Biotech* (October 8, 2007).

[xvii] See a news release of FUJIFILM holdings announced on February 13, 2008 (http://www.fujifilmhodings.com/en/news/2008/0213_01_01.html).

[xviii] According to a survey conducted by the Japan Biotechnology Association (2007), around 36.6 percent of the total dedicated biotech companies (586 companies in 2007) are academic start-up companies in which their core technology was sourced from either universities or the public research institutes.

[xix] A brief summary of various advances in biotechnology and their application to the drug discovery and development is found in Chugai Pharmaceutical Co., Ltd.(2003).

[xx] Product Biotech companies such as Genentech and Amgen are excluded from the US counterparts. The ten largest companies were selected by the magnitude of market capitalization.

[xxi] This is confirmed in *Financial Information* (Yukashoken Hokokusho) submitted by each company. For instance, the current CEO of OncoTherapy Science was a former president of AnGes MG. He succeeded in establishing AnGes MG, one of the most successful Japanese DBCs. He has quite a lot of experience in the field of pharmaceuticals. IBL also succeeded in recruiting people from a variety of fields such as a Japanese pharmaceutical company, a trading company, a chemical company, etc. J-TEC is a spin-off corporate venture.

[xxii] See and Chiesa and Chiaroni (2005) for the details.

[xxiii] In the U.S. the star scientist physically does his or her research at the firm's facilities in order for the collaborators to avoid the university's full or co-ownership of any resulting patents (Zucker and Darby 2001: 43)..

[xxiv] This can be applied only to large companies.