Current status and trends of Japan's bioindustry

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In Japan, the sales of modern biotechnology products and services in 2006 were worth 1,847 billion Japanese Yen (¥) (US$16.7 billion) [1]. The market has shown steady growth since 1989 (Figure 1). Conventional biotechnology products such as beer and sake are not covered in Figure 1. If we cover products of both conventional and modern biotechnology, the market size in 2005 was ¥7,692 billion (approximately equivalent to US$70 billion) [2]. Major modern biotechnology products sold in Japan in 2006 are shown in Table 1.

Pharmaceutical industry

The size of the world pharmaceutical market in 2005 was US$601.4 billion. Japan's share was approximately US$66 billion (11% of the world market), which is the second after the United States (44%) [3].

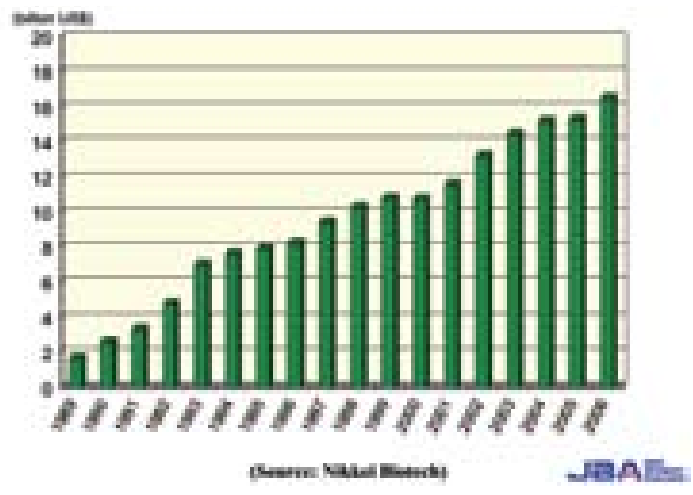

Figure 1. Growth of Japan's modern bioindustry market.

However, Japan's pharmaceutical industry has been facing a number of challenges. Firstly, the Ministry of Health, Labor and Welfare (MHLW) has continued to lower official drug prices to slow the increase of the government spending on the national medical insurance system which has been growing with the aging population. Lowering of the drug prices means slowing down the growth of the domestic pharmaceutical market. Secondly, like those in the United States and Europe, Japan's pharmaceutical companies have had to keep increasing their R&D spending to meet global competition. Thirdly, government regulations, including new good clinical practice guidelines, have made it more time consuming to bring products to market within Japan.

Table 1. Major modern biotechnology products in Japan (2006) [1].

Products	Sales (¥billion)
Therapeutics	
Erythropoietin	132.6
Human insulin	74.0
Interferons (α, β, γ)	58.3
Human growth hormone	55.8
Therapeutic antibodies	45.4
Granulocyte colony stimulating factor (G-CSF)	38.7
Diagnostics	
Monoclonal antibody diagnostics	90.0
Transgenic crops	
Soybeans	129.1
Corn	104.7
Rapeseeds	49.2
Cotton	4.0

In order to cope with these challenges, Japan's pharmaceutical companies have been strengthening their R&D and sales capabilities in overseas markets, particularly those in the United States and Europe. For example, during the period from 1996-2005, the combined overseas sales for seven major companies (including Takeda, Astellas, Eisai and Daiichi-Sankyo) increased by ¥1275 billion (US$11.6 billion). Furthermore, companies have been consolidating their strengths through merger, acquisition and other type of partnerships. Major mergers that took place in Japan in recent years include: Chugai-Nihon Roche (2002), Daiichi-Sankyo (2005), Yamanouchi & Fujisawa to create Astellas (2005), Dainihon-Sumitomo (2005), Tanabe-Mitsubishi (2007), and Kirin-Kyowa Hakko (scheduled for 2008).

Japan's government is also responding in policy making to the situation. For example, the annual meeting of the Life Science Summit that took place in Tokyo on 4 June 2007 focused on the reform of a national system for clinical trials as a major subject. The Life Science Summit is an event attended by decision makers from industry, academia, ministries and parliament who are responsible for the issues on life sciences and biotechnology. The Summit intensively discussed issues on the reform in clinical trials and associated research system in Japan, and adopted a declaration to endorse the need for the reform in the system [4]. Additionally, the government (i.e. MHLW) started a new 5 year 'clinical trials activation' plan in 2007.

Historically, Japan's pharmaceutical industry has strengths in microbial, natural, product-based drug discovery, as demonstrated by the worldwide blockbuster drugs such as pravastatin and tacrolimus. An example of more recent commercial success is micafungin. Some lead compounds originating from Japanese natural products are currently being tested in the clinical phases.

There are several reasons for the Japan's strengths. Japan has traditionally developed fermentation industries using Aspergillus, Saccharomyces, and other microbes. This tradition helped to nurture expertise in applied microbiology. For example, Jokichi Takamine, a pioneer in biotechnology in both Japan and the United States, developed and patented microbial enzymes for the first time in the world more than 100 years ago. Modern fermentation processes for amino acids and nucleotides have bloomed in Japan since the late 1950s. During the period when research and development in antibiotics prevailed, Hamao Umezawa and his group were a world leader. Discovery and development of natural product-based drugs require a wide diversity of researchers in different disciplines. Success depends on well-organised collaboration between these experts rather than one genius. This type of research collaboration is compatible with Japanese culture. Japan's strengths in this field seem to come from a combination of these elements.

However, the percentage of small-molecule drugs worldwide that include those of natural product origin are envisaged to decrease from 87% in 2005 down to perhaps 60% in 2025 according to a certain estimate. On one hand, the 'tsunami' of modern biotechnology-based drug discovery (for large-molecule drugs including proteinous and antibody drugs) and regenerative medicine have overwhelmed the world, including Japanese industry. On the other, the Convention on Biological Diversity (CBD) has negatively affected corporate management's incentives for investment in natural product-based drug discovery because of uncertainty about the regulatory procedures of a number of developing countries that are potential providers of genetic resources. Major Western pharmaceutical companies either withdrew or drastically reduced their capabilities in natural product-based drug discovery. Japanese pharmaceutical companies have been affected by this trend, but a number of them still manage to keep the function of their natural product drug discovery on a smaller scale. Continuous efforts are needed to keep the natural product drug discovery alive. In this sense, CBD-based collaboration with developing countries, such as efforts by Nimura Genetic Solutions in Malaysia, Mercian Corp. in Indonesia and HyphaGenesis Inc. in Vietnam, will be essential.

Agro-foods industry

Importation of transgenic crops (soybeans, corn, rapeseeds and cotton) to Japan has been steadily increasing. In 2006, ¥287 billion (US$2.6 billion) worth of these crops were imported from overseas, mainly North America (Table 1).

Japan has significantly contributed to the high-quality sequencing of rice genome in the International Rice Genome Sequencing Project by analysing 55% of the main part of the genome in 2002 [5]. Transgenic rice crops have not yet been commercialised in Japan, but significant developments have been taking place in horticulture.

Molecular geneticists of the Florigene-Suntory team achieved the development of a truly blue rose; this had eluded conventional rose breeders since 1840 when the horticultural societies of Britain and Belgium offered a prize of 500,000 Francs to the first person to produce a blue rose [6]. The Florigene-Suntory team cloned the delphinidin gene from a pansy, and directed pigment synthesis in the rose into the blue pathway. The team designed a gene by exploiting a new CSIRO-developed technology to switch off a rose gene that had frustrated their efforts to activate the delphinidin pathway in roses for nearly a decade. It is the first rose in the world with the genetic potential to produce true blue roses [6, 7].

Japan is the pioneer in the development of amino acid fermentation technology [8]. A recent trend on demands for amino acids as feed supplements is noteworthy. As the standards of living of countries become higher, people generally tend to consume more animal proteins. For the amino acid industry, this has resulted in a steady increase of demand for essential amino acids as supplements to animal feeds. Global demands in 2005 for lysine, threonine and tryptophan as feed supplements have been 850,000 tons (9.4% increase over the previous year), 85,000 tons (23.5% increase), and 1,800 tons (16.7% increase) respectively. Industry leaders in Japan foresee that this trend will continue into the next decade [1].

Biodegradable plastics

In recent years, the market for biodegradable plastics has been growing rapidly, particularly so after the World Exposition 2005 in Aichi, Japan. Japan BioPlastics Association (JBPA, formerly known as Biodegradable Plastics Society) has been working persistently since 1989 to lay the groundwork for the development of a

biodegradable plastic industry. The present market in Japan is mainly composed of poly-(butylene succinate), poly-(lactic acid), and starch blended with biodegradable plastics.

Currently, diversified industry sectors, including automobiles, electronics and food containers, are exploring novel concepts for using biomass-based plastics. Because of the price increase of crude oil and the social movement to prevent global warming, many companies see the commercial potentials of replacing petroleum-based plastics by biomass-based plastics. JBPA, for example, started in 2006 a certification and labelling system for biomass-based plastic products in order to make them clearly visible to the civil society [9]. Japan's domestic market for biodegradable plastics was estimated to be over 30,000 tons in 2005. According to a certain estimate, biodegradable plastics will come to occupy 10% of the entire plastics in Japan at some point in the next decade.

Development of entrepreneurial businesses

Biotechnology-related start-ups are called 'bioventures' in Japan. The number of bioventures in Japan has been steadily increasing. According to the survey conducted by JBA in 2006, cumulatively 586 bioventures have so far been created in Japan [10]. In regional distribution, the highest concentration (49% of the national total) was in the Tokyo metropolitan area and its vicinity, followed by Kinki district covering Osaka, Kyoto and Kobe (20%) and Hokkaido (8.9%) (Figure 2). Tokyo is home to the nation's highest concentration of established companies and, likewise, approximately one-third of the nation's bioventures are located in Tokyo. As for the distribution by business sector (as surveyed by a multiple-choices response method), the most prevailing sector was pharmaceuticals and healthcare (31.9%), followed by research support (customised research, instrument development, bioinformatics etc) (28.9%), consulting and other services (12.2%), environmental technologies (9.7%), agricultural technologies (8.9%) and custom production (8.4%).

The law to corporatise all the national universities took effect in April 2004 and made involvement of the faculty members in entrepreneurship legally acceptable. This deregulation measure seemed to have contributed to the continued creation of spin-off bioventures. The history of American Silicon-Valley type entrepreneurial business is still young in Japan, yet bioventures are expected to significantly contribute to Japan's technological innovation on a longer-term basis.

Development of science-technology infrastructure and platform technologies

Biological resources centres (BRCs)

In order to meet modern demands for the further advancement of biotechnology and life sciences, in 2001 the OECD introduced a new concept of repositories and providers of high quality biological materials and information – biological resources centres (BRCs) [11]. BRCs are considered to be one of the key elements for sustainable international scientific infrastructure which is necessary to underpin successful delivery of the benefits of biotechnology, whether within the health sector, the industrial sector or other sectors, and in turn ensure that these advances help drive growth [11].

Japan's government has designated life science and biotechnology as one of the strategic technologies. In that context, in 2002 the government created a microbial BRC within the National Institute of Technology and Evaluation (NITE) on the basis of the OECD policy guidance. NITE BRC has developed an organisational structure where the functions of microbial genomics and the conventional culture collection are integrated with a view to promoting interdisciplinary investigation and to adding value to microbial resources and the associated data [12]. Examples of two recent research results at NITE BRC on genomic and proteomic studies are given below.

Aspergillus oryzae is a filamentous fungus widely used in fermentation industries in Japan. It has been used for more than 1000 years in Japan for the production of fermented foods such as sake, soybean paste (miso), soy sauce (shoyu). It can also be used for other purposes in modern bioindustry, e.g. as a host for producing various enzymes and other proteins. NITE completed entire genome sequencing of *Aspergillus oryzae* [13]. The 37 megabase (Mb) genome of *A. oryzae* contains 12,074 genes and is longer by 7-9Mb than the genomes of *Aspergillus nidulans* and *Aspergillus fumigatus*. The *A. oryzae*-specific genomic stretches are rich in genes involved in the synthesis of secondary metabolites, amino acid metabolism and amino acid/sugar uptake as well as the genes for secondary hydrolytic enzymes, supporting the idea that *A. oryzae* is an ideal microorganism for fermentation industry.

Aeropyrum pernix K1 is an aerobic hyperthermophilic crenarchaeon isolated in 1993 from a coastal solfataric thermal vent in Kodakara-jima island of Kagoshima, Japan. Proteome analysis of *A. pernix* K1 was carried out. A total of 704 proteins were identified, 134 of which were unique to *A. pernix* K1; 19 were not described previously in the genomic annotation. Furthermore, the amino-terminal amino acid sequence analysis indicated that, surprisingly, the translation of 52% of their genes starts with TTG codon in contrast to ATG (28%) and GTG (20%). Thus, *A. pernix K1* is the first example of an organism in which TTG is the most predominant translational initiation codon [14].

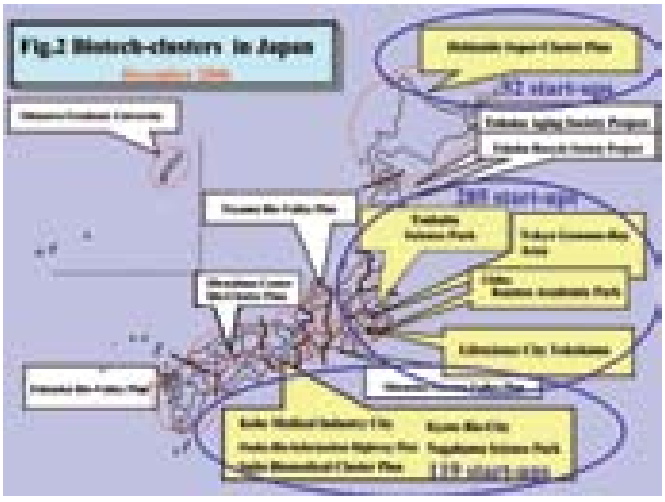

Figure 2. Biotech-clusters in Japan, December 2006.

Platform technologies

Development of platform technologies was advanced on a JBA-NEDO (New Energy and Industrial Technology Development Organization) project, aiming at breeding host microorganisms for industrial production. The basic concept employed was elimination of genes that are unnecessary or harmful for industrial purposes, while maintaining those genes that are necessary for active growth and further reinforcing those useful for increasing the production of targeted products [15]. The concept was referred to as 'minimum genome factory' (MGF). For the MGF development, three species were selected, i.e. a Gram-negative bacterium *Escherichia coli,* a Gram-positive bacterium *Bacillus subtilis* and a fission yeast *Schizosaccharomyces pombe.* Minimum-genome microbes are expected to be ideal platforms for further studies on metabolic engineering.

Bioindustry and the Convention on Biological Diversity

The Convention on Biological Diversity entered into force in 1993 [16]. Article 15 of the Convention addresses the terms and conditions for access to other countries' genetic resources and benefit sharing. It recognises the sovereign rights of States over genetic resources and provides that access to these resources shall be subject to the prior informed consent of the country providing such resources. It also provides that access shall be based on mutually agreed terms in order to ensure the sharing of benefits arising from the commercial and other utilisation of these genetic resources with the country providing such resources. In 2002, the Bonn Guidelines were adopted at the Conference of Parties to serve as a tool for the implementation of Article 15 and other relevant Articles of the Convention [16].

JBA and Ministry of Economy, Trade and Industry (METI) have been steadily implementing the Convention and the Bonn Guidelines by organising public seminars in major cities across the country. Furthermore, JBA and METI developed *The Guidelines on Access to Genetic Resources for Users in Japan* in consultation with experts from industry and academia in April 2005. The Japanese Guidelines are in conformity with the Bonn Guidelines, and are user-specific and user-friendly, with illustrations and frequently asked Q&As. They are intended to help both providers and users of genetic resources to build a win-win relationship, and to minimise the risk of getting involved in problems, while ensuring business flexibility. Its English translation is available [17].

Future prospects

The industrial landscape in Japan seems to be steadily transforming thanks to the penetration of modern biotechnology into existing industries. Existing industries – chemicals, food, pharmaceuticals, energy, paper and pulp, information technology and electronics – are becoming increasingly sophisticated and/or environmentally sustainable by incorporating elements of biotechnology innovations. For example, part of the chemical industry is undergoing transformation at three levels – firstly, a shift in the sourcing of raw material from fossil feedstock to biomasses; secondly, a shift in the manufacturing process from chemical process to a combination of chemical and biotechnological (e.g. enzymic) processes and; thirdly, a shift in the concept of product development increasingly focused on environmental sustainability (e.g. biodegradable plastics).

In the longer term, biotechnology will revolutionise the healthcare industry. Biotechnology will help reduce the number of patients requiring acute care through advanced preventive medicine and functional foods. Personalised medicine will be able to improve health with fewer side effects and shorter hospital stays. As individuals' genetic information will play such an important role in the forthcoming technological innovation, establishment and full implementation of rules and systems will be essential to ensure security and privacy protection of individuals' genetic information.

Due to a high longevity (highest in the world) and a low birth rate, Japan's population is aging faster than those of any other industrialised country. Technological innovation will definitely be one of the strategic tools to cope with this social challenge. Under these circumstances, Japan's government has designated life sciences and biotechnology as one of the priority areas for government's investment. Biotechnology, in combination with other advanced technologies such as nanotechnology, robotics and electronics, is expected to contribute to development of technological innovations.

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