JAPAN'S GROWING MAJOR MARKET FOR PHARMACEUTICALS AND MEDICAL DEVICES - MOVING TOWARD THE CUTTING EDGE

Japan's ageing society makes it a long-term growth market for pharmaceuticals and medical devices. To foster them as key industries and raise the quality of medical care in Japan, the government is working to eliminate or reduce lag times for new product approval , boost the percentage of generic drugs in the market, and create industrial clusters focused on these areas. This report introduces the measures being taken to bolster the market's internationalization and competitiveness, with expansion in mind, and the activities of foreign companies in the Japanese market.

With pharmaceutical sales of $82 billion in 2008*1 and medical device sales of $22 billion in 2005*2, Japan now accounts for about 10 per cent of the world's health-care market. That ranks it as one of the largest in the world. Next year, domestic pharmaceutical sales are projected to reach $84 - $88 billion,*3 while device sales will climb to about $24 billion*4.

*1. Source: Japan Pharmaceutical Market Sales, IMS 2008
*2. Source: 2008 briefing paper from the Ministry of Health, Labour and Welfare
*3. Source: 2008 IMS Health Forecasts
*4. Source: 2009 report on actual conditions of medical device market issued by the Ministry of Health, Labour and Welfare

National Health Insurance (NHI) price revisions and alterations in the healthcare system notwithstanding, Japan's medical market is expected to continue growing alongside Japan's increasingly graying society. In addition to the generic drug market, growth can also be foreseen in the development of new vaccines, while progress in endoscopic technology, catheter treatments, and other technologies hold promise for the device industry. In addition, advances in manufacturing fields where Japan is already strong—electronics, information technology, textiles—hold out further possibilities for the strengthening of Japan as a base for medical research and development.

With rising demand from patients, medical practitioners and companies for better access to and supply of better drugs and devices, the government is responding and taking in their needs with policies aimed at creating a more attractive market—one that can develop innovative drugs and medical devices and spread them even faster.

Government Policy - Elimination of Lengthy Approval Process

In April 2007, the Japanese government introduced an integrated package called the "5-Year Strategy for the Creation of Innovative Pharmaceuticals and Medical Devices." The plan called for concentrated financing of R&D, development of venture businesses, improving the environment for clinical trials, increasing tie-ups with other Asian countries, speedup and improvement of quality of review, and also an appropriate recognition of innovative products.

Behind this five-year plan is the determination to speedily deliver globally superior drugs, devices, and technologies to Japanese patients and to create an environment that allows product development simultaneously with the U.S. and Europe.

Towards this, the government is working to build prompt and effective assessment systems to measure the innovativeness of drugs and medical devices. This increasingly positive environment encourages foreign companies to place high priority on Japan's pharmaceutical and medical device market and to aggressively bring their cutting-edge drugs, devices, and technologies into this market.

As a part of this five-year strategy, the government has created an action program aimed at reducing lag times for new product approvals. As recommended by Japan's Expert Committee on FDI Promotion, a government-appointed council of advisers, this program focuses on the medical device industry, which is one of the most important from the aspect of economic revitalization, improvement of quality of life and attraction of foreign investment. The health ministry will implement the program from April 2009.

The program is premised on securing the quality, effectiveness and safety of such devices and considering the burdens on companies applying to introduce new products. This includes the bolstering of examination and consultation structures to reduce the time required for approval of new products. One goal is to

Action Program for acceleration of medical devices review process (Accomplish by 2013)

Development period → **Application for approval**

■**Expanding and strengthening consultation resources for applicants**

Increase personnel and training
To increase and train the new-product approval examiners up to 104 by 69 people in 5 years

Increase quality of pre-submission consultation
To advise on the speed up of the development time

■**Clarification of approval standards**
Guideline for the acceleration stability tasting application
Guideline for when clinical study is required

Shorten the time period before application by 12 months.

Review process period → **Approval**

■**Expanding and strengthening the approval framework**

Increase personnel and training

Improve and enhance the approval process
To introduce three tracks review system (brand-new, improved, similar)
To introduce short-term review system like real-time-review
To introduce the pre submission evaluation system like modular-review

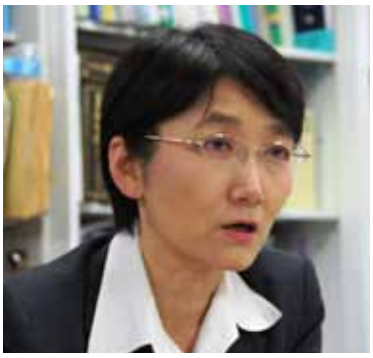
Focus on the high-risk devices' review
To switch over all Class 2 medical devices to a third party certification system

Shorten the time period of review by 7 months.

approval times by 19 months, from the current 33-34 months to about 14-15 months.

To achieve this, the Japanese government is making the necessary efforts by: 1) increasing the number of its reviewers for medical device; 2) clarifying the approval process depending on the degree of novelty (brand-new (SHIN), improved (KAIRYOU), similar (KOUHATSU)) and assigning specialized teams for each section; 3) increasing screening tracks to three from the current one-track process; 4) expanding consultation resources for applicants; and 5) setting the performance goal for each review tracks. Progress in these areas will be reviewed every two years by regulators and industries until desired completion of the plan after five years.

"With this action program, Japan's accelerated approval process for new medical devices will match that of the U.S.," vows Tomiko Tawaragi, director of the Office of Medical Devices Evaluation at the health ministry. While the government has been striving to reduce approval times, the target-oriented program and review process should certainly ensure that. This means global corporations should be able to proceed as quickly in Japan as in the U.S. and Europe with R&D and approvals, and provide products there in no more time and human expense than elsewhere.



Tomiko Tawaragi, director of the office of medical devices evaluation at the Ministry of Health, Labour and Welfare

At the same time, Tawaragi acknowledges that government efforts alone will not be sufficient. Without cooperation from applicants, reducing approval times will remain difficult. Doing so will require that companies submit sufficient and appropriate data in their materials. Then, she suggests, can major progress be made. "As administrators, our vision is to reach consensus with applicants to tackle the five-year strategy and the acceleration program. It is important that we shoulder our burden and cooperate with the private sector in finding points of agreement and going forward with them in a concrete way. Foreign companies that assign superior engineers/technical staff with good communications skills to Japan have been able to smooth approval processes and shorten review times."

Japan Medtronic – Expanding business by development in parallel with the U.S.

Already, one foreign company is eyeing growth in the changing Japanese environment that promotes development of medical devices in parallel with that in the U.S. That company is Medtronic, a leader in heart pacemakers and related products. In January 2009, it started selling a new pacemaker lead, Attain Ability OTW lead 4196, in Japan sooner than in the United States.

The company was founded in Minneapolis, Minnesota, in 1949 by Earl Bakken, inventor of the world's first external battery operated pacemaker. With more than 250 plants, sales offices, labs and training centers employing about 38,000 people worldwide, Medtronic sells and repairs medical devices, supplies various kinds of bionics, and offers pain-relief products to chronic sufferers.

Medtronic's new pacemaker lead, Attain Ability OTW lead 4196

To grasp the needs of Japanese medical practitioners and to deliver new products speedily, the company established Medtronic Japan Co. Ltd. in 1975. Since then it has been providing products to the local market, starting with pacemakers.

"Our aim is to supply state-of-the-art treatment to Japanese clinicians and patients faster," says Takashi Shimada, president of Medtronic Japan. "Until some years ago our introduction of new cardiac rhythm disease management products was slower in Japan compared to other countries. But we have been working hard to achieve simultaneous approvals in the U.S. and Japan by


Takashi Shimada, president of Medtronic Japan

striving for better cooperation with the government and regulatory agencies."

He cites the early introduction of a new pacemaker lead in Japan. "Last spring they were approved at about the same time in the U.S. and Japan, so the difference in product generations between the two countries is disappearing. But the health ministry's approval of the lead came a bit sooner than the FDA's, so we were able to offer it earlier in Japan."

In the process of pursuing simultaneous R&D in the U.S. and Japan, Medtronic was careful to provide for intimate communication between its researchers at the U.S. headquarters and those in Japan, and to help the U.S. side fully understand what kind of information was needed to meet Japan's approval criteria. In creating its R&D roadmaps, the company built organizational structures that took into account the need for efficient clinical testing and approval applications in Japan.

Two months after introducing the new lead to Japan, Medtronic is basking in high praise from both practitioners and patients. Market penetration has been faster than expected, probably because the company was able to address issues related to previous products.

"As a global leading-edge technology, medical devices are bound to become even more competitive," Shimada supposes. "So we are building stronger bases in relatively progressing fields such as cardiac rhythm disease management, including pacemakers, vascular stents and spinal-cord implants. While bringing these new technologies to Japan, we will continue striving to provide them to more local patients." In doing so, he hopes to expand Medtronic's business.

On the other hand, Shimada recognizes that as the term "device lag" suggests, arrival of new technology and devices in Japan still isn't progressing swiftly enough. At the same time, he expects the local market to keep growing. That is because there is still room for growth in fields where Japan lags behind and because Medtronic is challenging previously difficult new technologies such as aortal stent grafts.

"Among developed countries Japan is a huge market and a very important one for us," Shimada continues. "Japanese doctors' demands are quite high, which means we can make an important impact with new technologies and development of competitive products. Beyond the effort we've made until now to cooperate with Japanese practitioners on the development of new products, we will continue to strengthen those activities. What is more, Japan's industrial expanse is broad in high-tech materials, electronics and biology. Through tie-ups with advanced Japanese companies and mutual research with the country's universities I think we will see the emergence of new product development from Japan."

Medical Clusters - Enhancing international competitiveness

Under government leadership, Japan's pharmaceutical and medical device environments have been improving. At the same time, local authorities/governments are making it easier for companies to establish research facilities and concentrate activity in these medical-related industries.

Since 1998, for example, the city of Kobe has been promoting a municipal health-industry plan that already is progressing toward the creation of a leading-edge medical R&D-related cluster. Already established in the cluster are the RIKEN Center for Developmental Biology (CDB), the RIKEN Center for Molecular Imaging Science (CMIS) and the Institute of Biomedical Research and Innovation (IBRI), all of which are conducting world-class research. In all, the cluster has attracted 133 enterprises and organizations from Japan and abroad, including local universities and companies.

Another example is the Boehringer Ingelheim Kobe Pharma Research Institute, which opened a research facility at the Kobe Port Island in November 2008. Its parent, Germany's Boehringer Ingelheim Group, boasts 135 companies and 39,800 employees, ranking it among the world's 20 largest pharmaceutical makers. Its Japan unit has been operating for more than 40 years, and in addition to its globally oriented R&D center in Kobe, it manufactures pharmaceutical products in areas of respiratory, central nervous system, and circulatory in Yamagata prefecture for Japan's domestic market.


The Boehringer Ingelheim Kobe Pharma Research Institute

In order to consolidate its R&D function in Japan and make it more responsive to the market's needs, the company moved its research center from Kawanishi city in Hyogo prefecture to the Port Island business center in the heart of Kobe. The lab now employs about 100 researchers and support staff organized into three main sections—"Molecular & Cellular biology", "Chemistry, Manufacturing and control" and "Pharmacokinetics and Non-clinical Safety". All three groups participate in the company's global research as well as providing goods and services to meet domestic Japanese needs.

"The Boehringer Ingelheim group of companies made a strategic corporate decision to maintain their Pharmaceutical Research

Institute in Japan as an important global R&D site," says Dr. Andreas Barner, chairman of Boehringer Ingelheim. "The site contributes to international research and development activities and reflects the excellence of Japanese scientists in areas of biology and chemistry. We are confident that they will continue to make remarkable contributions."

From here on out, as one of their R&D centers, Kobe Pharma Research Institute conducts research and development activities for drug discovery and non-clinical development for new drug applications, thus contributing to global research and development in every phase. In support of drug discovery activities of Boehringer Ingelheim, Kobe Pharma Research Institute brings forward new target research proposals and provides cutting-edge technology in membrane protein research, enabling assay development for high throughput screening. Utilizing the unique local environment, and in close collaboration with other Boehringer Ingelheim research sites and Kobe Pharma Research Institute contribute to bringing new drug candidates into the Boehringer Ingelheim development pipeline.

"A broad range of research and development institutes which conduct basic research and clinical trials are gathered in Port Island," says Dr. Yoshiki Nishikawa, Director of the Kobe Pharma Research Institute Nippon Boehringer Ingelheim. "This location is an attractive business environment since pharmaceutical companies will profit from highly advanced medical science communities, through which researchers have accesses to leading edge technologies and clinical research. Also, Kobe Pharma Research Institute is conveniently located in close vicinity to a variety of public transportation. Therefore, better collaboration with its headquarters in Japan and global research and development sites is made possible. We are convinced that the inspirational presence of many superior researchers and medical doctors in such a quality atmosphere leads to continuous and substantial research and development achievements."

Sanofi-aventis – Work for Japan

In this improving environment, one foreign company is already expanding its ethical drugs business. That is France-based sanofi-aventis, Europe's biggest pharmaceutical company. With 100,000 employees in 100 countries, the company in 2008 recorded sales of 27.6 billion euros and a net profit of 7.2 billion euros worldwide. Fully 5.1% of its sales came from Japan. Among the biggest contributors are global blockbusters Plavix®, which is proven to help keep platelets from sticking together and forming clots can help protect against future heart attacks or strokes, and Allegra®, a new-generation antihistamine used to treat allergies. In addition, the company hopes to achieve the "double the sales" in Japan within three to four years from 2005.

"The Japanese market is an important one for us," says Patrick Chocat, president and representative director of sanofi-aventis K.K. "With its aging population and high health consciousness there will be opportunities to find new effective medicines with social high needs. To gain approval and introduce new products in this market is a lengthy procedure, but that is changing as globalization progresses. If we can introduce new products more quickly and with better timing, our business should improve."

While Plavix®, Allegra® as well as basal insulin Lantus®, oral anti-diabetic drug Amaryl®, and hypnotic agent Myslee® are driving growth now, the growing need for new drugs suggests that the company's sales will continue to grow. "Our focus therapeutic targets are cardiovascular, thrombosis, oncology, metabolic disorders, central nervous system and internal medicine and vaccine," Chocat explains. "Last April we started selling Clexane®, which is expected to greatly contribute to the prevention of venous thromboembolism and fulfill an important medical need for patients undergoing orthopedic surgery, and should become as big as Plavix and Allegra before long."

Patrick Chocat, president and representative director of sanofi-aventis K.K.

Still, Chocat continues to see characteristic marks. "In Japan, just providing scientific data is not enough to persuade patients and doctors," he observes. "Building a trustful 'person-to-person' relationship is also very important. So we here at sanofi-aventis K.K. have facilitated community-based business and adopted a 'Work for Japan' motto that developing drugs appropriate to the Japanese market based on our global strength. By achieving a balance between efficacy and safety, we can expand our business here by building on more blockbuster products for more Japanese patients."

The government, domestic and overseas companies are working together to create a better market environment for drugs and medical devices. With a population aging faster than in other major developed countries, Japan welcomes development of new drugs, devices, and technologies superior to those being created elsewhere. Creating a healthy market and receiving even more attention as a growth market for interested companies serve as a model for other developed countries.

With market growth and transformation, Japan's pharmaceutical and medical device industries promise a better R&D environment for domestic and overseas companies, and to provide better medication and new technologies for patient treatment. Drawing increasing international attention, the areas are expected to grow to a key industry and become fields with high future growth potential.