Kim Ribbink

The Sun Keeps Rising on JAPAN'S Pharma Industry

Japan's numerous universities and research institutions, cutting-edge research, state-of-the-art technology, and high-quality manufacturing facilities are the hallmarks of a leading market for the pharmaceutical industry.

Japan is one of the world's lead developers of pharmaceuticals and currently the leading pharmaceutical market in the Asia-Pacific. Japan's pharmaceutical market is forecast to grow at a faster pace than other developed markets and will maintain an 11% to 12% share of the global pharmaceutical market, according to Alan Thomas, director of business planning and analytics, IMS Japan.

"As the second-largest prescription market in the world, it is clear why companies are keen to secure a solid position in Japan," says Rohit Sahgal, director Asia Pacific, Ogilvy Health.

Mr. Sahgal notes that key growth drivers for branded pharmaceuticals in Japan include the growing use of chronic high-value innovative treatments driven by an increasingly elderly population, and the high proportion of the healthcare budget spent on pharmaceuticals compared with other developed pharmaceutical markets.

The universal medical insurance system and the National Health Insurance (NHI) official drug price scheme are the distinguishing characteristics of the Japanese market, says Hironao Yazaki, a partner at Ernst & Young based in Tokyo.

Japan has been successful in ensuring that anyone can obtain the medical care that they need whenever they need it, says Yutaka Tsuchiya, executive VP, Eisai.

There is also a significant emphasis by Japanese healthcare professionals on the quality of pharmaceutical products.

"When Japanese doctors select a prescription drug, they place high importance on the safety for patients," says Glenn Gormley, M.D., Ph.D., global head of R&D, senior executive officer, Daiichi Sankyo, and president, Daiichi Sankyo Pharma Development.

An Attractive Market

Among the factors that make Japan a highly attractive market to develop products are its numerous universities and research institutions that undertake cutting-edge research in the medical and scientific field, an abundance of talented scientists, and state-of-the-art technology.

"Collaborative efforts between these organizations, researchers, and pharma companies enable the creation of innovative, new Japan-originated drugs," Eisai's Mr. Tsuchiya says.

Japan has a strong track record on the number of notable drugs discovered, and is the third country next to the United States and the United Kingdom in terms of the number of blockbusters developed.

Moreover, in Japan sales of original products tend to be maintained for some time after the expiry of patents compared with the West, Dr. Gormley says. He adds, though, that generic options and biosimilars will play an increasing role in the R&D process.

"While generic drug usage has been extremely low compared with other major developed markets, it is now on the rise due to promotion measures by the financially strained government," Mr. Yazaki says.

Mr. Yazaki adds that Japan's manufacturing sector meets the world's highest level of quality control.

"Japan is an advantageous country for the commercialization of products given its high income levels, strong awareness of health, and a continually expanding healthcare market," he says.

In addition, while the global pharmaceutical market has been hit with downsizing in most parts of the world, the majority of global pharma companies in Japan have not been so severely hit as they face less risk and exposure in the Japan market compared with other global markets and they have continued to invest strongly in development, Mr. Thomas says.

""This is not the case with Japanese companies that are less well-positioned in the Japan market and only a handful of Japanese companies are truly global players with the top five Japanese companies ranked globally accounting for 90% of all sales for Japanese companies outside of Japan," he says.

> "As the second-largest prescription market in the world, it is clear why companies are keen to secure a solid position in Japan."
>
> **ROHIT SAHGAL** / Ogilvy Health

> "Japan has a very experienced clinical trial system with rigorous standards and excellent quality control."
>
> **DR. GLENN GORMLEY** / Daiichi Sankyo

In terms of government support, the new growth strategy approved by the Japanese Cabinet in 2010 classified the pharmaceutical industry as a "life-innovation-based field and positioned it as one of Japan's growth industries," Mr. Tsuchiya says.

"The Japanese government, in addition to establishing The Medical Innovation Promotion Office within the Cabinet Secretariat as a means of reinforcing the organizational framework under which industry-government-academia work together, aims to maximize the country's strengths in R&D to facilitate the continuous creation of innovative new drugs," he continues.

The Medical Innovation Promotion Office was established in January 2011 as a central body tasked with giving rise to medical innovation that will lead to the creation of Japan-originated pharmaceutical products, medical devices, regenerative medicine, and so forth.

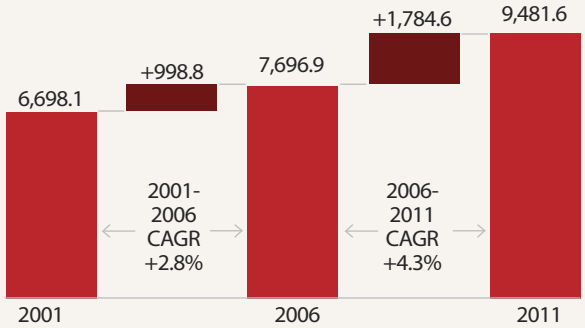
Mr. Tsuchiya was appointed as Deputy Head of The Medical Innovation Promotion Office as a representative of Japan's pharmaceutical manufacturing sector.

While Japan has tended to lag other developed markets in terms of new chemical entity (NCE) launches, with just 44 NCE launches between 2007 and September 2011 compared with 135 NCE launches globally, this has been changing over the past two to three years as a result of several major mergers and acquisitions, Mr. Thomas says.

"Examples include Takeda's acquisition of Millennium and Nycomed and Astellas's acquisition of OSI Pharmaceuticals," Mr. Yazaki says. "Major global re-organizations of R&D activities and enhancing efficiencies are also significant areas of focus post M&A."

Japan Ethical Audited Market 2001-2011

Sales and Absolute Growth (Billion Yen)



Source:IMS Japan, IMSBase JPM (Japan Pharmaceutical Market). Rx only, NHI Price

Global and Local Markets

Many years ago, Japanese pharma companies focused on domestic markets and relied on key strategic partnerships with Western companies to establish a global presence.

Today, several major Japanese pharma companies have developed a true global presence in commercial, manufacturing, and R&D capabilities.

"We certainly consider Daiichi Sankyo the role model for others, and it was among the first of the Japanese-based companies to take this step," Dr. Gormley says. "The global development capabilities of Daiichi Sankyo have been established in Japan, the United States, the European Union, and Asia allowing for efficient conduct of global clinical trials." Furthermore, academic collaborations with leading scientific institutions around the globe have provided a global network of scientific expertise. From this position of strength, Japan-based companies can effectively compete with Western counterparts to bring truly innovative medicines to the patients who need them the most.

Mr. Yazaki says the many small and mid-sized pharma companies that tended to be protected by the stable medical system may be vulnerable in the future

"As a result of the changes in the market, many of these companies are not expected to remain independent in an increasingly competitive market," he says.

Mr. Tsuchiya says with the downturn in growth of pharmaceutical markets in developed countries, Japanese pharma companies are strengthening business infrastructures in emerging markets, which are expected to drive future growth.

Despite its strengths, Japan does face some challenges in the R&D realm.

For example, there could be a more proactive effort to facilitate the coordination and cooperation among three important bodies; industry, academia, and government. For example in the United States, the NIH makes a great contribution to coordinating and supporting biomedical R&D and the support of The Medical Research Council (MRC) in the United Kingdom seems to be quite aggressive compared with Japan, says Tadataka Yamada, M.D., chief medical & scientific officer, Takeda Pharmaceutical Company Ltd.

Experts say that over the past 10 years, most large Western pharmaceutical companies that had a research presence in Japan have closed these facilities, and in their place have established research facilities in China or Singapore, where the governments strongly support and assist pharma R&D activities.

Research Trends

Japanese pharmaceutical R&D, like the rest of the world, is focusing on the highest unmet medical needs.

Dr. Yamada of Takeda notes that there are particularly worrying trends in Japan, including the aging of the Japanese population and the rise of obesity and diabetes.

"These trends emphasize the importance of research into diseases of aging, such as Alzheimer's disease, and the continuing focus on promoting cardiovascular health through

> "With the decreasing feasibility or sustainability of a business model that relies heavily on blockbusters, Japanese R&D is likely to show an increasing focus on key unmet medical needs."
>
> **DR. TADATAKA YAMADA**
> Takeda Pharmaceutical Company

better control of blood pressure, effective treatment of diabetes, and prevention or maintenance of the complications of metabolic syndrome," Dr. Yamada says

Mr. Tsuchiya says the rise in the number of people with conditions such as cancer and Alzheimer's, caused largely by the fact that Japan is the world's most rapidly aging nation, has meant that a growing number of Japanese pharmaceutical companies have started to pursue the development of drug products for these difficult-to-treat diseases in addition to treatments for lifestyle-related diseases, which has traditionally been their main area of therapeutic focus.

"At Eisai, we are making use of cutting-edge technologies, namely stem cell technologies such as iPS as well as -omics technologies, together with genome analysis as we focus our R&D efforts in the fields of oncology, which constitutes an area with high medical needs, and diseases of the central nervous system including epilepsy and Alzheimer's disease," he says.

Dr. Gormley notes that in addition to diseases related to a growing geriatric population, diseases such as heart disease, metabolic disorders, and cancer will certainly be on the rise in Japan.

"For these and other reasons, Daiichi Sankyo is focused on several core therapeutic areas such as cardiovascular and metabolic disorders (CV-M), and oncology," he says.

Jotaro Shinagawa, M.D., head of clinical development, Quintiles Japan, says there is a trend toward investigating products in the areas of oncology; CNS; and autoimmune diseases, such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, and multiple sclerosis.

"Previous nonexistent niche areas include Fabry disease, Gaucher's disease, medical devices, and vaccines," he adds.

With the decreasing feasibility or sustainability of a business model that relies heavily on blockbusters, Japanese R&D is likely to show an increasing focus on key unmet medical needs, even if mega-selling medicines may be difficult to produce in the near future, Dr. Yamada says.

"More Japanese companies have become aware of the importance of using external resources through alliances, in-licensing and M&A, and open innovation among industry and academia," he says. "Takeda is not an exception, and we are now more focused on such therapeutic fields but we are not giving up the challenges in the metabolic fields."

Takeda positions as its core R&D therapeutic areas: exploring immunology/inflammatory diseases; establishing a CNS focus; growing its oncology research; and establishing a presence in metabolic disorders such as obesity and diabetes.

Japan Ethical Audited Pharmaceutical Market 2011 Leading Companies

Rank	Company	Sales*	Absolute Growth	CAGR	Y to Y% 2006-11 %	Market Share
	Total Japan	**9,481.6**	**608.0**	**6.9**	**4.3**	**100.0**
1	Pfizer	575.8	55.7	10.7	1.4	6.1
2	Takeda	559.5	22.3	4.2	4.0	5.9
3	Daiichi Sankyo	480.1	10.4	2.2	1.1	5.1
4	Mitsubishi Tanabe	404.2	11.7	3.0	1.7	4.3
5	MSD	399.8	54.9	15.9	5.8	4.2
6	Chugai	389.2	-2.4	-0.6	4.0	4.1
7	Novartis	380.5	20.2	5.6	4.5	4.0
8	Eisai	374.1	20.0	5.6	7.2	3.9
9	GSK	319.8	72.3	29.2	8.7	3.4
10	Sanofi-Aventis	315.4	30.3	10.6	10.8	3.3
11	Astellas	283.5	-18.0	-6.0	-2.4	3.0
12	AstraZeneca	262.9	13.6	5.4	5.7	2.8
13	Otsuka	259.3	12.8	5.2	5.0	2.7
14	Kyowa Hakko Kirin	220.9	20.7	10.3	3.1	2.3
15	Dainippon Sumitomo	210.4	4.7	2.3	0.3	2.2

Source: IMS Japan, IMSBase JPM (Japan Pharmaceutical Market). Rx only, NHI Price; * Billion Yen

Clinical Research

Ministry of Health, Labour, and Welfare (MHLW) initiatives have expanded the clinical trial network and will continue to do so with the announced plans to establish five new early-stage clinical research centers, with the MHLW injecting 3 billion yen ($35.9 million) into the project.

"Changes to guidelines around clinical research are also being improved and as a result the time it takes to obtain approval for clinical trials has dropped by two-thirds since 2007 to 30 days," Mr. Thomas says.

One of the challenges for clinical research in Japan is the difficulty in recruiting a large number of patients in each medical institute, resulting in high per-patient costs due to insufficient infrastructure of medical institutes for clinical trials, Mr. Tsuchiya notes.

These issues are further exacerbated by the fact that the Pharmaceuticals and Medical Devices Agency (PMDA), Japan's regulatory agency, presupposes that there is a difference between ethnicities, a stance that has long been an issue in regard to trials in Japan as part of global development programs, which has resulted in the delay between Japan and the West (the United States and Europe) in approving drugs.

> **"Japan has an abundance of talented scientists, including chemists, who, in comparison with the United States or Europe, are likely to be employed by the same company or organization over the longer term."**
>
> **YUTAKA TSUCHIYA** / Eisai

"With this drug lag considered a social problem, the Japanese government is taking measures to develop a clinical research infrastructure, including strengthening the regulatory framework and establishing translational research support centers, early-stage/exploratory clinical trial sites, and global clinical research hubs," Mr. Tsuchiya says.

In more recent years, Japan has started to accept global clinical trial data, reducing costs and speeding timelines, Mr. Thomas notes.

"Contributing to moving this initiative forward is the establishment of the Japan–China–Korea clinical triangle," he says. "Evaluation of comparative trial outcomes under the clinical triangle looks promising with all three countries agreeing to begin sharing clinical data."

Japanese Rules and Regulations

The MHLW is in charge of pharmaceutical regulatory affairs in Japan. As the expiration term of many patent-protected brands comes to an end in 2012, Japan, like most of the developed world, has included specific legislation to ensure there is a controlled level of biosimilars and generics in the market. For that purpose, generics have to apply for extended clinical study periods of up to eight years in some cases.

The review period for new drug applications in Japan has tended to lag that of other countries, and the time from application to launch could be as long as four years. However the Japanese government has taken measures to address this problem, and the PMDA has said it is aiming to reduce new drug review times to nine months for priority items and 12 months' total time for standard items by April 1, 2012.

"The Japan regulatory agency has for several years now been taking steps to enhance and improve the regulatory review process and speed for both drugs and devices," Dr. Gormley says "This will provide more opportunity for participation in global clinical trials without any time delay, which is important for patients in need of treatment options. This opportunity will further allow sponsors to submit applications globally at the same time."

With regard to reimbursement, the (NHI) Drug Price List is a list of drugs for which medical providers can be reimbursed under the health insurance programs as specified in the regulations for hospitals and nursing homes covered by health insurance. Over the years, several efforts have been made to improve the discrepancy between the purchase price by medical institutions and the NHI reimbursement price.

The NHI official drug price scheme prohibits the free setting of prices for drugs, a situation that was exacerbated when the NHI official drug prices, which are revised every two years, were recently reduced, Mr. Yazaki says.

However, Mr. Thomas says the April 2010 NHI price review allowed for the trial introduction of the "premium for development of new drugs and elimination of off-label use." Under this system, products were eligible for a lower NHI price cut provided they had been on the NHI price list less than 15 years, had not been discounted more than the market average, and there were no generic equivalents available. In 2010, 337 active ingredi-

Organization and Function of the Ministry of Health, Labour and Welfare

The Ministry of Health, Labour, and Welfare (MHLW) (Koseirodosho in Japanese) was established by a merger of the Ministry of Health and Welfare (MHW) and the Ministry of Labour, on Jan. 6, 2001, as part of the government program for reorganizing government ministries. The MHLW, which was originally established in 1938, has been in charge of the improvement and promotion of social welfare, social security, and public health, and the new organization has the same tasks. It consists of the ministry proper, affiliated institutions, councils, local branches, and an external organization. The ministry proper includes the Minister's Secretariat, 11 bureaus, and the Director-General for Policy Planning and Evaluation. Councils include the Social Insurance Council, Pharmaceutical Affairs and Food Sanitation Council (PAFSC), and other organizations. Affiliated institutions include national hospitals and the National Institute of Health Sciences. Local branches are regional bureaus of health and welfare and prefectural labor bureaus. The external organizations are the Social Insurance Agency and the Central Labor Relations Commission.

The MHLW is in charge of pharmaceutical regulatory affairs in Japan (veterinary drugs are under the jurisdiction of the Ministry of Agriculture, Forestry and Fisheries), and the Pharmaceutical and Food Safety Bureau (PFSB) undertakes main duties and functions of the Ministry: it handles clinical studies, approval reviews and postmarketing safety measures, i.e., approvals and licensing. The Health Policy Bureau handles promotion of R&D, production, distribution policies, and drug pricing, i.e., functions related to pharmaceutical companies. The Pharmaceuticals and Medical Devices Evaluation Center (Evaluation Center) in the National Institute of Health Sciences was established to strengthen approval reviews on July 1, 1997.

To confirm the reliability of reviews and application data, the Organization for Pharmaceutical Safety and Research (OPSR) conducted compliance reviews on application data.

The OPSR also began offering consultation services on protocols at the clinical trial stage. This was followed by the integration of the aforementioned Evaluation Center, OPSR, and part of the Medical Devices Center on April 1, 2004, to form a new independent administrative organization, the Pharmaceutical and Medical Devices Agency (PMDA, KIKO). The role of the PMDA is to provide consultations concerning the clinical trials of new drugs and medical devices, and to conduct approval reviews and surveys of the reliability of application data.

Following this reorganization, the MHLW and PMDA handle a wide range of activities from clinical studies to approval reviews, reviews throughout postmarketing stage, and pharmaceutical safety measures.

Source: Pharmaceutical Administration and Regulations in Japan, March 2011.
For more information, visit nihs.go.jp/mhlw/yakuji/yakuji-e_20110502-02.pdf.

ents received the premium with 367 active ingredients eligible in 2012.

In return for the premium, pharma companies committed to the development of new drugs and additional indications for existing drugs, specifically for products and indications identified by the MHLW.

"The industry estimates for the cost of developing these products was close to 400 billion yen ($4.98 billion), including the cost of PMS programs," Mr. Thomas says. "This increased level of investment in R&D weighed against the premium affected companies very differently depending on the number of products in each of these two groups. However, the improvements around the R&D environment, including use of foreign clinical trials/data, have alleviated some of the concern around this trade-off and may make it easier for companies to develop and launch in Japan."

Adding to this was an overall improvement in median drug approval times in the last two years, which fell from about 22 months to about 15 months through March 2011. Additionally, the approval time for products under priority review has dropped from around 15 months to just more than nine months.

> "Japan is also an advantageous country for the commercialization of products given its high income levels, strong awareness of health, and a continually expanding healthcare market."
>
> **HIRONANO YAZAKI** / Ernst & Young

> "Initiatives that the MHLW has put in place over the last few years have resulted in a far more attractive R&D environment in Japan."
>
> **ALAN THOMAS** / IMS Japan

Promotion

Japan has strict regulations when it comes to defining over the counter (OTC), behind-the-counter (BTC), or prescribed medications.

"With such scheduled classifications, there is an interesting dynamic when it comes to providing patients with the right type of knowledge and empowerment to ask for the right drug/treatment," Mr. Sahgal says. "Communications companies must take a leading partner role in helping improve patient access. With an ever-increasing aging population that is suffering both chronic and acute conditions, there is going to be a heavy burden on Japan's primary-care infrastructure."

Providing the right information to the right patient, when they need it most, can be achieved through an effective combination of public-private partnership with pharma companies, the healthcare fraternity and government, and a responsible innovative method of transferring product and category education, Mr. Sahgal continues.

Going forward, Mr. Sahgal says restrictions on pharma branded DTC communications are likely to stay the same, but more professional guidelines on how education to doctors may be imparted are expected. PV

EXPERTS

GLENN GORMLEY, M.D., PH.D. Global Head, Research & Development, Senior Executive Officer, Daiichi Sankyo, and President, Daiichi Sankyo Pharma Development, a global pharmaceutical company dedicated to the creation and supply of innovative pharmaceutical products to address the diversified, unmet medical needs of patients in both mature and emerging markets. For more information, visit daiichisankyo.com.

ROHIT SAHGAL. Director Asia Pacific, Ogilvy Health, a part of the Ogilvy & Mather network and a WPP company, which provides marketing services, including brand identity and development, clinical trial recruitment, digital/interactive services, direct-to-consumer, direct-to-patient, global integration, managed care marketing, market research and analytics, media planning and buying, medical advertising and promotion, medical education, public affairs and relations, relationship marketing, and strategic consulting. For more information, visit ogilvychww.com.

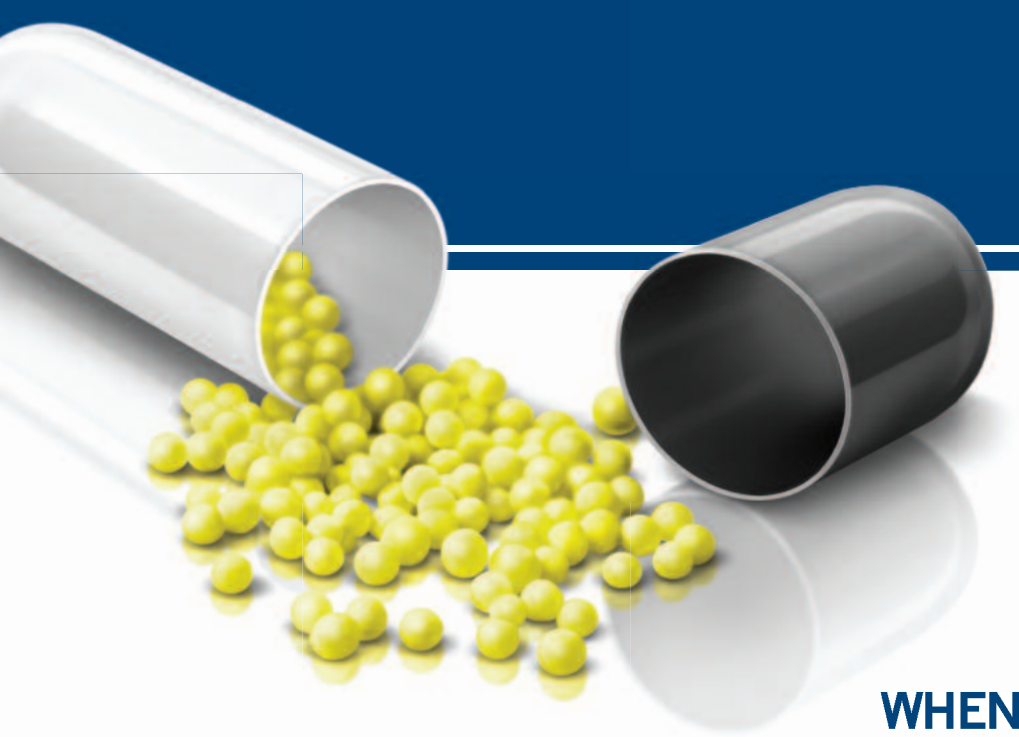
JOTARO SHINAGAWA, M.D. Head of Clinical Development Japan, Quintiles, an integrated bio and pharmaceutical services provider offering clinical, commercial, consulting, and capital solutions. For more information, visit quintiles.com.

ALAN THOMAS. Director, Business Planning and Analytics, IMS Japan, a division of IMS Health, a provider of information services for the healthcare industry, covering more than 100 countries around the world. For more information visit imshealth.com.

YUTAKA TSUCHIYA. Executive VP, Eisai Co. Ltd., a research-oriented, global pharmaceutical company committed to addressing unmet medical needs. For more information, visit eisai.com.

TADATAKA YAMADA, M.D. Chief Medical & Scientific Officer, Takeda Pharmaceutical Company Ltd., a research-based global pharmaceutical company. For more information, visit takeda.com.

HIRONAO YAZAKI. Partner, Ernst & Young Tokyo, a global provider of assurance, tax, transaction, and advisory services. For more information, visit ey.com.



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