Pharma Intelligence
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Key Market Access Considerations For The Asian Market

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Key Market Access Considerations For The Asian Market

Market access is a fluid term but can broadly be described as the set of considerations around getting a therapy to patients on a commercial basis. It might therefore range from measures necessary for meeting local manufacturing requirements, to challenges around policy and regulations, to having an appropriate sales and distribution network in place.

These issues are often particularly pertinent in emerging markets, which may have less developed or ambiguous regulatory frameworks, or unique sets of challenges related to infrastructure or medical care systems. They can also pose proportionately greater hurdles to mid- or small-sized companies, which commonly have a narrower and less well-developed global presence and cannot always rely on direct local resources to elucidate and address problems. But even in some larger markets, major multinationals with an on-the-ground presence can still face challenges.

One high-profile example is China, where despite multiple rounds of positive regulatory reforms over the past few years, new drug legislation still leaves some concerns around intellectual property protection and the use of the marketing authorization holder system. Other outstanding access issues in this huge and growing market include reimbursement and pricing strategy and marketing initiatives in lower-tier cities.

The good news is that there continue to be numerous positive steps taken by regulators in Asia to streamline and simplify requirements to get needed drugs to patients faster. Expedited and conditional review programs and the improved availability of English-language information are just two examples.

In Asia's dynamic and diversified environment, working with appropriate partners to better understand and benefit from these changes remains an important way for companies to ensure their market access efforts are appropriately tailored and optimized, to the ultimate benefit of patients and their business.

We hope the content in this e-book provides some useful insights to this end.

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China's New Pharma Law Leaves Key Questions Unanswered

BY BRIAN YANG

China's newly approved Drug Administration Law (DAL), released on August 26, is the country's most comprehensive legislation governing pharmaceutical affairs ever. It covers many aspects of pharmaceutical regulation, from encouraging innovation to focusing on dynamic inspections and ensuring stable supply of medicines.

The new law, set to take effect on December 1, formally codifies many major initiatives implemented by the Chinese government since 2015, when reform-minded leaders took the reign at the country's regulatory agency. The marketing authorization holder (MAH) mechanism, conditional approvals, compassionate use and priority reviews for anticancer, pediatric and orphan drugs are all now formalized.

There are also notable shifts in regulating and inspecting pharmaceutical manufacturing sites. The new DAL emphasizes more dynamic inspections including unannounced checks to be conducted of pharma manufacturers and distributors. In effect, the new law explicitly notes that both domestic and international drugmakers, as well as their vendors and suppliers, should be prepared for more frequent inspections.

Online Sales Moves

One of the hotly debated issue is whether e-commerce sites should be allowed to sell prescription drugs online. Given the fact that China is the largest market for e-commerce, the opening of such sales could be considered a Pandora's box.

While some suggest the opening up of online drug sales will increase competition in the current situation, where over 80% of drug sales are dominated by hospital pharmacies, leading to a lower cost of filling prescriptions, others see such a move as leading to the abuse and overuse of medicines. The new DAL doesn't outright ban such online sales, except for certain pharma products with high risks and strict use supervision requirements.

"Given the two different views, we incorporated various opinions and decided to use the same standards to apply to both online and off-line drug sales," noted Jie Yuan, director of the Legal Affairs Office on the standing commission of China's National People's Congress, during a press briefing held in Beijing on August 26.

The new DAL leaves regulating such sales to specific rules and regulations to be outlined by China's cabinet, the State Council, and its pharmaceutical regulatory agencies, the National Medical Products Administration (NMPA) and the National Health Commission.

Counterfeits Redefined

Highlighted in the Chinese blockbuster movie *Dying to Survive*, counterfeit drugs is another issue taken up by the new DAL. In the past, unapproved drugs from overseas were broadly deemed to be fake and counterfeit, and the importing of such products, mostly from India, was subject to criminal prosecution.

The new DAL however revises that definition. Now, unapproved imported drugs are not deemed fake, and importing small quantities of drugs that have yet to be approved in China might not be subject to punishment, if the violation is considered to be petty. On the other hand, manufacturing, importing and selling counterfeits are still subject to punishment.

"The change is a response to common Chinese people's concerns," noted Yuan.

Key Questions Unanswered

While the new DAL encourages innovation and shows flexibility over online drugs sales and importation of small quantities of unapproved drugs, there were many issues pertinent to pharma R&D left unanswered, noted Katherine Wang, a partner in law firm Rope & Gray's Shanghai practice.

Key remaining issues include patent linkage and clinical data protection, which have been concerns to many innovative new drugmakers. Despite several rounds of discussions, the essential elements to protecting intellectual property rights are not included in the new DAL.

Whether the new law will provide the same level of flexibility as the marketing authorization holder (MAH) system is another key topic, noted Wang. "Under the new DAL, the MAH system applies equally to imported and domestic drugs," the lawyer said in a August 30 note to clients. Upon approval from the NMPA, the MAH can be transferred from one company to another without changing contract manufacturers.

"These changes could potentially result in a convergence of the bifurcated pathways and enable Chinese MAHs to work with overseas CMOs [contract manufacturing organizations]."

The change will potentially allow more multinationals to divest their non-core assets in China to domestic firms, Wang observed.

New Korean Law On Cutting-Edge Biologics Raises Hopes And Concerns

BY JUNG WON SHIN

The South Korean parliament has passed a new law to support and ensure the safety of novel regenerative medicines and biologics, giving a potential boost to cell, gene and other biological therapies using the latest technologies.

The Cutting-Edge Regenerative Medicine and Biologics Support and Safety Act, which was finalized after repeated delays and modifications, was first proposed back in 2016 as regenerative medicine began to receive the spotlight as a future technology for treating rare and intractable diseases and others that are difficult to address through conventional methods.

The industry has welcomed the new law amid what they see as the need for customized policy, given that companies are jumping into the development of innovative biologics and as biotechnology is advancing rapidly worldwide. It also expects the legislation to help ease worries over the safety of biologics through tougher management of manufacturing and quality control.

Separate Law Needed

The pharma industry has been calling for a dedicated law because of the different considerations required for the approval and safety management of such products versus conventional synthetic drugs. South Korea's current Medical Service Act and Pharmaceutical Affairs Act do not reflect these distinct characteristics.

Cutting-edge biologics for the scope of the new law refers to cell and gene therapies, tissue-engineered products and biotechnology-convergence products (excluding those whose main function is as a medical device) and other therapies that contain cell, tissue or gene components.

The new act, which will be formally implemented one year after passage, aims to more systematically manage biological drugs and support the development of innovative drugs for refractory diseases, and provide new treatment opportunities to patients with rare and intractable diseases, the government said.

It will also enable the country to more systematically deal with new manufacturing and approval processes, reflecting the characteristics of novel products based on living cells, proteins and genes.

Invossa Incident Raises Worries

However, the new law comes amid public and political concerns raised in the wake of the cancellation earlier this year in South Korea of the approval of Invossa (TG-C), the world's first allogeneic cell-mediated gene therapy for degenerative osteoarthritis of the knee, due to a discrepancy in its cell components. *(Also see "Invossa Approval Revoked As Korea Confirms False Data Submission" - Pink Sheet, May 28, 2019.)*

The Ministry of Food and Drug Safety concluded Kolon Life Science Inc. submitted false data to support the approval of the pioneering product and asked prosecutors to press criminal charges against the company.

The incident led to calls for a suspension of any further easing of relevant regulations, which critics believed may have partly led to the Invossa woes. However, the drug ministry had urged the need for a separate cutting-edge biologics law to help step up the safety management of such therapies.

The new law is also in line with South Korea's policy of nurturing the biotechnology sector as a major economic growth engine, and will help the country to become more harmonized with advanced markets such as the US, Europe and Japan, which have implemented separate laws to support the development of innovative biological drugs. *(Also see "Korea Pledges Broad Innovation, Policy Support As It Eyes Global Stage" - Pink Sheet, May 23, 2019.)*

Regulatory Reforms To Help Access

The Ministry of Food and Drug Safety and the Ministry of Health and Welfare expect the new act to provide new treatment options to desperate patients with rare and intractable diseases, and to step up the general competitiveness of the country's regenerative medicine technology.

The ministries intend to reorganize the drug approval and verification system, which has been operating with a focus on synthetic drugs, in ways suitable for the characteristics of cutting-edge biologics, and also beef up drug authorities' approval and review capabilities. Safety management networks will be set up for all stages of product cycles from extraction of cells to final use.

The new law is set to accelerate approvals of novel biologics through fast-track reviews and a conditional approval system. Products will need to meet one of the following conditions to be eligible for accelerated reviews: have no alternative therapies; be for the treatment of serious diseases such as cancer; or be aimed at rare diseases or the prevention or treatment of infectious diseases caused by biological terror attacks or pandemics.

The government says it also plans to draw up a clinical research system like those in major countries to enable patients to receive regenerative therapies for life-threatening diseases. Clinical research will need to go through strict reviews by state committees to determine urgency, safety and efficacy and gain consent from patients. Such treatments would only be administered at health ministry-designated medical institutions and the cost of the clinical research would be fully supported by the state.

The South Korean Centers for Disease Control And Prevention will be designated as the safety management institution to track adverse reactions, keep mandatory records of clinical research, and follow high-risk patients over the long term.

Korea Eases Stock Rules To Help Bioventures Stay Listed, Focus On R&D

BY JUNG WON SHIN

South Korea has revised initial public offering and stock listing management rules to lower the barriers for innovative companies, including bioventures, seeking to go public. The changes are designed to enable such firms to remain listed and focus on R&D and continued growth without having to worry about meeting revenue requirements.

At present, biotech firms that debuted on the Kosdaq market under the special listing systems, which allow companies that don't meet standard profitability requirements to list if they met technology parameters, or allow companies with strong growth potential to float upon a recommendation from IPO lead managers, must meet an annual KRW3bn ($2.6m) revenue requirement five years after listing. If they don't, their stocks will be placed under the supervision of the exchange and face possible delisting.

To meet the requirement, companies have sometimes engaged in other businesses such as beauty or functional health foods, rather than their core new drug development activities, in order to raise sales.

Revenue Requirement Exemptions

Under the new rules unveiled by the Financial Services Commission (FSC), companies won't be placed under the exchange's supervision even if they don't meet the annual KRW3bn revenue requirement, if their combined sales in the last three years exceed KRW9bn.

In addition, companies that are officially designated as "innovative pharmas" by the Ministry of Health and Welfare, or companies that are performing well in the stock market with a daily market capitalization above KRW400bn, will be exempt from the revenue requirements.

To evaluate bioventures' business continuity, the exchange will conduct more detailed reviews that reflect the characteristics of the biotech industry. These will include whether firms possess proprietary technologies, experience in licensing-out deals, multiple pipeline assets and clinical stage projects, experience or plans in co-research or co-development with partners, as well as the past research performance of their core research workforce.

In addition, the country will now allow scale-up companies as well as foreign companies to be listed on Kosdaq using the listing system for special technology entities, which at present only permits local small- and medium-sized companies. Scale-up refers to non-small or medium-sized firms whose average sales in the past two fiscal years rose by more than 20%.

Foreign companies listed under the special technology system will be subject to external audit rules, and will need to receive an A rating or above in technology from multiple recognized rating agencies.

In Line With Government Support

The latest rule changes, which are in line with the South Korean government's ongoing support for the broad bio-health sector, will help many bioventures currently traded on Kosdaq to remain listed without having to worry about raising revenues.

According to local media, 19 bioventures that debuted on Kosdaq under the special technology listing system reported sales of less than KRW3bn in 2018, although it hasn't yet been five years since they floated on the market.

Companies such as Helixmith (formerly known as ViroMed Co. Ltd.), CrystalGenomics Inc., Genexine Inc., Alteogen Inc. and ABL Bio Corp. are "innovative pharmas" designated by the health ministry and whose market capitalization exceeds KRW400bn.

A number of bioventures, such as TiumBio, SCM Lifescience and MedPacto, as well as SK Group's new drug development arm SK Biopharmaceuticals Co. Ltd., are expected to attempt to launch IPOs later this year.

The country first began to actively ease the Kosdaq listing rules in 2015 in line with the government's drive to nurture the biotech industry and boost the number of venture capital-invested start-ups.

In early 2018, the FSC allowed even start-ups with capital erosion and losses to launch IPOs on Kosdaq and raise new funds. The measures also included plans to reinvigorate the creation of funds that invest in venture capital-backed start-ups and companies already listed on Kosdaq, and in low-capital, Kosdaq-listed shares of companies with growth potential. *(Also see "Incentives, Novel Tech Seen Driving Multiple Korean IPOs In 2018" - Scrip, Feb 7, 2018.)*

Takeda Brings Rare Disease Drugs To India But Access Questions Linger

BY ANJU GHANGURDE

Takeda Pharmaceutical Co. Ltd. has introduced a line of products for lysosomal storage disorders in India, signalling early efforts by the Japanese company to dip into the ex-Shire PLC portfolio and step up momentum for the post-merger operation in the country.

Takeda, which completed its $62bn acquisition of Shire in January this year, said that it had introduced idursulfase (available as Elaprase globally) for Hunter syndrome, velaglucerase alpha (VPRIV) for Gaucher disease and agalsidase alfa (Replagal) for Fabry disease on the Indian market.

The launches, the firm said, build on its "heritage and commitment" to India and legacy of providing better health and a brighter future to patients with rare diseases, although it provided no details on how it expects to ensure access to the therapies in the largely self-pay Indian market.

"Losing Patients Regularly"

The international prices of the products are way beyond the reach of most patients in India, and patient groups are pressing for affordable access given that they view mere availability as of little consequence. For example, Elaprase intravenous solution (2mg/mL) is said to cost around $3,282 for a supply of 3mL in the US going by data online, while VPRIV intravenous powder for injection 400 units comes in at around $1,446; *Scrip* could not immediately verify if there have been any revisions to these prices.

Prasanna Shirol, co-founder of the Organization for Rare Diseases India (ORDI), a national organization

representing patients with rare diseases in the country, told *Scrip* that currently there is "no option" for most patients to access these new Takeda/Shire therapies in India.

"We are a losing lot of patients regularly," said Shirol, who is seeking an expansion of Shire's Charitable Access Program for the products to more patients in the country.

On whether innovative financing plans such as equal monthly installment (EMI) schemes could help improve access, Shirol declared: "The treatments are costly and no one can even afford installments." EMI-based schemes typically allow patients to stagger the cost of therapy over a specified period. The annual cost of Elaprase was estimated at around INR4,400,000 ($64,056) for a 10kg patient, going by data in a previous government policy document on rare diseases, which is currently on hold.

ORDI, however, indicated that it was open to suggestions on "creative" financial schemes to be worked out in-parallel by key stakeholders, including insurance companies and bankers.

"At ORDI, we are initiating no-interest or low-interest loans to support families affected by rare diseases," Dr. Harsha Rajasimha, co-founder of ORDI and co-director, Rare Diseases Systems Biology Initiative, George Mason University in Fairfax, US, told *Scrip*. Currently this initiative is understood to be targeted toward emergency medical needs.

Patient numbers for Gaucher/Fabry disease and Hunter syndrome in India could not immediately be verified. Globally Gaucher disease, a rare inherited metabolic condition, is known to affect approximately 1 in 100,000 people in the general population, while nearly 8,000 to 10,000 people worldwide are affected by Fabry. Hunter syndrome is a serious genetic disorder that interferes with the body's ability to break down specific mucopolysaccharides, also known as glycosaminoglycans or GAGs.

Policy Flip-Flop

The Indian access situation for the Takeda/Shire rare disease drugs is further complicated by the overall policy flip-flop for such therapies in the country. In December last year, India said it was keeping in abeyance the National Policy for Treatment of Rare Diseases announced in 2017, dashing hopes for access to a corpus fund with an initial outlay of INR1bn toward financing treatment of rare genetic diseases proposed in the policy.

ORDI told *Scrip* that it is aware that India's ministry of health and family welfare is preparing the rare diseases policy based on the deadline they have from the court. The government had earlier this year sought nine months to come up with a new policy in a hearing before the Delhi High Court; orders in certain previous writ petitions had directed the government to develop a national policy for tackling rare diseases.

"But so far patient advocacy groups have not been called for the consultation meeting; we are hopeful that [they] call us for a discussion to take inputs from patient groups," ORDI's Shirol said.

Shift In Gears?

Pricing and access issues notwithstanding, Takeda's latest launch initiatives could be indicative of a shift in the Japanese firm's overall approach to India following the sealing of the Shire deal.

Takeda's general tone toward this market over the years has been markedly measured compared with some other global peers, and also against the backdrop of its own bullish outlook in 2010, when it first outlined medium- to long-term strategies for business expansion in India.

The Shire deal brought with it a range of on-market products in India, largely in the hematology segment including Advate (rDNA factor VIII), Recombinate (rDNA antihemophilic factor) and FEIBA (anti-inhibitor coagulant complex) and probably now gives Takeda's local portfolio the girth to move at a faster clip. *(Also see "Takeda-Shire In India: Sleeping Giant?" - Scrip, May 21, 2018.)*

Takeda has also recently rejigged some key executive positions in the ICMEA (India, CIS, the Middle East (including Turkey) and Africa) region, where it hopes to sharpen its focus and emerge more agile following the integration of Shire.

Earlier this year, the Japanese firm appointed Andrey Potapov as area head, ICMEA, while another key executive, Taka Horii, who led the NEMEA (Near East, Middle East and Africa) area, was shifted to a new role as general manager for the Middle East. Takeda expects to evolve its operational focus from the NEMEA region to ICMEA as the acquisition and integration of Shire progresses.

The move will reduce complexity within the organization while increasing agility and moving Takeda "closer to the patients it serves," the company said at the time. *(Also see "Takeda Executive Rejig In ICMEA Region As Shire Integration Shapes" - Scrip, Apr 30, 2019.)*

New Indian Public Shareholding Proposal Stumps Pharma

BY ANJU GHANGURDE

India has proposed to increase the minimum public shareholding in listed companies from the current 25% to 35%, jolting large multinational companies such as GlaxoSmithKline PLC, Novartis AG and AstraZeneca PLC that have listed entities in the country.

The proposal, quite a "googly," as one financial expert put it, formed part of finance minister Nirmala Sitharaman's recent budget announcement for 2019-20. If implemented, it would mean that the public float in the Indian arms of GlaxoSmithKline, Novartis and AstraZeneca would need to be scaled up significantly from existing levels with the promoter groups expected to pare down their holding in the listed entity. Zydus Cadila's flagship, Cadila Healthcare Ltd., is the key front-line domestic pharma firm that stands to be affected by the proposed change, besides Alembic Pharma Ltd. and some others.

The public float in GlaxoSmithKline Pharmaceuticals Ltd., Novartis India Ltd., AstraZeneca and Cadila Healthcare Ltd. stood at 25%, 29.32%, 25% and 25.21% respectively as of March 31, 2019. The promoter group (parent and group firms) held 75% in GSK's Indian arm, 70.68% in Novartis India Ltd., 75% in AstraZeneca Pharma India Ltd. and 74.79% in Cadila Healthcare during the period. The public float of peers like Sanofi India Ltd., Pfizer Ltd., Dr. Reddy's Laboratories Ltd. and Cipla Ltd. already meet the new proposed requirements – indeed, some of them surpass the proposed norms by a significant percentage.

"It is [the] right time to consider increasing minimum public shareholding in listed companies. I have asked SEBI [the Securities and Exchange Board of India] to consider raising the current threshold of 25% to 35%," finance minister Sitharaman said as part of her maiden budget announcement.

Pharma Still Assessing Proposal

The government, some reports in the local media suggested, believes that a higher public float could help curb market manipulation, foster an equity culture and aid tax mobilization through capital gains. An estimated 1,000-plus actively traded firms across sectors in India have promoter holdings in excess of 65% and would need to align with the new public float requirements if the proposal is implemented.

High promoter group holdings in cash-rich companies could potentially be reduced via divestments to private investors to meet the new public shareholding threshold, though tools such as follow-on public offers (FPOs) or Qualified Institutional Placements (QIPs) are among the other options that can be deployed.

None of the impacted pharma firms provided any definitive comments on the issue. GSK India *told* Scrip that it was reviewing the budget proposal to "assess the implications," while Novartis said that it was yet to study the detail of the announcement and was hence unable to comment. Zydus Cadila declined to comment on the issue. Some of the other firms could not immediately be reached for a comment.

Proposal Does Not Lend Itself To Greater Liquidity

The government's proposal has, in general, received mixed responses with some experts saying it is positive for minority shareholders and will lead to a better price discovery and corporate governance standards. Public shareholders will typically have a more decisive say in special resolutions, if the new thresholds are implemented, they said.

Others, however, do not see much merit in the proposal and expect some foreign firms with low public float to opt to delist their shares on Indian bourses.

Navroz Mahudawala, managing director of the investment banking and consulting services firm Candle Partners, told *Scrip* that increasing public float does not lend itself to greater liquidity and that most pharma multinational companies are "thinly traded stocks" and it's unlikely a 10% float is going to "dramatically change the scenario."

"The proposal is onerous and may not finally go through," Mahudawala declared.

The investment banker believes that foreign firms may consider a delisting of shares in India rather than meeting the public holding requirements. "This (delisting) is a distinct possibility. These companies' parent shareholders do not require any capital or liquidity," Mahudawala added.

The new public float proposal could also make mergers and acquisitions of listed entities more complicated as acquirers who breach the 65% promoter holding level would need to offload shares in the market.

Mahudawala explained that because of open offer challenges most global acquirers anyway preferred doing deals in private domains as buying a listed company is "cumbersome" from a timeline perspective. "Also, one has limited control on the pricing in case the scrip runs up during the evaluation period. This [the new proposal] would bring in one more area of complexity," he added.

New Japan PMDA Head Brings Strong Clinical, Patient Focus To Role

JAPAN PMDA AIMS FOR SMOOTH REGULATORY FLOW

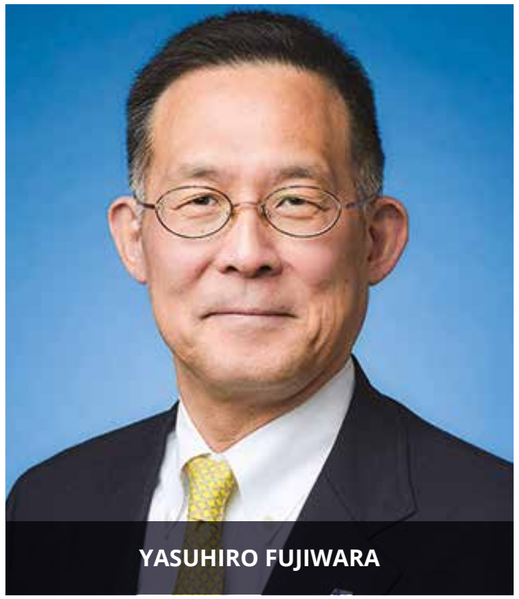
BY IAN HAYDOCK

Dr. Yasuhiro Fujiwara, the new chief executive of Japan's Pharmaceuticals and Medical Devices Agency (PMDA), was clear when asked about the key priorities for his initial five-year tenure. "There are four points as my main goals: patients first, improving treatment access, ensuring safety and building collaboration with Asia."

The cancer clinician took over the position in April, succeeding Dr. Tatsuya Kondo, who had headed the PMDA since 2008 and is now honorary chief executive. Most recently director-general of the Strategic Planning Bureau at Japan's National Cancer Center (NCC) and deputy director for research of NCC Hospital in Tokyo, it is clear Fujiwara will bring a keen clinical focus to the post.

Another major priority under his leadership will be to increase the amount of information that the PMDA releases in English, such as translations of product reviews and regulatory policy, said the medical doctor, himself a fluent English speaker.

Speaking exclusively to *In Vivo*'s sister publication *Pink Sheet* at the PMDA's head office in Tokyo, the chief executive pointed to the importance of the agency's staff – many of which he noted are "quite young" – to take a clinical view as part of their role. "Many of our staff do not have such [clinical] experience but there is a need to understand this and give priority to taking care of patients," he stressed. Fujiwara has had previous stints at the PMDA (former Pharmaceuticals and Medical Devices Evaluation Center) and as a deputy secretary general



YASUHIRO FUJIWARA

at the Office of Medical Innovation within Japan's Cabinet Secretariat, and the *Pink Sheet* interviewed him in his NCC role last year. *(Also see "Master Key Project Aims To Unlock Japan Rare Cancer Drug Development" - Pink Sheet, Oct 4, 2018.)*

Progress So Far

The PMDA and the systems it has introduced since its formation have been central to substantial improvements over the years in key regulatory metrics in Japan. Most notably big reductions in review times under both standard and priority pathways and increased reviewer numbers, cutting the previous "drug lag" there versus the US and Europe. In 2006, the average delay before an approval in Japan was around four years following the first global approval of a new drug, but the country now regularly approves products in parallel with, and increasingly ahead of, other major markets such as the US and Europe.

Another core component of speedier approvals for highly needed new drugs has been the "sakigake" system of expedited review and approval for pioneering or significantly improved new therapies that are being developed in Japan in parallel with or before other countries. This was first introduced on a trial basis in the year beginning April 2015 and has been an important component in closing the previous drug gap.

Sakigake designation confers a variety of benefits including priority consultations, use of a "concierge" to advise and shepherd applications and approval within a total time of six months. In some cases, Phase III results can be submitted after formal submission. So far, around 40 products (including devices) have been awarded the designation, which opens the way to approvals within six months, often much less.

Conditional approvals for new medicine products and conditional and time-limited approvals for regenerative medicine products are designed to ensure early patient access while ensuring safety in actual use and providing the option for products to be pulled from the market if there are any problems.

The agency has been steadily increasing its percentile targets for approval times (as measured by total time from application to approval), and since the fiscal year ended March 2018, was aiming to approve 80% of priority applications within the target nine months, and 80% of standard reviews within the targeted 12 months. It approved 126 new drugs in fiscal 2018, along with 453 partial changes to approved products, 620 new generics, 336 new over-the-counter products and 60 diagnostics and 1,491 quasi-drugs, along with 544 new medical devices.

These targets have been achieved, and Fujiwara commented: "We are on track for targets, and there is really no need to shorten review times further, particularly with the introduction of the sakigake scheme. We are now comparable to, or faster than, the FDA and EMA [European Medicines Agency]." The median approval time for the PMDA in 2018 was 323 days for new active substances, second only to the US FDA's 244 days. Among major global regulatory agencies, the PMDA also had the smallest time differential in 2017 between standard and expedited median review times, another indicator that standard review times have come down. Japan is now regularly issuing first approvals globally for novel products, including in March for AbbVie Inc.'s anti-interleukin-23 antibody Skyrizi (risankizumab).

Fujiwara said that the hope is to increase this number of international firsts, the main emphasis from the PMDA's view being to bring important new therapies to patients as quickly as possible. "We hope oncology will be an important pioneering area, along with rare and inherited disorders and other products for small markets. This is very important for patients."

Staffing Plans

The PMDA's total staff had risen to 936 by April 2019, including some 560 reviewers, and the aim is to increase the overall figure to just over 1,000 in the mid-term and to around 1,065 eventually. "Our main issue is motivation," Fujiwara said. He was not referring to a lack of this, but rather to instill in reviewers and others at the agency that they do their work for what he sees as the "right" reasons.

He stressed the need for reviewers to keep in mind their ultimate purpose of ensuring timely patient access to safe and effective new therapies. "Reviewers, given their position and even though they are young, can sometimes be treated deferentially by applicants. But it is important

they maintain their humility," he stressed.

The new chief executive sees continued staff training and internationalization as important, goals that take on added significance given the ongoing emphasis being given to collaboration with other regulatory agencies across Asia. This takes the form of regular summits, training sessions and staff exchanges, the over-arching goal being to improve regional access to medical products, he said.

He is also particularly proud of Japan's well-developed and "very strong" pharmacovigilance system, which he believes can be a model to help other Asia agencies looking at improving safety, and sees it as a reason why there have been relatively few post-marketing product withdrawals in Japan.

Asia Initiatives

The agency continues to be a strong proponent and coordinator of education and training programs across the region, particularly in countries that might have less developed regulatory systems. The PMDA set up an Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs in April 2016 within its Tokyo headquarters along with an on-site learning facility in Toyama to better coordinate these efforts.

The new center plans, designs and coordinates training programs for regulatory authority staff mainly in, but not limited to, Asia and shares the PMDA's experience with drawing up and applying regulatory frameworks to help build regulatory capabilities and capacity in other countries, through seminars and on-site training. In fiscal 2018, the center provided training to around 267 regulators from 31 countries and regions.

Fujiwara stressed these initiatives are very much about working together with other agencies in Asia, based on local resources and needs, rather than Japan telling them what to do. "We want to enhance communication with each other in Asia, and under the Asia Network meeting, 11 countries talk about key challenges, which we see as very important for the future."

The day after the interview, he was heading to Thailand as part of continuing exchanges with that country. "Southeast Asia is very important – PMDA's [translated] product reviews should be worth referring when they are doing their own reviews, but their resources are sometimes scarce for this," Fujiwara noted.

Every year, 40 product evaluation reports become available in English, and now it adds up to more than 220 evaluation reports available in English as of June 5, 2019. While there are "substantial costs and time associated with this, due to the technical nature of the documents," such materials are proving extremely useful for other regulatory agencies in Asia as they build their own capabilities, Fujiwara noted.

The chief executive noted that the main focus at the moment in ongoing discussions with China and South Korea is for bilateral cooperation. "China is establishing many new regulations," Fujiwara noted. The country's main drugs regulator, the National Medical Product Administration, "recognizes some similarities and accepts some supporting clinical data from Japan, on a case-by-case basis," he added.

As for continuing global regulatory harmonization efforts under the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, Fujiwara said he sees input from academic researchers as an important part of this process. "There are very few clinicians involved in the process, but there is a need for input from that area." The PMDA sees it as key that the ICH process has "a strong patient focus and is practical."

Other Regulatory Priorities

The PMDA is now in the first year of its new mid-term plan, under which Fujiwara said the basic aim is to continue the progress of the past few years in rationalizing requirements. "Our key aims are to address new innovative technology like real-world evidence [RWE], catch up with cutting-edge tech and further strengthen the pharmacovigilance system," he said. "After five or seven years we will review real-world evidence and decide if we can review it as part of regular submissions. There are already some cases of approvals in another country that have used this approach, such as in oncology."

The use of RWE potentially opens the way for the acceptance of single arm, rather than larger randomized, clinical trials as the basis of approvals, Fujiwara noted, given that the RWE and data can effectively act as a control set. "Here again, the importance of a strong pharmacovigilance system is very evident, as is the existing re-evaluation scheme to ensuring safety."

The well-established re-evaluation scheme involves a review of accumulated safety and efficacy data after a set period for marketed products, and forms part of post-marketing surveillance measures. Here too, Fujiwara sees potential for cooperation with Asian counterparts.

Fujiwara revealed that "next year [fiscal 2020] we plan to finalize and publish after expert discussion guidance on how to use registry data to support approval submissions, and we will be launching a new consultation process on registry data utilization and reliability. There have been some political discussions around using such data to support the approval of rare disease drugs and the use of 'synthetic placebos,'" the executive said.

This fiscal year, draft points to consider on the use of such data in regulatory filings and on ensuring data reliability will be developed.

He sees the PMDA as already "well equipped" for the new generation of cell, regenerative and gene therapies, in terms of clear frameworks, pointing again to the central role of strong pharmacovigilance in backing up early approvals.

Following some international criticism of Japan's approval late last year of a stem cell therapy for spinal cord injury – Nipro Corp.'s Stemirac – based on a small non-double-blind trial, Fujiwara's predecessor Kondo mounted a robust defense of the agency's actions. Speaking at a meeting in March, he stressed that "the approval was both conditional and time-limited, and the PMDA was considering the potential benefits to patients with severe injuries."

The product was cleared under the conditional, time-limited approval system and had sakigake status.

Kondo further explained the regulatory approach, adding: "We solicited opinions from experts as part of the [approval] decision, and another point is that the conditional approval requires the conduct of all-patient post-marketing surveillance studies to confirm and ensure safety and efficacy. Also, the approval can be cancelled if the therapy is not shown to be effective."

Looking Ahead

Asked how he would like the PMDA to look in five years' time at the end of his first tenure, Fujiwara said that he would like the agency to "become more international, to provide more materials in English, and to make more global-leading approvals." Rare diseases are becoming an increasing focus of development globally, and the hope is that the new approaches he outlined will enable Japan to take a lead in that field, while the first re-evaluations of pioneering regenerative medicines are also coming up in the next few years.

Another important challenge for the next five years, he stressed, is genomic medicine. "This will be one of the cutting-edge technologies and it is so important for precision medicine in the oncology area." The agency's science board is currently looking at methodologies for risk assessment of products that use genome editing technology. Patient access and safety will remain the key priorities, Fujiwara declared. "We will make our determinations neutrally and based on science, without political influence."

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