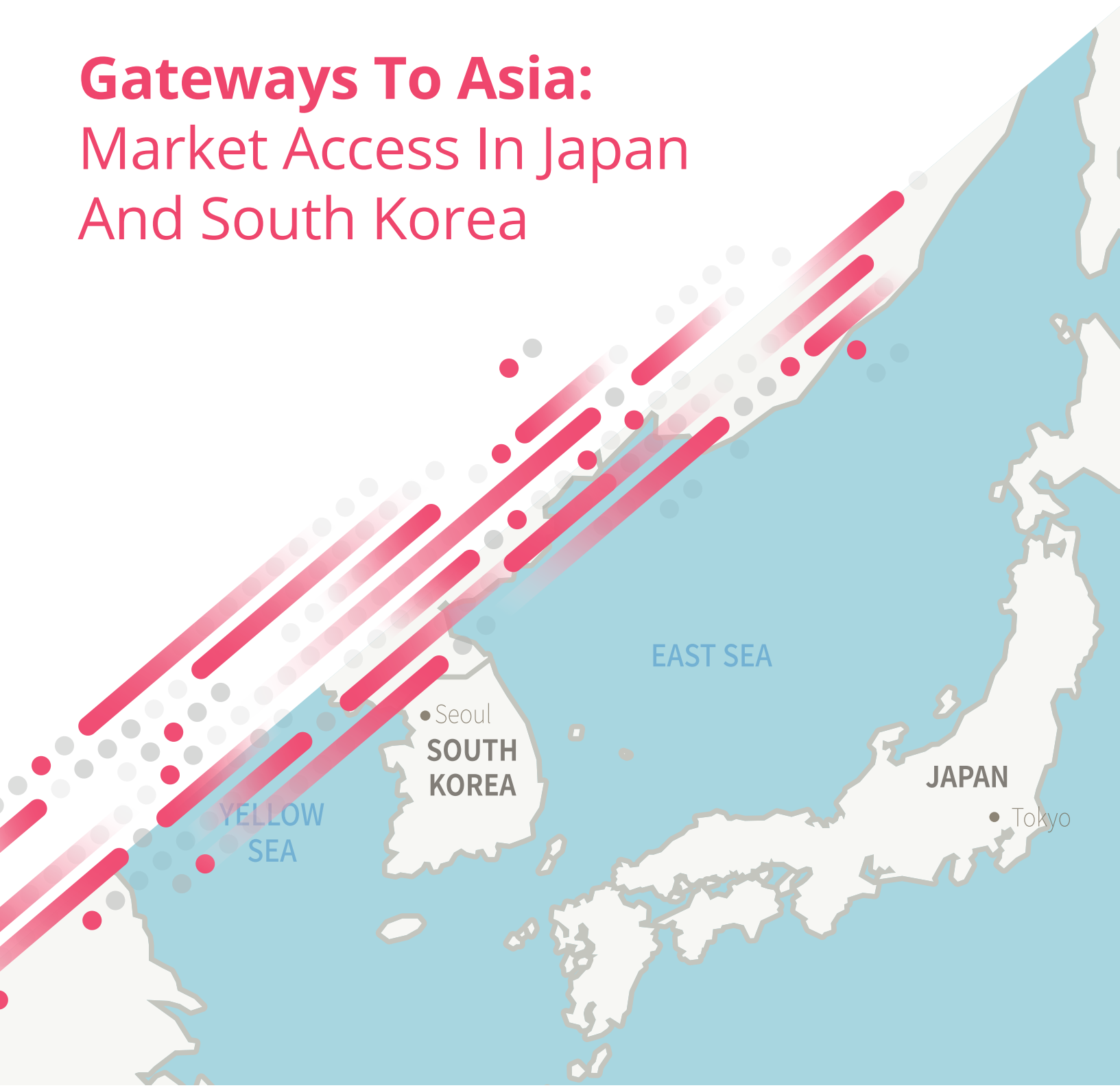
Pharma Intelligence
Informa

Gateways To Asia:
Market Access In Japan And South Korea



POWERED BY PINK SHEET & SCRIP

BROUGHT TO YOU BY CMIC Pharmaceutical Value Creator

Gateways To Asia:
Market Access In Japan And South Korea

Asia offers rich opportunities for pharmaceutical companies seeking alternatives to the mature markets in North America or Europe. Two essential pillars of the region are Japan and South Korea. Both have been progressively opening up to the globalization of the pharmaceutical industry.

That has lowered market access barriers while positioning Japan and South Korea as gateways to more comprehensive expansion in Asia. This white paper addresses recent market access and regulatory developments in the two countries that should be on the radar of any pharmaceutical company scoping out possibilities in Asia.

In the past few years, Japan has eased market access barriers with incentives such as premium pricing and fast-track approvals for innovative medicines, as well as reduced drug-review lags. There have also been new challenges, such as new cost-effectiveness assessment (CEA) criteria for high-volume or high-priced launches.

The most noticeable evolution has been an increasingly consultative attitude to clinical trials. This goes hand in hand with an international outlook favoring Japan's integration into global clinical development programs, rather than relying on sequential local studies.

Japan's Pharmaceuticals and Medical Devices Agency (PMDA) was an early advocate of global studies. Non-Japanese clinical data are also permitted in drug-approval applications. Ultimately, it is for the applicant to decide which clinical data to generate for Japanese approval and where, bearing in mind the need to justify these decisions in new

drug application (NDA) submissions.

Companies are strongly advised to use PMDA's consulting services, even though consultation is not compulsory. The agency will check whether a proposed study complies with the regulatory specifications. It can also give advice on how the study might be improved. Moreover, the consultation process forms part of the product review once the approval application is filed. There are no specific documentation requirements, although usually discussions may include, for example, a draft of the study protocol or investigator's brochure.

Into The Real World

PMDA has also responded to growing interest in real-world data (RWD) as a way to substantiate or accelerate approval applications. As Philippe Auvaro, president and representative director of CMIC Group affiliate OrphanPacific notes, in March 2021 the Ministry of Health, Labour and Welfare (MHLW) issued guidelines establishing a basic policy for use of patient-registry data in approval submissions. For the time being, companies should consult with PMDA before applying this strategy, especially to ensure that the proposed registry will generate reliable enough data to support approval.

In the post-marketing setting, RWD may be used to back up conditional early approvals for new medicines in areas of highly unmet need. In August 2020, the Pharmaceutical Safety and Environmental Health Bureau issued a notification (No. 0831/2) recognizing the difficulty of conducting clinical trials in Japan for serious diseases where few effective treatments are available and patient numbers are small.

If these circumstances mean protracted clinical development, consideration should be given to conditional early approval supplemented by post-marketing surveillance and data analysis, the notification said. Legislation underpinning conditional approvals and *Sakigake* designations (the expedited-approval pathway for first-in-Japan filings of breakthrough therapies) was approved through an amendment to the Pharmaceuticals and Medical Devices Act implemented on September 1, 2020. The *Sakigake* designation also puts more emphasis on collecting and reviewing RWD post-launch.

Innovation And Value

The road to market for novel medicines in Japan has brightened considerably with the introduction of expedited-review and conditional-approval mechanisms, together with substantial price premiums for usefulness, innovation, pediatric indications or *Sakigake* drugs. The trade-off, though, is closer attention to value for money, exemplified by the still-evolving CEA scheme.

Launched in April 2019, CEA applies incremental cost-effectiveness ratio thresholds to newly or already listed products above defined levels of forecast or actual peak sales. CEA evaluations are now part of annual drug price discussions between the MHLW and Japan's Central Social Insur-

"Companies are strongly advised to use PMDA's consulting services, even though consultation is not compulsory. The agency will check whether a proposed study complies with the regulatory specifications."

ance Medical Council (*Chuikyo*). Pre-2021, National Health Insurance (NHI) reimbursement prices were reviewed and revised on a biennial basis.

Chuikyo was expected to discuss the first round of CEA-related price adjustments with manufacturers during April 2021 at the earliest. Following NHI listing, manufacturers of selected drugs conduct independent CEA analyses, based on an agreed framework. These findings are then reviewed by appointed universities and academic institutions. The CEA organization further appraises the data and reports its own findings to *Chuikyo*.

Once appraisal results are approved, price-adjustment proposals go to *Chuikyo's* general assembly, in conjunction with quarterly new drug listings. The panel then decides on the revised NHI prices, to be applied three months after they are announced. CEA-related price adjustments depend on several factors, including the basis (Categories H1 to H5) for inclusion in the scheme and, when the drug's NHI price is determined through a cost-based formula (no comparator drug available), how much transparency there is around manufacturing costs (see translated table below from MHLW website).

Product Categories and Selection Criteria

	Category	Comparator method	Cost-based method	Selection criteria
(i) Newly listed products (to be listed after CEA introduction)*1	H1	Premiums granted*2	Premiums granted*2, or cost disclosure levels below 50%*3	• Peak sales forecast: 10 billion yen or more
	H2			• Peak sales forecast: 5 billion-below 10 billion yen
	H3			• Products selected by *Chuikyo* due to significantly high prices, etc.*4
(ii) Already listed products (listed before CEA introduction)	H4	Premiums granted*2 (irrespective of pricing methods)		• Sales: 100 billion yen or more • Products selected by *Chuikyo* due to significantly high prices, etc.*4
Similar products	H5	Products similar to H1-H4 products		• Drugs for which reference drugs used in pricing are subject to CEAs • Medical devices for which reference products used in pricing are subject to CEAs, and which are in the same "function category"

**1: Even if a product's peak sales forecast does not meet the selection criteria upon listing, it will be selected if it's annual sales exceeds 5 billion yen due to market expansions. In this case, this product will be placed into either "H1" or "H2" depending on the size of its annual sales.*
**2: Products that have received premiums for innovativeness/usefulness (drugs/medical devices), and premiums for improvement (medical devices).*
**3: For medical devices, products that do not carry the breakdown of manufacturing costs apply.*
**4: Products selected by Chuikyo for priority assessments include products with significantly high unit prices, and products that have already gone through the CEA process, but need reexaminations due to new major scientific knowledge obtained after CEAs.*

On March 24, 2021, *Chuikyo* endorsed the appraisal results for Novartis' CAR-T cell therapy Kymriah and GlaxoSmithKline's COPD treatment Trelegy. These two products, the first to go through the CEA process, now face price cuts. Kymriah was priced on a cost basis at around 33.5 million yen in May 2019, putting it in the H3 category of the CEA scheme. A 35% utility premium was reduced to 7% due to Kymriah's low cost-disclosure ratio.

Under CEA rules, low cost-disclosure products granted launch premiums are subject to adjustments not only to the premium portion of their NHI prices, but also to the operating-profit component. On the other hand, since Kymriah targets both pediatric and adult cancer indications (acute lymphoblastic leukemia and B-cell lymphoma), it meets requirements for special consideration in NHI price adjustments.

Price And Value Pressure

While the CEA concept is "still in its infancy" in Japan, "I can hardly imagine it is designed to increase prices," Auvaro comments. CEA comes against the background of a more value-oriented health care strategy, geared to lowering costs while improving efficiency and outcomes. This was outlined in the Japan Vision: Health Care 2035 report, published by the government in June 2015. The vision now needs revisiting in light of the COVID-19 pandemic and the demographic challenges weighing on public finances in Japan, Auvaro believes.

From Cure To Care

Foremost among those challenges is a huge ageing population. The over-75s make up around 20% of the Japanese population and absorb something like 40% of overall health care spending. Having introduced one of Asia's first universal-coverage systems in 1961, Japan has achieved quantitative life extension but at the cost of high demand and poor quality of life in the terminal phase of life, Auvaro says.

That calls for a shift from "cure to care," with more attention to prevention and exploiting digital technologies for health management. All of this has implications, good and bad, for the pharmaceutical industry. On the downside is a risk of more stringent pricing for speciality drugs granted expedited approvals and subject to value scrutiny through CEA.

For example, the three months' grace given to premium prices of CEA drugs following price adjustment may be hard to sustain, Auvaro cautions. At the same time, growing acceptance of RWD as a post-market trade-off for accelerated approvals may give companies an opportunity to demonstrate real-world value as a price-maintenance tool.

The pricing rules are "changing all the time," Auvaro adds. This may reflect to some degree a need to gain more experience in health economics and a shortage of expert input. Only five products have been assessed for cost-effectiveness so far, while health economics is not even studied yet at medical faculties in Japan. The current CEA

methodology does not account for disease burden and makes only very marginal use of QALY (quality-adjusted life year) measurements, Auvaro notes.

He remains confident that innovative companies, particularly those focused on unmet medical needs, rare diseases and novel mechanisms of action, or embracing prevention and "beyond-the-pill" strategies, can ride out these changes. All the same, the burden of proof for health care transformation will continue to grow, Auvaro warns.

The gatekeepers are "creating a lot of new channels and procedures to accelerate innovation," he comments. "At the same time, they are increasing the regulatory requirement for this innovation to come at the fairest price possible."

Lowering Approval Hurdles In South Korea

Some of the trends outlined in Japan are also evident in South Korea, especially the challenges of ageing and a strong commitment to innovation. Probably the most significant changes of late in the regulatory arena were the creation last year of two new units at the Ministry of Food and Drug Safety (MFDS), the Expedited Review Division and the Pre-Submission Consultation Division; and the implementation in August 2020 of the Act on the Safety and Support for Advanced Regenerative Medicine and Advanced Biopharmaceuticals.

The aim of the new MFDS divisions is to shorten review periods for new drug- and biologics-license applications. A separate screening procedure for biologics previously regulated by the Pharmaceutical Affairs Act, but now falling under the advanced biopharmaceuticals act (e.g., cell and gene therapies), should also expedite approvals in this segment, notes Hyesook Park, executive director and head of CMIC Korea.

The concepts of expedited review and pre-submission consultations are not new in South Korea. Under previous arrangements, however, the review targets and procedures lacked clarity and the dedicated review division was deficient. The MFDS now wants to shave 25% off the review period by linking the newly established divisions.

The goal for NDAs is to reduce the review period from the current 120 to 90 working days. Specially designated products, such as therapies for life-threatening or critical diseases, or medicines for preventing or treating large-scale infectious diseases, are eligible for expedited review under the new provisions. Companies can apply for expedited-review status as soon as their preclinical data are available.

While the official review period for new drugs is 120 days at present, in reality the process can take one year or longer, mainly due to handling of additional queries. Even if a drug is not designated for expedited review, though, proactive consultations either before or during submission will ultimately shorten processing time, by reducing the volume and complexity of queries, Park observes.

Gains For Multinationals

The MFDS has also moved to lower hurdles specific to companies entering the South Korean market. For example, approval procedures for new and orphan drugs no longer require submission of a certificate of pharmaceutical product.

Also streamlined is the review process for drug master files. MFDS will now only check whether mandatory drug master file (DMF) requirements are met prior to signing off approvals of drug substances. Technical assessment of DMF data will be left until the drug-product registration comes up for review. This should reduce the DMF evaluation period substantially from 120 to 20 working days, Park says.

One other welcome development for multinationals is amendments to the MFDS' Expanded Access Program (EAP). In the future, companies may import investigational drugs under development in other countries, but not in clinical trials locally, for use in Korean patients under the EAP scheme.

A process has already been established for EAP imports through the Korea Orphan Drug Center, and associated revisions to the Pharmaceutical Affairs Act are in hand. The MFDS is also removing import restrictions on other investigational drugs supplied through expanded access, which should make EAPs a more prominent feature of the market access landscape.

"In the future, companies may import investigational drugs under development in other countries, but not in clinical trials locally, for use in Korean patients under the EAP scheme."

Clinical Trial Focus

Another key focus of South Korea's efforts to facilitate market access has been clinical trials. With its high population density, westernized diseases and world-class health care infrastructure, South Korea is a destination of choice for clinical research. However, growth in local trials has been stagnant since 2012, Park notes. In 2019, the MFDS announced a five-year plan to address this trend. While some elements of the plan are still under development, others are already in place.

The first priority was the safety of trial participants. This included establishing a publicly owned central Institutional Review Board (IRB) and a nationwide support center to protect the safety and rights of patients. The central IRB will review clinical-trial proposals and provide consultation services to IRBs in clinical trial institutes. The support center will provide information on specific clinical trials and input on issues such as informed consent, as well as manage education and public relations.

The MFDS is also simplifying approval mechanisms for investigational new drugs (INDs). It wants to introduce a graduated approval procedure for drugs with a favorable safety profile, with information requirements limited to aspects such as intellectual-property status, selected institutes and IRB approvals. Good laboratory (GLP) data from non-OECD countries such as China are now permitted in clinical trial dossiers, while non-quality issues may be addressed more quickly through amendments.

In conjunction with the new consultation system, the statutory review period for INDs will be shortened from 30 to seven days if elements of the final review, such as safety assessment, are completed at the pre-review stage. Expedited approvals are available for EAP submissions, and can take effect the day they are filed. A central-laboratory hub will be established for analysis of clinical trial samples in South Korea, in another bid to attract multinational studies into the market.

At the same time, there will be more outreach to potential trial participants. With a new information-sharing system now in operation, the public can get reliable advance notice of trials launching in South Korea. This system is mandatory, which did not apply with the previous (and hence neglected) CRiS disclosure system for clinical trials.

INDs And Biologics

These initiatives are having a palpable impact. According to the MFDS, the number of IND applications filed in South Korea rose to 714 in 2019, up by 5.2% from the previous year and by 8.5% from 2017. The country hosted 266 trials in 2019, accounting for 3.25% of all studies worldwide and making South Korea the number eight clinical-trial location globally.

Another clear growth driver in South Korea is the biologics market. This was worth 2.6 trillion won in 2019, up by 16.6% from 2018, with 16.7% of the increase coming from imports. IND approvals for biologics in South Korea tracked consistently at some 200 per year during 2015–2019.

There is also a vigorous export market for biologics, particularly as biosimilars gain traction in other markets. Exports of recombinant products from South Korea totalled US$874.52 million in 2019, of which 68.2% was biosimilars. Currently, three local companies are exporting five different biosimilars between them. One of these, Celltrion's Remsima, is now licensed in 44 countries overall.

Attuned To Globalization

As this overview illustrates, Japan and South Korea are key Asian pharmaceutical markets with market access trends broadly attuned to globalization, even if the emphasis or stage of change may vary. For example, pharmacoeconomic assessment is more advanced in South Korea for newly approved drugs seeking reimbursement under the National Health Insurance scheme.

Pricing in South Korea is also quite strict. Price referencing, both to the same drug in other markets and to comparable drugs on the local market, feeds into the negotiated maximum reimbursement price. Nonetheless, Park views South Korea as an ideal gateway market, citing its large patient pool, well-established universal coverage and high rates of growth, coupled with Western-style medical practice and a disease profile more westernized than in other Asian markets. "Korea would be a very good test location between the Asian and Western markets," Park comments.

Japan and South Korea should be at the forefront of strategic planning for any pharmaceutical or biotechnology company with serious ambitions in the wider Asian region. An experienced in-country clinical caretaker such as CMIC, with a strong foothold in both markets, can be an invaluable resource in determining and executing the right market-access approach.

Pink Sheet
Informa Pharma Intelligence

Scrip
Informa Pharma Intelligence

CMIC
Pharmaceutical Value Creator

CMIC Group is the largest clinical CRO in Japan with a global footprint. CMIC supports trials in 13 countries in the Asia-Pacific region – Japan, China, South Korea, Taiwan, Singapore, Hong Kong, Thailand, Vietnam, Malaysia, Indonesia, Philippines, Australia and New Zealand. It provides end-to-end solutions for drug development, from preclinical testing to clinical trial management, and from manufacturing to sales and marketing. CMIC strategically supports pharmaceutical, biotech and medical device companies entering the Asia-Pacific market.

Please visit our website at **https://en.cmicgroup.com/** to learn more, or tell us more about your current project needs at **https://en.cmicgroup.com/contact/**.