

POLITICS, POLICY & LAW

ACCESS AND INNOVATION IN JAPAN

BY ERIN MCCALLISTER, SENIOR EDITOR

Regulatory reforms have paved the way for innovative therapies to launch in Japan before anywhere else in the world. This should result in earlier access to more innovative medicines than ever before — but only if policies on drug pricing can catch up.

As the [Ministry of Health, Labour and Welfare](#) (MHLW) rushes to implement across-the-board pricing reforms by the start of FY18 next April 1, it has the opportunity to devise a value-based system for breakthrough therapies whose early but limited data make them ripe for novel pricing approaches.

The early signs are this level of regulatory innovation may not be ready to match the ambitions of Japan's drug approval renaissance, but MHLW says it still will be possible to embrace both innovation and affordability.

Japan controls drug spending via a system managed by MHLW's Central Social Insurance Medical Council (Chuikyo), a body that imposes mandatory price reviews — and usually reductions — every two years. First-in-class drugs receive an initial price based on a combination of cost-plus and reference pricing methods and can be eligible for premiums. Until recently these drugs were nearly always approved in the U.S. or Europe first.

Next-in-class drugs with proven benefits over a reference drug, Orphan drugs and drugs approved for some pediatric indications also can receive premiums (see "Japan's Way").

[Ono Pharmaceutical Co. Ltd.](#)'s [Opdivo](#) nivolumab, a breakthrough drug launched first in Japan, showed weaknesses in the system. With no foreign price to use as a reference and an initial approval for an Orphan indication, Opdivo garnered a price tag almost three times that of the eventual U.S. listed price.

As the [PD-1](#) inhibitor added large new indications, spending ballooned by more than 150% that expected

by the ministry, and Chuikyo conducted an *ad hoc* assessment, cutting the mAb's price by 50%.

Now, led by concerns from the Ministry of Finance that other breakthrough drugs could threaten the government's ability to provide comprehensive healthcare for all citizens, MHLW has outlined reforms that could amount to a complete overhaul.

"The conventional pricing system could not sufficiently accommodate the market trends with drugs like Opdivo and the hepatitis drugs, so the challenge we have now is to review and advise on how to provide a sustainable system for everyone," said Masami Sakoi, director of the medical economics division at MHLW's Health Insurance Bureau.

The proposals include annual repricing for all drugs and additional scheduled reviews for drugs that get expanded labels, along with changes to how reference price is determined.

MHLW also will implement a cost-effectiveness assessment that has been in pilot testing.

The ministry told BioCentury any drug could be subject to cost-effectiveness review, though in practice these would likely be limited to high-cost drugs. There may also be changes to the way Chuikyo determines what drugs will be given premium pricing.

Industry groups think a complete overhaul is unnecessary, and fear it would put at risk the progress gained under the Sakigake accelerated approval pathway, which has led increasing numbers of companies to launch in Japan either first, or at the same time as other major markets.

They also say scrapping mechanisms that allow premiums for innovation could make Japan a less attractive place to launch drugs.



THINKSTOCK

The drug developers think a better solution would be to devise a methodology for pricing drugs approved via Sakigake, and to increase the uptake of generic drugs to create headroom to pay for them.

Many of these drugs will come to market with limited data to support their clinical benefit, making them ideally suited to new pricing models such as indication-based or pay-for-performance arrangements. However, MHLW said it isn't yet considering these new models.

Industry will make its case at a May 17 public hearing. More details on the reforms could come as early as July, when the Ministry of Finance releases its FY18 budget framework.

CRACKS IN THE MACHINE

Until recently, Japan had experienced a drug lag: it could take as long as five years for new therapies to reach Japanese patients after being launched in the U.S. and Europe.

But in 2014, Japan's [Pharmaceuticals and Medical Devices Agency](#) (PMDA) announced it would provide priority review and accelerated approval to new breakthrough therapies that could be launched first in Japan. The Sakigake pathway was officially launched in 2015.

Much like [FDA's](#) breakthrough designation, Sakigake designation is given to drugs that show "prominent effectiveness" or "radical improvement" over existing therapies based on preclinical or early clinical studies.

Opdivo did not have Sakigake designation but did receive priority review and was approved for melanoma in July 2014, the first approval of a PD-1 inhibitor anywhere in the world.

Chuikyo used a cost-plus method to calculate Opdivo's price and gave it three premiums: an innovation premium for being first in class; a

pioneering premium for launching in Japan before other markets; and an Orphan drug premium, as melanoma occurs in fewer than 50,000 individuals in Japan.

When it was all totted up, the launch price was ¥729,849 (\$7,007) for the 100 mg dose. Nine months later, when partner [Bristol-Myers Squibb Co.](#) launched the drug in the U.S., the American list price was nearly two-thirds less, at \$2,545.15.

Initially, Opdivo's price had little budgetary effect in Japan. But in December 2015, PMDA approved Opdivo for non-small cell lung cancer (NSCLC), the most common cancer in the country. As total expenditures increased, MHLW invoked the "huge seller" rule it created *ad hoc* in January 2016 to deal with the unexpected increase in spending for HCV drugs. Ono, which markets Opdivo in Japan, South Korea and Taiwan, reported product sales of ¥98.1 billion (\$834 million) for 2016, a 1,343% increase from the previous calendar year.

The rule calls for repricing of drugs with sales that increase 1.5x more than originally expected. Thus, in November, less than a year after the NSCLC indication was added to Opdivo's label, Chuikyo halved the mAb's price to ¥364,924 (\$3,247), putting it more in line with the U.S. published wholesale acquisition cost (WAC).

CHANGE AFOOT

The increased spending for HCV and Opdivo caught the attention of Prime Minister Shinzo Abe. At a November 2016 meeting with the Council on Economic and Fiscal Policy, he said the country needed to rethink its policies for revising drug prices, including transparent policies that reflect a drug's cost effectiveness.

That task has fallen to MHLW.

“Among the goals of the revised system is to achieve sustainability of universal insurance for all and to promote innovation. We must also achieve an improvement in the quality of the medical services that are provided to the people and at the same time reduce the burden borne by the Japanese people,” Sakoi told BioCentury in an interview at MHLW’s offices in Tokyo.

The ministry released a draft reform [framework](#) on Dec. 20, 2016, which includes annual pricing reviews for all drugs. Sakoi said drugs would be repriced if there is a “wide gap” between the price reimbursed by MHLW and the wholesale price, but he declined to quantify how big that gap needed to be.

In addition, the framework stipulates that Chuikyo will review drugs that received expanded labels or had unexpected increases in volume during the previous quarter.

In the English translation of the draft framework, the reforms are described as “zero-based,” which Sakoi said means a “fundamental review of the system from scratch. We will revisit or review the system itself and the entire rules.”

At the BIO Asia meeting in Tokyo in March, Yasuhiro Suzuki, director general of MHLW’s Health Insurance Bureau, said one element of the zero-based review is to ensure innovation premiums are used as intended. “It was intended for truly innovative products, but some

less innovative products are managing to take advantage of it,” he said.

Even the definition of innovation is subject to re-evaluation.

“We have to properly adapt to changes in the market and be able to properly evaluate innovation as the market changes,” Sakoi told BioCentury. “What could be called innovative could potentially be very diverse, and one challenge going forward is how we should evaluate very effective drugs and how that relates to whether it is innovative.”

Even the pioneering premium that would be awarded to Sakigake-designated drugs is open for review, according to Sakoi. “Everything is or will be under review,” he said.

COST EFFECTIVENESS CONUNDRUM

MHLW also proposes to implement cost-effectiveness analysis to set and re-evaluate prices.

Last year, Chuikyo started a pilot for a handful of drugs, including Opdivo and [Kadcyla](#) ado-trastuzumab emtansine for HER2-positive breast cancer. Kadcyla is marketed in Japan by [Chugai Pharmaceutical Co. Ltd.](#), which is majority owned by [Roche](#).

MHLW hasn’t yet reported results from the program.

JAPAN’S WAY

Japan’s current drug pricing system starts with a launch price that is set by the [Ministry of Health Labour and Welfare](#)’s Chuikyo body and is subject to biannual review. The initial price is determined using a complex system that comprises manufacturer costs, foreign prices and a series of premiums intended to reward innovation.

To arrive at a launch price for first-in-class drugs, the Central Social Insurance Medical Council (Chuikyo) starts by adding a 50% margin to manufacturer-reported costs to develop, produce and sell a drug. The agency then adjusts the calculation to ensure the MHLW-reimbursed price is at least 75% but no more than 150% of the average foreign price. The average foreign price includes published list prices in the U.S., the U.K., Germany and France.

For new entrants into existing drug classes, Chuikyo uses reference pricing based on existing members of the class.

First-in-class drugs and new entrants into an existing class are eligible for a clinical usefulness premium if they demonstrate better efficacy and safety than standard of care, a pioneering premium if the drug is first approved in Japan, and premiums for Orphan or pediatric indications.

First-in-class drugs are also eligible for an innovation premium based on a new mechanism of action that leads to clinical benefit, as well as having efficacy and safety that are better than standard of care.

In total, the premiums can add 5-120% for best-in-class drugs, and 50-100% for first-in-class drugs.

Biannual price reviews — which usually result in price reductions — ensure the MHLW-reimbursed prices are no more than 2% above wholesale prices. This benchmark tends to drop as wholesalers try to improve on a guaranteed 2% margin by negotiating aggressively with manufacturers.

A “new drug discovery premium” exempts some drugs from repricing if they have been on the market for less than 15 years and no generics exist. The sponsor also must have drug candidates in development “that could truly contribute to the improvement of medical care quality.” About one-third of branded drugs in Japan have this designation.

For drugs approved in Japan before anywhere else, Chuikyo relies on the cost provided by the manufacturer as well as the forecast market size to set the initial price. At the biannual price review, if the market size has doubled or if annual sales exceeded ¥15 billion (\$136 million), the drug is repriced.

Any drug with annual sales 1.5x more than originally expected also is subject to repricing under the “huge seller” rule that was implemented in January 2016 in response to unexpected increases in spending on HCV drugs. While the rule is intended to be used during the biannual repricing, it’s also been applied *ad hoc* to control some drug costs.

— BY ERIN MCCALLISTER



“THE CHALLENGE WE HAVE NOW IS TO REVIEW AND ADVISE ON HOW TO PROVIDE A SUSTAINABLE SYSTEM FOR EVERYONE.”

MASAMI SAKOI, MHLW

“We are working one-by-one with the manufacturers to obtain the data and analyze it, and then we will have a final comprehensive appraisal,” Sakoi said.

MHLW does not have the resources to analyze cost-effectiveness of all new drugs or all drugs identified for repricing, and does not envision trying to do so.

That does not mean more resources won't be employed, however. “Unless we do this, we will have a significant impact on the medical cost to the country and a significant impact on the fiscal budget — not only medical, but the entire national budget,” Sakoi told BioCentury. “So in order to maintain the soundness of budget and increase the sustainability of medical insurance, this is something that we cannot avoid.”

He added: “The specifics of which types of drugs is to be discussed going forward, but some of the considerations will be the ethical and social factors of the product.”

According to [documents](#) outlining the pilot program, medicines or medical devices for rare diseases and HIV would not undergo cost-effectiveness analysis when the program is fully implemented. Additionally, the documents outline the criteria MHLW would use to determine which new drugs might undergo cost-effectiveness analysis, including therapies that are expected “to have large financial impact, innovation and usefulness.”

According to Sakoi, the ministry has drafted “high-level principles” for implementation of the process, but “the specific details are still being discussed.”

The cost-effectiveness analysis would be conducted by a group of health insurance experts as well as insurer and patient stakeholders, economists and individuals who specialize in cost-effectiveness evaluation.

In the pilot study, MHLW is calculating an incremental cost effectiveness ratio (ICER) based on the quality-adjusted life year (QALY) metric.

In principle, a cost-effectiveness assessment could push prices down or up. “For items with extremely high cost-effectiveness, a higher

price could result from the price adjustment,” Sakoi said, adding it is yet to be determined how cost-effectiveness results would be factored into the drug price calculation.

MHLW also is considering removing the U.S. from the calculation of reference prices or average foreign price, assigning different weights to published list prices in different countries and other options to prevent the U.S. price from skewing the calculation.

“When it comes to the U.K., Germany and France, and we compare the prices in those countries with the Japan average price, it's probably 1.1 to 1.2 times higher in those markets,” Sakoi said. “For the United States, it's 2.6 times higher compared to the Japanese prices, and those are the median values.”

INDUSTRY REACTION

While industry welcomes a more transparent process than *ad hoc* rules and repricings, it is concerned the proposed reforms could undo progress made under Sakigake.

Since PMDA first began describing its plans for Sakigake in 2014, nine non-Japanese multinational companies have launched 13 new drugs in Japan either first or at nearly the same time as other major markets, including the U.S. and Europe (see “First in Japan”).

There are now 10 Sakigake-designated drugs, including two that are in Phase III for indications that are big in Japan. One of these is [Biogen Inc.](#)'s aducanumab, a mAb targeting [beta amyloid](#) for Alzheimer's disease (AD). The other is [Astellas Pharma Inc.](#)'s gilteritinib, a small molecule [AXL receptor tyrosine kinase](#) (AXL; UFO) and [FMS-like tyrosine kinase 3](#) (FLT3; CD135) inhibitor to treat acute myelogenous leukemia. AML is the most common leukemia in Japan (see “Sakigake Pipeline”).

In an emailed response to BioCentury's request for comments on the proposed pricing reforms, Astellas wrote: “The price of medicines should reflect the benefits provided to patients, healthcare systems and society as a whole, and these benefits should be supported by high-quality evidence.”

The pharma added it is working with stakeholders to improve health around the world.

Biogen declined to comment.

Other biopharmas have been moving to integrate Japan as part of their global regulatory strategy, motivated both by Sakigake and the 2010 New Drug Discovery rule's pricing exemption for drugs that do not have generic alternatives. According to a survey of members in PhRMA and the European Federation of Pharmaceutical Industries and Associations (EFPIA), 49% have already filed or plan to file regulatory applications simultaneously in Japan, the U.S. and/or Europe (see "Filing in Japan").

"PMDA has spent a lot of effort to hire reviewers and to expedite the process for drugs and medical devices. They have really pushed for innovations. However, this movement now is completely going against that," said Ray Fujii, managing director at healthcare consultancy L.E.K.'s Tokyo office.

Patrick Branch, life sciences principal at L.E.K., noted an undisclosed client is considering aborting plans to launch in Japan at all.

"They are developing an innovative therapy for a high unmet need," Branch said. "Coming in, the client thought that the pricing might be more favorable in Japan, but now with the proposed reforms, they're starting to view the business case less favorably and this may not justify launching the drug in Japan."

"The proposals are potentially much more stringent towards innovative products and we're concerned that it could reverse the last five years or so of progress and the fact that Japan has become a much more attractive place for drug development," said Joseph Damond, SVP of international affairs at BIO.

He is concerned, for example, that an exemption from repricing, provided under the New Drug Discovery rule, "could be undercut with some open-ended review to reassess a product's innovative value."

PhRMA would like to see MHLW focus on faster uptake and greater penetration of generics, which could create enough headroom to pay for innovative new therapies covered by the New Drug Discovery rule.

Patients in Japan are generally hesitant to switch to generics from off-patent branded drugs, which are called "long-listed" drugs in Japan. Long-listed drugs can cost up to 15% more than generics.

Other industry representatives told BioCentury MHLW should develop new policies to handle drugs like Opdivo, rather than overhauling existing policies they think are working well.

"The system works well and the amount spent on pharmaceuticals in Japan has been stable," said Amy Jackson, PhRMA's Japan representative. "While a few new innovative drugs have posed a challenge for the current system, we should work together to fix these anomalies," she told BioCentury.

Reed Maurer, president of consultancy International Alliances Ltd., thinks that is exactly what will happen.

"I don't think there's going to be a wholesale revamp because the system actually works pretty well. I think the focus is going to be on how to deal with these outliers like Opdivo," he said.

FIRST IN JAPAN

Since Japan's **Pharmaceuticals and Medical Devices Agency** (PMDA) introduced the Sakigake accelerated approval pathway, more multinationals have chosen to seek approval in Japan before or at the same time as the U.S. or Europe. According to PMDA's data, since FY12, 13 drugs with non-Japanese multinational sponsors and "new active ingredients" have received their first approvals in Japan. Nine were approved in or after FY14, when PMDA began to implement Sakigake. **Bristol-Myers Squibb Co.** (NYSE:BMS) has had the most, with three first-in-Japan approvals in or after FY14. PMDA's fiscal year begins April 1. (A) First approval worldwide for the new active ingredient beclabuvir and the three-drug combination; (B) Sponsored by **Chugai Pharmaceutical Co. Ltd.** (Tokyo:4519), which is majority-owned by **Roche** (SIX:ROG; OTCQX:RHHBY); (C) PMDA simultaneously approved an NDA for tofogliflozin from **Kowa Co. Ltd.**; (D) EC approved Seebri Breezhaler on the same day; *Source: PMDA; BioCentury analysis*

Company	Drug	Indication	Date
Alexion Pharmaceuticals Inc. (NASDAQ:ALXN)	Stensiq asfotase alfa	Hypophosphatasia	7/3/15
Bristol-Myers Squibb Co. (NYSE:BMS)	Ximency daclatasvir / asunaprevir / beclabuvir (A)	HCV	12/19/16
	Daklinza daclatasvir	HCV	7/4/14
	Sunvepra asunaprevir	HCV	7/4/14
Johnson & Johnson (NYSE:JNJ)	Sovriad simeprevir	HCV	9/27/13
Merck & Co. Inc. (NYSE:MRK)	Marizev omarigliptin	Type II diabetes	9/28/15
	Vanihep vaniprevir	HCV	9/26/14
Mundipharma International Ltd.	Mundesine forodesine	T cell lymphoma	3/29/17
Novartis AG (NYSE:NVS; SIX:NOVN)	Cosentyx secukinumab	Psoriasis	12/26/14
	Seebri Breezhaler glycopyrronium bromide	Chronic obstructive pulmonary disease	9/28/12 (D)
Novo Nordisk A/S (CSE:NOVOB B; NYSE:NVO)	Tresiba insulin degludec	Type II diabetes	9/28/12
Roche (SIX:ROG; OTCQX:RHHBY)	Alecensa alectinib (B)	Non-small cell lung cancer (NSCLC)	7/4/14
Sanofi (Euronext:SAN; NYSE:SNY)	Apleway tofogliflozin (C)	Type II diabetes	3/24/14

In the end, Maurer thinks new Sakigake drugs may not get prices as high as Opdivo's, but that the prices will still be high enough to keep companies interested in launching new drugs in the country first or simultaneously as the other major markets.

"Japan will continue to reward innovation. I don't see any effort to discourage or not reward it," he told BioCentury.

"There are many different initiatives underway at MHLW, PMDA and AMED to get new ideas from the lab bench to patients as soon as possible so premium prices for innovative drugs are not the only incentive to develop drugs in Japan at least simultaneously as in the U.S. or Europe," Maurer added.

Japan's Agency for Medical Research and Development (AMED) has been likened to NIH and was established in 2015 to drive basic research and foster translation of home-grown research.

"I do not know anyone in Japan who expects a return of the drug lag," Maurer concluded.

One way to address the outliers would be to implement value-based pricing. Such schemes would help align payment for breakthrough drugs that come to market with smaller data sets with the real-world benefits they provide. But they aren't part of MHLW's near-term plans.

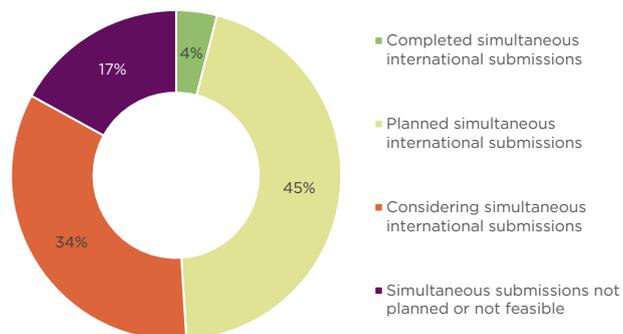
"We are aware that some countries are trying to test or have introduced new pricing models already and, in Japan, we will continue the discussion as we observe what's happening in these other countries," Sakoi told BioCentury.

Japan does have at least one model for performance-based reimbursement — for rehabilitation services. MHLW calculates

its payment to hospitals based on improvement in functional independence, a measure of disability that includes how much assistance is required for the individual to carry out activities of daily living.

PLANNED IN JAPAN

In a survey of 28 member companies, PhRMA and the **European Federation of Pharmaceutical Industries and Associations (EFPIA)** found that just under half had either submitted or planned to submit an NDA in Japan within three months of submission in another territory such as the U.S. or Europe. Another third of the companies were considering simultaneous submissions. *Source: PhRMA/EFPIA*



SAKIGAKE PIPELINE

Japan's **Pharmaceuticals and Medical Devices Agency (PMDA)** has granted Sakigake designation to at least 10 pharmaceutical products. The accelerated approval pathway is intended to halve review times for breakthrough drugs that could launch in Japan before any other market. The pathway can also be used for new indications or new formulations for previously approved drugs. Opdivo nivolumab from **Ono Pharmaceutical Co. Ltd.** (Tokyo:4528) and Keytruda pembrolizumab from **Merck & Co. Inc.** (NYSE:MRK) are approved in Japan for other indications, and **Nobelpharma Co. Ltd.** markets an oral formulation of sirolimus to treat lymphangioleiomyomatosis, a rare lung disorder. The table excludes regenerative medicine products. *Source: PMDA, company websites*

Company	Compound	Indication	Japan status
Astellas Pharma Ltd. (Tokyo:4503)	Gilteritinib	Acute myelogenous leukemia (AML)	Ph III
Biogen Inc. (NASDAQ:BIIB)	Aducanumab	Alzheimer's disease (AD)	Ph III
Merck & Co. Inc. (NYSE:MRK)	Keytruda pembrolizumab	Gastric cancer	Ph III
Nobelpharma Co. Ltd.	Sirolimus topical gel (NPC-12G)	Angiofibroma in tuberous sclerosis	Ph III
Shionogi & Co. Ltd. (Tokyo:4507)	S-033188	Influenza	Ph III
Sanofi (Euronext:SAN; NYSE:SNY)	Olipudase Alfa	Acid sphingomyelinase deficiency	Ph II/III
Daiichi Sankyo Co. Ltd. (Tokyo:4568)	DS-5141b	Duchenne muscular dystrophy (DMD)	Ph I/II
Nippon Shinyaku Co. Ltd. (Tokyo:4516)	NS-065/NCNP-01	DMD	Ph I/II
BioCryst Pharmaceuticals Inc. (NASDAQ:BCRX)	BCX7353	Hereditary angioedema	Ph I complete
Ono Pharmaceutical Co. Ltd. (Tokyo:4528)	Opdivo nivolumab	Biliary tract cancer	Ph I

MHLW said that it has been meeting with industry to get feedback on the proposed reforms and will have a “detailed” action plan by year end.

In the meantime, Chuikyo will hold an open public comment session in May where industry stakeholders, including groups like PhRMA expect to voice some of their concerns.

“The sustainability of nationwide insurance and the promotion of innovation are compatible,” Sakoi told BioCentury, reiterating that the reforms will promote innovation while meeting its other goals, including the provision of high quality healthcare. 

Bristol-Myers Squibb Co. (NYSE:BMJ), New York, N.Y.

Chugai Pharmaceutical Co. Ltd. (Tokyo:4519), Tokyo, Japan

European Federation of Pharmaceutical Industries and Associations (EFPIA), Brussels, Belgium

Japan Agency for Medical Research and Development (AMED), Tokyo, Japan

Ministry of Health, Labour and Welfare (MHLW), Tokyo, Japan

Ono Pharmaceutical Co. Ltd. (Tokyo:4528), Osaka, Japan

Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan

Pharmaceutical Research and Manufacturers of America (PhRMA), Washington, D.C.

Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

U.S. Food and Drug Administration (FDA), Silver Spring, Md.

COMPANIES AND INSTITUTIONS MENTIONED

Astellas Pharma Inc. (Tokyo:4503), Tokyo, Japan

Biogen Inc. (NASDAQ:BILB), Cambridge, Mass.

Biotechnology Innovation Organization (BIO), Washington, D.C.

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