

# New Realities of Drug Pricing and Access in Japan



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# Overview

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Japan's drug pricing system is changing. The market is moving away from a system that has historically provided relatively favorable pricing and access to one that is likely to be more value-oriented and restrictive. The lack of a cohesive vision directing this change is creating growing uncertainty among companies doing business in the country. In this special report, L.E.K. Consulting summarizes the issues, proposes possible future states and highlights imperatives for the pharmaceutical industry to adapt to the changing reality of the Japanese market.

*Editor's note, the situation is rapidly changing and the following report is based on the situation as we saw it in late January/early February 2017.*

For decades, Japan has been a stalwart market for both international and domestic pharma companies. While the attractiveness of many markets elsewhere has been battered by pricing and access pressures, Japan's healthcare system generally



has provided manufacturers with a somewhat favorable and predictable pricing and access environment. This, combined with Japan's large population and relatively accessible physicians, has made it a key market for most companies.

However, Japan is by no means immune to the financial pressures facing healthcare systems in other major markets. Japanese policymakers, just like their counterparts in the EU and the U.S., are searching for ways to "bend the cost curve" and steer healthcare finances onto more sustainable footing. The recent launch of several highly innovative, expensive drugs is seen to have put further pressure on finances while exposing flaws in Japan's

drug pricing system. These dynamics, combined with a sense that Japan pays too much for drugs, have resulted in substantial and in some cases unexpected changes to Japan's reimbursement system. These changes in turn are prompting pharma companies to revisit fundamental assumptions about the attractiveness of the market.

Looking forward over the near-term horizon, we expect further pressure to mount on Japan's pricing system and further modifications (rather than wholesale change) to the pricing status quo. We expect these changes to potentially include more "one-offs" similar to the Opdivo (nivolumab) case; more frequent repricings; the introduction of more restrictive prescribing guidelines around high-cost drugs, as was abortively seen with Taltz (ixekizumab); and other tweaks to existing rules as policymakers struggle to manage growing demand, the launch of more costly therapies and finite resources. Innovative, transformative drugs may end up bearing much of the impact of additional change. These changes, if executed in an ad hoc fashion, add to growing market uncertainty, which in turn will further complicate investment planning and potentially jeopardize patient access to innovation.

Over the longer term, given the inadequacy of the status quo and signals from many stakeholders, we expect Japan's pricing system to undergo more substantive reform. While it is hard to say at present what the future "steady state" will look like, we expect it to contain the following elements:

- Measures that allow for better alignment of drug pricing with clinical and economic value, most likely through the introduction of health technology assessments, to more rationally inform pricing decisions for innovative and potentially high-cost therapies
- Stronger restrictions on prescribing, with guidelines permitting use only in indications and patient segments where value — clinical and, increasingly, economic — is demonstrable
- Greater pricing and access pressure on therapies that add little to the standard of care, resulting in a small pricing and (potentially) volume opportunity for "me-too" and long-listed drugs
- A departure from Japan's existing rigid rule-based approach to pricing, in favor of access to a system that is more flexible and pragmatic (perhaps akin to France's)

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Despite the prevailing uncertainty and the clear impulse to reduce pharmaceutical spend, we believe that Japan will remain a relatively attractive market from a pricing and access standpoint when compared with many other healthcare systems. Notably, the government remains committed to both broad, world-class access for its population and Japan's strategically important pharma industry; these two factors should moderate the extent of change.

The near-term uncertainty and the potential for material reform over the longer term present several imperatives for pharma companies doing business in the Japanese market. The game is clearly changing, and for individual companies as well as the industry as a whole, there is a need to adapt. The following points summarize key initiatives that pharma companies and the overall industry should consider in order to best navigate Japan's evolving price and access landscape:

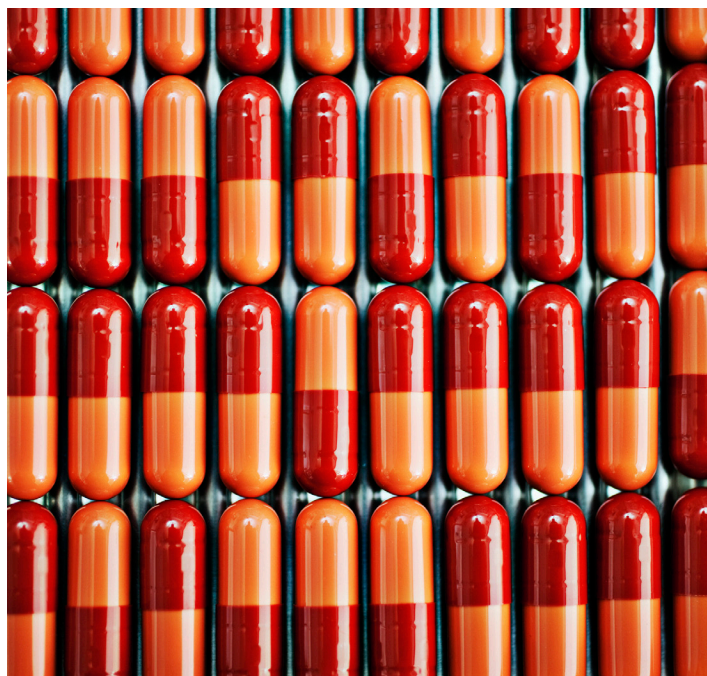
#### 1. From a business planning perspective:

We recommend that companies develop a thorough understanding of recent and ongoing changes in the pricing landscape, and also develop a view on the near- and longer-term future state, to inform assumptions guiding business and investment planning. Companies should develop scenarios that reflect what the future state may look like (i.e., what new rules may or may not be introduced, under what timelines, with what degree of certainty) rather than rely on a single perspective. Companies should then use this deeper understanding to identify drugs within their portfolios that are at risk in either the current or the future state, to examine the commercial implications of this risk and to adjust business plans accordingly, so they reflect the impact of potentially more modest pricing and/or increased pricing uncertainty.

#### 2. In terms of pricing and market access:

In the immediate term, first pricing and access teams should adjust their philosophy to reflect Japan's "new normal." Pricing strategies such as that pursued for Opdivo will likely be viewed as egregious going forward and are thus ill-advised, perhaps with the exception of orphan-and rare-disease drugs. Despite Japan's rules-based system, there is flexibility to pursue conservative price points that are more sustainable for both the system and individual patients; such strategies may be applauded by prescribers and rewarded with share. Second, pricing and access teams should review

their portfolios and identify brands that may prompt material concern and interventions from policymakers. Companies should strive to anticipate any such challenges; pre-empt concerns as best they can through proactive discussion with the Ministry of Health, Labour and Welfare (MHLW); and consider what the best tactical response may be in the event that the MHLW takes an aggressive stance. Companies may need to adopt a more transparent approach to how they communicate the full commercial potential of their drugs during pricing discussions with the MHLW, including deliberate discussion of additional indications and the full expected budgetary impact.



Toward the longer term, pharma companies should anticipate greater use of HTAs (health technology assessments) and higher evidence thresholds to support pricing and access. Companies should begin to (a) develop in-house healthcare economics expertise; (b) consider how to best design prospective studies with the changing Japanese context in mind, to support successful launches (e.g., carefully consider which patient segments to include in trials, incorporate endpoints that will support a compelling clinical and economic value proposition, collect real-world data that best illustrates value); (c) develop compelling value dossiers to support

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pricing discussions; and (d) identify how to collect real-world data and develop retrospective analyses to better support the value proposition of in-market brands. Furthermore, we believe that the shifting landscape may present opportunities for companies to differentiate in the eyes of payers and thus achieve preferential access. Companies that can collect and analyze real-world data may be able to pursue risk-sharing deals that position their drugs favorably versus less capable competitors.

### 3. From an advocacy perspective:

In the immediate term, first, there is a need to challenge the shift to ad hoc rule changes and to highlight how uncertainty can jeopardize investment decisions and thus impact patients, companies and the Japanese economy. Second, advocacy bodies should seek to negotiate measures from the government that may offset the business impact of lower pricing and greater uncertainty (e.g., more flexible trial requirements). There is also work to be done to improve the industry's standing among pricing stakeholders and the broader public. Recent debates unduly "discount" the value of

innovation and often ignore the investment and risk incurred in bringing innovation to market. *(Note: We understand advocacy bodies are already pursuing these routes.)*

Toward the longer term, we encourage the industry to proactively engage with other stakeholders in the healthcare system to shape the future state and ensure innovation is rewarded and access is not compromised. We believe the pharma industry is in a unique position to articulate the various benefits and drawbacks of the globe's various pricing systems, as well as to understand Japan's unique needs. The industry is well-placed to propose a vision for the future state of pricing and access in Japan, and we recommend that pharma take an active lead in driving the debate in a productive direction.



# Background on financial pressures facing the Japanese healthcare system

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The introduction of Japan's universal healthcare system in 1961 coincided with the beginning of nearly three decades of rapid economic growth and Japan's emergence as a leading global economy. The underlying promise of the Japanese system has been and still is to provide world-class healthcare to its citizens. The outcomes produced by the system (most notably longevity, with the average Japanese person long enjoying life expectancy significantly in excess of American and European counterparts) have resulted in the prevailing view of Japan's healthcare system as being among the best in the world. On a percentage-of-GDP basis, expenditures are broadly in line with those in Western European markets, despite a diffuse delivery infrastructure and a largely fee-for-service reimbursement system.



Japan's healthcare system, when compared with other markets, has generally been kind to pharma. The underlying market is large (its population is one-third that of the U.S.) and aging, resulting in growing demand for drugs treating complex conditions such as cancer, diabetes and Alzheimer's disease. Unlike in the EU and (increasingly) the U.S., considerable discretion remains in the hands of prescribers. Prescribers also remain relatively accessible to drug companies when compared with other major markets.

From a reimbursement perspective, pricing levels are typically second only to the U.S., with manufacturers facing little of the scrutiny and risk of exclusion from the market that has dogged their subsidiaries in the EU and that may soon become the norm in the U.S. Until fairly recently, incentives designed to drive generic substitution for off-patent brands have proven ineffective, with

both clinicians and patients distrustful of generics and insensitive to the financial benefits of generics. Given that, product life cycles have tended to far exceed patent life.

To be fair, Japan also presents challenges: Pharma companies addressing the Japanese market have until recently been saddled by local clinical data requirements and ponderous regulatory decision-making, resulting in launches several years after those in the EU and the U.S. Foreign manufacturers have faced cultural barriers, limiting their ability to scale in the market without considerable investment. While access to physicians is favorable, these same physicians are widely dispersed, thus requiring sizable and costly commercial organizations. And pricing decisions, while ostensibly formulaic, are ultimately made behind closed doors. Nevertheless, Japan is a key market for pharma companies — both local and foreign — and a major contributor to sales and profitability. Moreover, its challenges have generally proven to be predictable and thus manageable.

However, as with other major markets, Japan faces the compounding challenges of an aging population, growing demand for healthcare, increasingly sophisticated yet costly healthcare, and a shrinking workforce and tax base. Sprawling, economically inefficient healthcare delivery and an archaic reimbursement system are further exacerbating the situation. As a result, healthcare expenditure is growing at a rate that is believed to be unsustainable over the mid- to long term, and thus there is a clear imperative for measures to better manage costs.

The MHLW is exploring a range of reforms to reduce costs and improve system efficiency, including delivery infrastructure rationalization, payment system reform and efforts to enhance IT infrastructure. However, these initiatives are long term in nature and, in the case of reform of the delivery and payment system, politically difficult to implement. When compared with other possible levers that could generate savings, pharmaceutical pricing is an "easier" target: Not only do drug price cuts "move the needle" in terms of overall healthcare expenditures, but from a political perspective, pharma is a far easier target for cuts than are funds going to doctors or hospitals. From a "moral" perspective, pharma is widely viewed as a deserving victim of the government's efforts to manage healthcare costs.

# Overview of recent drug reimbursement upheaval in Japan

There have long been grumblings among pricing stakeholders regarding the high prices paid by Japan relative to other markets. As in many other markets, the recent launch and subsequent rapid uptake of Sovaldi put considerable pressure on payers and created considerable alarm, despite the drug's intuitive value story. However, the launch of Opdivo at a price point greater than two times that of the list price in the U.S., the subsequent rapid expansion of the drug's label to include multiple other cancers and the accompanying outrage among pricing stakeholders have precipitated a number of recent measures putting considerable downward pressure on drug pricing, especially for innovative and expensive drugs.

Opdivo was launched in Japan in 2014, with an initial indication of melanoma, a relatively low-prevalence cancer in Japan, and with a price per 100 mg vial at JPY 729,849 (approximately \$7,298 at an exchange rate of 100 JPY:1 USD). The highly innovative drug launched first in Japan, and thus was priced using the "cost-based" methodology with no moderating foreign pricing adjustment exercised. After Opdivo's initial approval, local pharma company Ono Pharmaceutical subsequently sought and received approvals for two additional indications through September 2016, including non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC), on the back of very compelling clinical data. These new indications greatly expanded the addressable population for Opdivo — more so than the MHLW had ever imagined when it first approved the drug for melanoma — inducing panic among policymakers and payers over the potential budgetary impact.

Senior physicians and policymakers subsequently accused Ono of a cynical life-cycle management strategy designed to maximize revenues at the expense of a blindsided MHLW and Ministry of Finance. The furor around Opdivo has reached such heights that the drug was discussed in the *Japanese Diet* by Prime Minister Shinzo Abe, who expressed concern about the drug's price and its implications for broader healthcare finances. The fact that Opdivo has for many patients offered a transformative new option with the potential to delay progression and generate durable, long-lasting responses has been somewhat lost.

As a result of the brewing controversy around Opdivo, policymakers introduced the "ultra-expensive drug repricing rule" early in 2016, a measure targeted at drugs that have far exceeded the revenue forecasts provided by respective manufacturers to the MHLW at the time of pricing. As a result, four drugs (and, by default,

drugs that reference these for pricing purposes) were subjected to large cuts early in 2016 as "huge sellers": Sovaldi (sofosbuvir), Harvoni (sofosbuvir + ledipasvir), Avastin (bevacizumab) and Plavix (clopidogrel). The extent of the cuts ranged from 10.9% for Avastin to 31.7% for Sovaldi and Harvoni. However, Opdivo itself was not eligible for repricing under this new method; its revenues, although rapidly ramping, did not meet the threshold required for the "expensive drug" classification at the time the rule was applied.

Opdivo was singled out for a one-off repricing in November 2016, with prices targeted to fall by 50% as of February 2017. Ono accepted the price cut without complaint, although industry stakeholders expressed dismay; a joint statement issued by two pharmaceutical manufacturers' associations in Japan on the day of the Opdivo decision read, "Such measures should never



happen again, as this is greatly deviated from current price revision rules." Ono's companywide revenues are expected to fall commensurately, and the market capitalization of the company has similarly suffered; Ono's share price retreated from a 2016 high of approximately 5,500 JPY (\$55) in mid-April 2016 to about 2,500 JPY (\$25) by the end of the year.

Policymakers appear to have been sufficiently emboldened by this experience to turn their sights on other drugs that have been perceived as expensive. Taltz (ixekizumab), an innovative and relatively high-priced therapy used for the treatment of psoriasis, does not come close to Opdivo's commercial potential in Japan. Lilly received approval for Taltz in July 2016 and set pricing in

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August through a fairly standard route of Taltz being compared to a local benchmark, Cosentyx (secukinumab), and then being subjected to a foreign reference pricing adjustment to reflect the fact that Taltz is marketed in the U.S. and UK. Based on this initial price of approximately 246,000 JPY per 80 ml syringe/autoinjector (\$2,460), peak revenues in Japan were forecasted at JPY 18.2 billion (approximately \$180 million). However, Taltz's price was 70% greater than that of its competitor in the same class, Lumicef (brodalumab) from Kyowa Hakko Kirin, which did not benefit from an FRP adjustment, as no ex-Japan price was available.



A pricing difference of this magnitude between drugs in the same class is not unprecedented. A number of therapies have benefited from an upward adjustment due to foreign reference pricing (FRP) over recent years. For example, Eisai's antiepileptic Fycompa (perampanel), which launched in May 2016, was given a 100% premium over its benchmarked comparable drug, GSK's Lamictal (lamotrigine), due to an upward FRP adjustment. Conversely, other therapies have suffered at the hands of the FRP adjustment — for example, Minophagen Pharmaceutical's Targretin (bexarotene) for cutaneous T-cell lymphoma, which, after being priced based on a method comparable to that used on MSD's Zolinza (vorinostat) in April 2016, saw its price adjusted downward 25% relative to Zolinza based on the price of Targretin in the UK, France and Germany. The U.S. was excluded due to its price being greater than three times the lowest price in the four foreign markets.

Given the reasonably modest potential of Taltz in Japan, there was no particular reason to suspect that Taltz would prompt concerns among pricing decision-makers. However, the MHLW took issue with the price difference between the competing therapies, and announced it would take the unprecedented action of providing guidance to physicians about limiting Taltz to a final line of therapy on account of its cost, thus drastically limiting the commercial potential of the drug. Lilly used a similarly unusual tactic, which in turn took the MHLW somewhat by surprise: withdrawing its pricing application altogether.

The Taltz issue resolved itself three or so months after the initial debacle when Lilly reapplied for pricing and received a more palatable reimbursement rate of 146,000 JPY (\$1,460, a decline of over 40%), due to the impact of Brexit on the sterling exchange rate used in the FRP calculation. However, it took a fairly unusual macro-event several thousand kilometers away to bring Taltz's price down enough that Lilly could avoid the proposed access limitations.

The FRP (foreign reference pricing) basket has also come under fire recently. In January of 2017, the drug pricing subcommittee agreed that the U.S. should be removed from the current FRP basket. U.S. prices are generally much higher than those offered in other major markets, and Japanese policymakers had increasingly seen U.S. pricing as an aberration rather than a comparator. While specific next steps regarding this policy change were not made public at the time of this writing, it is feasible also that Japan may choose to replace the U.S. in the basket with another "developed" market, possibly Australia or Canada, which may materially reduce the average used in FRP pricing decisions.



# Development-stage therapies at risk in Japan's "new normal" reimbursement system

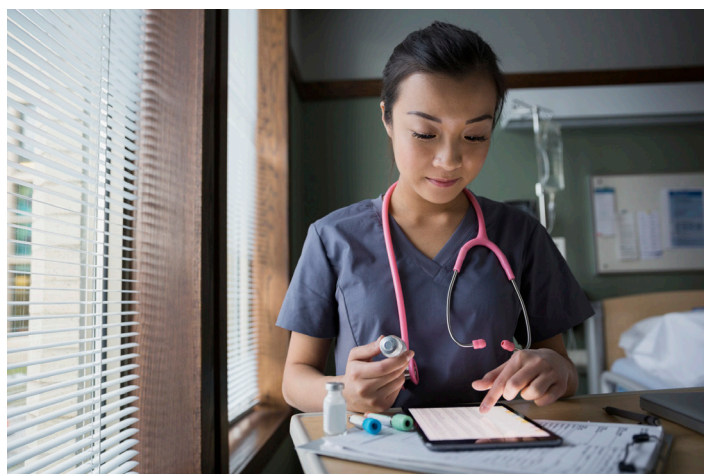
The Opdivo and Taltz examples have naturally created a lot of concern within the industry. The framework of rules governing pricing and access has informed assumptions guiding decisions around significant clinical development and commercialization investments. Had Ono known that it would face a 50% price cut within the first two years of launching Opdivo, would the company have made different investment decisions? Would it have chosen to prioritize different indications? Similarly, had Lilly known there was a risk that Taltz would be limited to its application as a last-line therapy for psoriasis on account of the FRP adjustment, would the company have thought differently about its investments?

In a similar vein, many companies are (or should be) revisiting the assumptions that inform business cases for their clinical and commercial plans. There are a number of potentially transformative drugs under development that target diseases with high unmet need and sometimes large patient populations. Should they reach the market, these drugs will potentially warrant high pricing. Just as was the case with Sovaldi and Opdivo, these therapies may be at risk of falling within the bounds of ultra-expensive drug repricing rules or triggering ad hoc pricing cuts on account of their commercial "success" and potential budgetary impact.

Specifically, the following classes and therapies — although by no means an exhaustive list — may be "at risk" in the new normal of pricing uncertainty in Japan (note: all insights and information shared are based on publicly available data):

- **Disease-modifying therapies for Alzheimer's disease.** Companies including Biogen, Lilly and Roche are developing potentially transformative Alzheimer's disease therapies, which require very large, costly and risky trials, but which have the potential to change the lives of millions in Japan should they show efficacy. As such, they are likely to be relatively high-priced. Even pipeline symptomatic therapies have the potential to become blockbuster therapies on account of Japan's large patient population and the reasonably favorable price points historically seen for analogous branded drugs in Alzheimer's disease, e.g., Memary (memantine).
- **Mono and combination immunotherapies for oncology.** Opdivo alone has prompted substantial concern within the MHLW and Ministry of Finance (MOF) due to its rapid label expansion. Now Merck Sharpe Dohme (MSD)/Taiho is gearing up to launch its own immunotherapy, Keytruda

(pembrolizumab). Keytruda received approval in first-line NSCLC in Japan at the end of 2016, and is expected to be priced by February or March 2017, potentially adding to the financial pressure on Japan's healthcare system. If priced comparably to Opdivo (even incorporating the recently agreed-upon 50% price cut), Keytruda has the potential to add several billion dollars to Japan's annual drug budget. Companies such as AstraZeneca, Chugai and Eisai are developing combination immunotherapies that will likely add to Japan's drug expenses. Especially for latecomers to the market, modest or uncertain pricing expectations may prompt companies to choose different clinical paths in Japan or to reconsider entry altogether.



- **Therapies for treatment of NASH.** Nonalcoholic steatohepatitis affects approximately one million people in Japan and results in progressive liver fibrosis, cirrhosis, and potentially HCC and liver failure. There are no treatments for the disease today, despite the clear unmet need and the societal burden of disease. A number of companies, including Intercept/Dainippon Sumitomo and Gilead, are developing drugs for the disease. Given the size and risk of the required trials and the need they are addressing, these companies are likely anticipating relatively high prices. Again, companies investing in the space may need to reconsider their Japan strategies given recent unpredictability around pricing.
- **Therapies for orphan and rare diseases.** We are not aware of discussions pointing in this direction, and the tone of discussion around rare-disease drug prices has been benign to date (e.g., intractable disease drugs are explicitly excluded

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from consideration for HTAs). Indeed, prevailing price points for rare-disease drugs offer policymakers a useful foil for arguments that they are quashing innovation with low pricing. Given recent developments, however, it may be prudent for orphan- and rare-disease drug companies to consider the possibility of a more challenging price environment in the future. On a one-off basis, any single high-priced rare-disease drug typically has little impact on Japan's overall healthcare budget, and Japan has historically been willing to pay high prices. However, we see increased activity in the space with a number of programs in development in Japan. Given the prices currently "up for grabs" in Japan (in the hundreds of thousands of dollars, and broadly equivalent to those in the U.S.), will rare-disease drugs as a whole at some point fall under the scrutiny of policymakers? Right now the answer

appears to be "no," but as prices continue to rise, eventually the weight of opinion may swing against orphan- and rare-disease drugs. This point is especially critical given that many rare-disease companies have gone or are planning to go "direct" in Japan and a number of rare diseases are becoming fairly crowded. Business plans would no doubt need to change if substantial price cuts were applied to current projections.

The discussion above represents select examples of disease areas and therapies that we believe are at risk given their potential to transform the treatment of high-need diseases and thus potential pricing power and budgetary impact. Other therapies that may also put pressure on budgets include CAR-T therapies for hematology oncology indications, novel small molecule and anti-sense therapies for inflammatory bowel disease (IBD), and novel therapies for heart failure.

# Levers for pricing system change over the near term (2017-2020)

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Given the wide array of transformative yet likely costly therapies in late-stage development, combined with continued financial pressures on Japan's healthcare system, it is prudent for companies to expect and plan for more pricing change beyond that already seen. The following appear to be possible levers that the government may exercise over the coming two to three years as it struggles to manage increasing healthcare costs:

- **Annual price revisions.** There have been mounting calls for the pharmaceutical pricing revision process to occur annually instead of biennially. While such a change in theory may lead to reduced reimbursement rates paid out by the Japanese



government, the financial burden of conducting an annual pricing survey — coupled with the real risk that manufacturers defend against price erosion by setting high invoice prices, and that wholesalers avoid entering into longer-term discounting contracts to preserve margins as much as possible — means the impact on the government's bottom line of annual versus biennial revisions is unclear.

- **Targeted use of HTA assessments to inform repricings.** The MHLW has formally announced that it intends to incorporate HTA findings into the repricing decisions for HCV antiviral therapies as well as for both Opdivo and Kadcyla (ado-trastuzumab emtansine) in its 2018 round of price cuts. It is not yet clear how the findings of the HTAs will be incorporated into repricing decisions for these therapies. Nor is it clear how other therapies in the same class as those included in the

program will be affected (e.g., how will findings from Opdivo's HTA affect Keytruda pricing decisions, if at all?). Manufacturers should likely expect a broadening of the therapies included formally in the MHLW's nascent HTA program going forward.

- **Overhaul of the cost-based pricing method.** One of the consequences of Japan's recent streamlining of clinical data and regulatory requirements has been more drugs launching without local or international comparators, and thus an increase in drugs being priced using the cost-based pricing method. Inputs driving pricing are largely provided by the manufacturer, are subject to negotiation and can result in very favorable prices for manufacturers, especially when no overseas benchmarks exist to subsequently reduce pricing. For example, Opdivo was priced using the cost-based approach, and its resulting Japan price was greater than two times the eventual U.S. list price. Thus, this cost-based pricing method may be overhauled in the near term.
- **Normalization of "one-off" repricings for "ultra-expensive" drugs.** The Opdivo example may become the Japanese government's default tactic for drugs that are seen to threaten healthcare finances despite not having been anticipated at launch to do so. Absent a pricing mechanism that takes into account the full commercial potential of a given drug, and not just its first-launch indication, similar issues are likely to arise with many of the therapies described above — especially in oncology, a field in which target pathways stretch across indications.
- **Initial and/or dynamic pricing decisions that take into account expected label expansions.** The Japanese government may begin to require more insight from manufacturers as to label expansion plans in order to avoid getting caught unawares again, as was the case with Opdivo. One can envision manufacturers being required to prepare more detailed forecasts for new drugs, delineating revenues anticipated for each new indication and the associated likelihood of success, so as to inform a risk-adjusted view of the government's total "exposure" over time. This analysis would then be incorporated into pricing decision-making. Also recently raised has been the idea to conduct quarterly price reviews for indication-added drugs, to reassess prices based on patient numbers and sales figures projected for new indications.

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- **Increasingly prescriptive treatment guidelines for expensive drugs.** In April 2016, the first PCSK9 inhibitor in Japan, Repatha (evolocumab), went on sale. Due to the large patient population (people with familial hypercholesterolemia or hypercholesterolemia with high risk of cardiovascular events who do not respond to statins), the MHLW issued a notification requiring physicians to justify Repatha's use in treated patients by putting a number of details in the remark column in medical bills. In July 2016, the government announced plans to draw up "optimal use guidelines" for expensive medicines, starting with Opdivo (and, by extension, other PD-1 inhibitors such as Keytruda) and Repatha (and, by extension, Praluent [alirocumab]). While optimal use guidelines were initially to be implemented on a pilot basis for these select products, the government plans to regularly utilize these guidelines to limit use of innovative drugs to restrictively defined indicated patients for FY2017.
  - **Normalization of "step-edits" for "inappropriately" expensive drugs.** The Taltz example may become a default approach to managing budgetary impact from high-priced drugs that are perceived to have unfairly benefited from FRP adjustments when other drugs within the same class are available at a much lower price.



- **Overall greater assertiveness and willingness to act among policymakers.** For better or worse, recent changes have signaled a new assertiveness in policymakers; interactions with the pharma industry were minimal before the recent changes were implemented. The industry should do its utmost to reposition itself in the discussion so as to ensure that its concerns and ideas are heard.



# Possible trigger points for change over the coming years

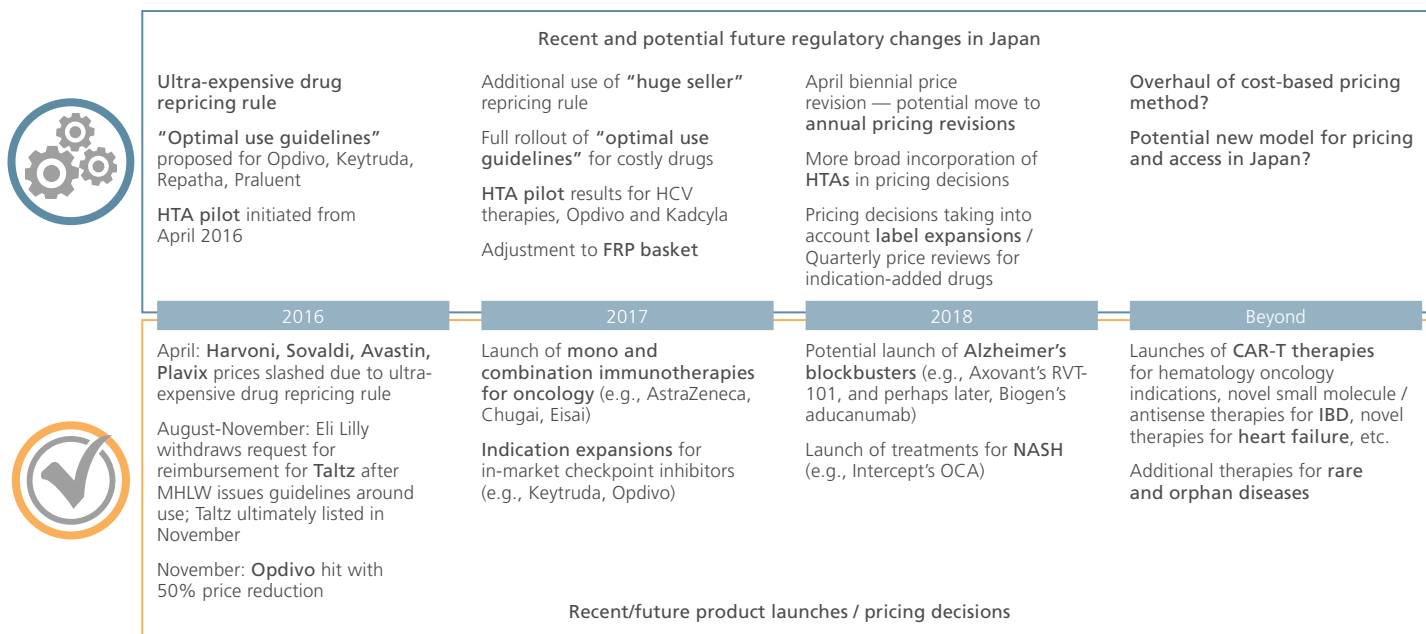
In terms of trigger points for change in the near term, we are looking with interest both at key dates on the Japan reimbursement calendar and at some upcoming drug launches that may precipitate further changes in the pricing landscape as envisioned above.

Further change beyond measures already undertaken are not expected to occur in FY2017, (April 1, 2017 to March 31, 2018), leaving April 2018 the earliest possible date for additional major policy changes. However, much discussion is anticipated throughout 2017 and the outlook for the 2018-2020 window should become increasingly clear as the year goes on.

The next round of pricing revisions (historically a biennial process) is due in 2018. A number of key changes are likely to occur in this round of revisions, and while all of these changes have been given a deadline to be finalized by the government “by the end of 2017,” specific near-term deadlines remain unclear. Prime Minister Abe tasked four state ministers in December 2016 with drawing up an initial plan for overhauling the drug pricing system in Japan. The initial proposal, unveiled at the end of 2016, called for several key changes:

- **Quarterly reviews of additional indication-listed drugs** (to combat drugs that may benefit from an increased revenue potential when approved for additional indications).
- **Annual price revisions** (though the first instance of such a revision may be delayed until April 2021, due to a potential one-off repricing in October 2019, when the Japanese consumption tax is slated to increase from 8% to 10%).
- **Full-scale cost effectiveness assessments to inform drug pricing**, starting with an initial readout of the seven currently trialed HTA products, expected by March 2017. The findings will be incorporated into repricing for these therapies in 2018, with the goal of implementing a broader HTA system by the FY2018 cycle. Major issues with the introduction of an HTA system remain unresolved, including which organizations will be responsible for conducting the assessments, what methodology will be used and how eventual recommendations will be weighed in overall pricing decisions.

Timetable of near-term trigger points for change





Additional proposals also on the table for discussion in FY2018 include many of the levers for change described above (e.g., overhaul of the cost-based pricing method, and normalization of such policies as the ultra-expensive drug repricing rules). The Japanese government also plans to introduce additional optimal use guidelines over the course of 2017, though it remains unclear for which specific drugs and diseases these guidelines will be drafted.

In addition to the policy calendar, several new product launches in the near term may place the current system under additional strain and potentially induce further change. Besides potentially falling within the bounds of existing rules around ultra-expensive

drugs and optimal use promotion guidelines, these drugs may create sufficient pressure to prompt further measures to manage the healthcare budget. In particular, we will be closely watching launches of potentially transformative drugs as well as policymaker reactions over the coming years, including the following:

- **Keytruda:** MSD / Taiho's anti PD-1 immuno oncology drug has yet to be priced but is already approved for first-line NSCLC, and is targeting multiple other indications
- **Ocaliva:** Intercept / Dainippon Sumitomo's PBC and NASH therapy has potential application in a large number of patients who today are at risk of progressive cirrhosis, potentially leading to liver transplant
- **Durvalumab/tremelimumab combination:** AstraZeneca hopes to be first to market with its combination immune oncology regimen, which is in phase III studies as a first-line therapy for NSCLC
- **Aducanumab:** Biogen/Eisai's Phase III beta-amyloid targeted Alzheimer's drug is highly risky but could bring huge benefits to the large number of Japanese people with MCI and mild Alzheimer's disease

# Outlook for further, more substantive pricing reform over the longer term (c. 2020 onward)

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Recent events have shown Japan's existing pricing and reimbursement system to be cracking. The system in its present form is struggling to satisfy many stakeholders: Drugs such as Opdivo are being awarded prices that are viewed by payers as unsustainable. Reactive, ad hoc changes to pricing rules are unsettling drug manufacturers and making them rethink investment decisions. Patients are potentially faced with the prospect of delayed access or no access at all to innovative therapies.

Fundamentally, Japan is struggling with a disconnect between the price, clinical and economic value "created," and the resources available to the system to pay for the drug. While Japan's economy was still growing and the population was young, this was not problematic; there was money to spare, and care for the population was relatively inexpensive. But that is no longer the case. Recent changes in clinical and regulatory timelines, as well as the unprecedented level of innovation in biopharma, have further exposed the system's limitations. The HTA pilots underway and discussion around usage guidelines point to a new direction of Japanese drug pricing and access. However, bolting such small-scale initiatives onto a modified version of the status quo is unlikely to be sufficient to manage costs while maintaining a favorable environment for access and innovation on an ongoing basis.

Given that, what seems to be needed in Japan over the longer term (i.e., beyond the next two to three years, which we expect to be characterized by ad hoc modifications) is a new pricing model that will enable the country to better manage its healthcare resources vis-à-vis its healthcare priorities. We believe those priorities will be incorporated into a system that:

- Supports longer-term sustainability of Japan's healthcare budget
- Permits broad, world-class access to innovative medicines for patients
- Fosters global competitiveness of the local pharma industry
- Does not overburden government or industry with the need for new or excessively expanded capabilities

In terms of what specific attributes this new healthcare system will incorporate, and the potential impact of these on market attractiveness, we envision the following (see table on page 16).

We expect the system that will emerge from the efforts to manage these priorities will result in more pricing pressure on pharmaceuticals than we have seen historically, yet will deliver a pricing environment that is more favorable than we see in the EU. While greater thought is likely needed to envision what such a system may look like, given the competing priorities described above, either France or possibly Germany may offer a pricing system for Japan to model.

We believe the UK's approach — which relies strongly on economic assessments — will prove to be unpalatable for many stakeholders in Japan (not just the pharma industry) and will likely be impractical given Japan's limited HTA capabilities. We do not expect Japanese policymakers to consider walking away from innovative therapies on cost-effectiveness grounds, as has been the case in the UK and other markets that use HTAs aggressively. (Case in point: The UK, Ireland, Canada and Australia refused to cover Vertex's Orkambi [lumacaftor/ivacaftor] on cost-effectiveness grounds.)

France may offer a potential model, as it combines a scientific and economic appraisal of new drugs: Economic assessments are targeted at the most innovative and potentially most impactful drugs from a budget standpoint, yet HTAs are not the only consideration for a synthesized decision that takes into account other clinical and scientific factors.

Vision for Japan pharmaceutical pricing over the longer term (circa 2020 onward):  
Healthcare priorities, key system attributes and impact on market attractiveness

Hypothesized healthcare system priorities	Possible system attributes	Impact on pricing attractiveness vs. today
Supports longer-term sustainability of Japan's healthcare budget	Shares risk with manufacturers, whereby manufacturers are required to pay back the difference when drugs exceed expected prices and / or volumes	↘
	Legitimizes one-off negotiations for exceptional drugs that jeopardize budget stability	↘
Permits broad, world-class access to innovative medicines for patients	Offers favorable pricing for innovative drugs sufficient to incentivize development and commercialization in the Japanese market	↔
	Offers manufacturers an acceptably predictable reimbursement system	↗
	Rewards innovation appropriately by combining scientific and economic appraisals of innovative drugs to ensure a rational price is paid	↔
	Uses increasingly prescriptive, evidence-based guidelines for use of drugs, limiting use to patient segments where clinical (and potentially economic) value is evident	↘
	Creates compelling incentives in the value chain for substitution of brand-name small-molecule drugs and biologics with generics and biosimilars, respectively	↘
	Moves away from Japan's historically rigid "mechanical" approach to pricing that has left Japan's healthcare finances increasingly exposed	↔
Fosters global competitiveness of the local pharma industry	Offers favorable pricing for innovative drugs, sufficient to incentivize development and commercialization in the Japan market	↔
	Offers manufacturers an acceptably predictable reimbursement system	↗
	Rewards innovation appropriately by combining scientific and economics appraisals of innovative drugs to ensure a "rational" price is paid	↔
Does not overburden government or industry with the need for new or excessively expanded capabilities	Uses targeted HTAs that do not overburden the MHLW or the pharma industry in terms of data collection and analytical requirements (e.g., need for real-world data, need for health economic analyses)	↔



# Action plan for pharma in Japan

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Given this uncertainty, we believe it prudent for pharma companies to proactively plan for different scenarios that may impact their drugs' commercial potential. Pharma companies also should enhance their pricing and reimbursement capabilities and determine how to work better together as an industry to shape the conversation with policymakers. As the Taltz example shows us, it is not only manufacturers developing potential blockbusters that

need to be concerned; even companies marketing smaller products need to plan for this "new normal" of pricing and access.

Specifically, we recommend that pharma consider the following action steps — both immediate to-dos that should be on the agenda as soon as possible, and longer-term initiatives — in order to navigate the years ahead:

## 1. Business planning and strategy

Over the immediate term...

- ☐ Develop an **internal view on how the landscape will evolve, both over the near term and in the longer term**, and consider the implications for your development-stage and in-market portfolio. Identify different "future states" rather than develop one single view of the future.
- ☐ Understand different **trigger points and scenarios**, the potential impact of each scenario on your portfolio, and the likelihood of occurrence.
- ☐ Assess the **impact of potential cuts for products that may face the ultra-expensive drug repricing rule or may be singled out for special attention**, and determine the implications for planned investment decisions. Remember, your brands may not be directly targeted but may be affected alongside reference drugs.
- ☐ For your late-stage development portfolio, **scenario-plan around possible shifts in FRP pricing** and, as necessary, **changes to cost-based pricing**. Again, consider the implications for any shifts for planned investments and the likelihood of any changes occurring.
- ☐ **Account for more prescriptive guidelines** around use and how that affects the annual volume opportunity for your portfolio.

Over the longer term...

- ☐ **Incorporate different longer-term pricing and reimbursement scenarios in assumptions around earlier-stage portfolio** and associated investment decisions.
- ☐ **Develop leaner, more efficient and more flexible commercial organizations to offset the economic impact of uncertainty and pricing pressure**, e.g., by fostering more meritocratic sales organizations and exploring flexible, lower-cost sales models (contracted sales force, syndicated sales force, virtual sales force, etc.).

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## 2. Pricing and access

Over the immediate term...

- ☐ **Recalibrate pricing philosophy in the Japan market to the “new normal.”** Even if a very high price is possible under the pricing rules, if viewed as egregious, the costs (e.g., public backlash, key opinion leader/physician pushback) may well outweigh the benefits. The pricing system, while rules-based, offers flexibility both ways, and a price that is viewed as more sustainable to both the system and the patient may be viewed favorably by the public as well as prescribers.
- ☐ **Anticipate and prepare for ad hoc restrictions resulting from favorable reimbursement decisions** (i.e., situations similar to those that faced Eli Lilly with Taltz) and consider tactics to mitigate these, such as withdrawing a listing request or seeking to adjust the FRP basket.
- ☐ **Understand the potential budgetary impact of your launch portfolio** under different pricing and label assumptions, and identify potential “tipping points” where combined price and patient volumes may precipitate attention from policymakers.
- ☐ **Consider addressing upfront the possibility of label expansions rather than basing pricing negotiations on a limited forecast**, which can result in a price that will be inappropriate once the true commercial potential of your drug comes to light.

Over the longer term...

- ☐ **Invest in the development of a local health economic analysis team.** Leverage the best practices and expertise of the global team, and determine the path forward to develop the Japan division.
- ☐ **Design prospective trials to clearly demonstrate the clinical and economic value of your products**, identify which patient segments are most likely to benefit, and identify the endpoints — clinical and economic — that matter most to Japanese pricing stakeholders as well as to prescribers. Consider how to incorporate real-world data into your development programs to further bolster your value story to ensure favorable pricing and access.
- ☐ **Expand the value proposition of your marketed portfolio to include economic considerations.** Leverage real-world data and retrospective analyses to differentiate your products based not only on clinical outcomes but also on possible savings to the system.
- ☐ **Develop and propose innovative pricing schemes** that may generate preferred access for your brands.

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### 3. Advocacy

Over the immediate term...

- ☐ **More forcefully insert industry into the discussion** on pricing, and ensure that industry's voice is heard before further material changes are made. (We admit that this is easier said than done.)
- ☐ **Continue to advocate against one-off adjustments** to rules by communicating the pressures this uncertainty places on investment planning and the possible negative effect this has on access to new therapies.
- ☐ **Work with the MHLW to identify avenues that may offset the business impact of an increasingly aggressive and uncertain pricing environment.** For example, integrate more leniency in study design requirements in order to minimize duplication of efforts to satisfy regulators across multiple geographies. Or improve communication and collaboration in planning studies in order to minimize clinical and regulatory risk, reduce the burden of post-marketing surveys, etc.
- ☐ **Seek to better educate government, other stakeholders (such as senior physicians and payers) and the broader public** on the biopharma business model, the magnitude of investment and risk involved, and the need to generate returns on the few programs that reach the market in order to sustain future investment.
- ☐ **Emphasize the value of the pharma industry (both local and foreign) to Japan's economy** in terms of employment, contribution to Japan's knowledge base and contribution to tax receipts.

Over the longer term...

- ☐ **Place renewed emphasis on the value of innovative drugs and the benefits drugs bring to individuals and society as a whole.** Inject this message in discussions with stakeholders involved in the pricing and reimbursement debate, but also seek to extend the reach of this message to the broader public.
- ☐ **Develop a vision of the key tenants of a pricing and access system** that maximizes benefit for both manufacturers and the government (and ultimately, society).
- ☐ **Draw upon knowledge from across your members' global organizations** to present your case, comparing and contrasting the alternatives seen in other global markets.

*New Realities of Drug Pricing and Access in Japan* was written by **Patrick Branch**, Principal, **John Gill**, Consultant, and **Ray Fujii**, Managing Director, in L.E.K. Consulting's Tokyo office.

For more information, contact [info-tokyo@lek.com](mailto:info-tokyo@lek.com).



**Patrick Branch**  
Principal



**John Gill**  
Consultant



**Ray Fujii**  
Managing Director

