OBSERVATIONS ON DRUG PRICING AND INNOVATION IN JAPAN

KEY FINDINGS

- As the Government of Japan (GOJ) seeks to re-invigorate Japan's pharmaceutical industry as a sector for innovation and growth, it can make impactful changes to specific pricing policies that will support Japanese patients' access to the most innovative medicines.

- The Asia Group (TAG) has identified two very specific pharmaceutical pricing measures that directly undermine the government's goal of promoting startups and bringing innovative new pharmaceutical products to market. The negative impact of these policies is particularly severe for innovative drugs for rare diseases, for which there are often no alternative treatments,

    1. Strict **cost disclosure requirements,** especially the "co-factor zero" rule introduced in the cost-based price calculation method in 2022, are effectively canceling out many premiums that were intended to reward innovation and novelty.

    2. **Corporate status criteria** associated with the Price Maintenance Premium (PMP) system favor companies with a long track record of business in Japan and limit premium benefits for new market entrants.

- The intended purpose of these rules is to improve transparency in a product's total cost while providing incentives for drug launches in Japan. But the two-fold impact of these rules, particularly penalizing new market entrants and foreign entrants, has undermined the intended effect of these measures.

- Eliminating these two specific punitive pricing policies represents a "low-hanging fruit" for policy change, which can have an immediate impact on the availability of important new drugs, while being relatively inexpensive in fiscal terms.

    - These changes will stimulate future successful launches and early entrance to Japan, benefitting patients.

1. OVERALL BACKGROUND: JAPAN'S PHARMACEUTICAL INNOVATION ENVIRONMENT

Japan's policies to incentivize innovation in prior years made progress in narrowing the extent of the infamous "drug lag" – the delay in approval time in Japan relative to the United States and the European Union. At the peak of the "drug lag" in the early 2000s and 2010s, it took up to four years for new drugs to reach the Japanese market, leaving Japanese citizens behind in access to innovative medicines.

Programs like the *sakigake* designation system, which was officially launched in 2020 to encourage innovative development through prioritized consultation, rapid review, premium drug pricing, and an extended data-protection period, contributed to reducing the lag. Together with this, a newly introduced Price Maintenance Premium (PMP) system also helped address the "drug lag." However, increasingly harsh cost-cutting policies reversed this success, undermining the Government of Japan's (GOJ) overall efforts to strengthen public health.

The government has pointed to the importance of securing high-quality, innovative pharmaceuticals in key policy documents. The Ministry of Health, Labour and Welfare

(MHLW)'s 2021 vision for the pharmaceutical industry laid out the goal of "[realizing] the extension of healthy lifespans and [protecting] the public against health crises," as well as contributing to Japan's economic growth and development of the pharmaceutical industry. The vision looked to address weaknesses exposed by the COVID-19 pandemic, including the absence of a made-in-Japan vaccine and the impact of the annual drug pricing scheme. The Japanese government's 2022 Basic Policy for Economic and Fiscal Management Reform *(honebuto)* also referenced the importance of Japan's pharmaceutical industry as a growth sector and as matter of economic security, stating that "the government should strengthen drug discovery capabilities, while securing the quality and stable supply of medicines, to advance scientific technologies and innovation."

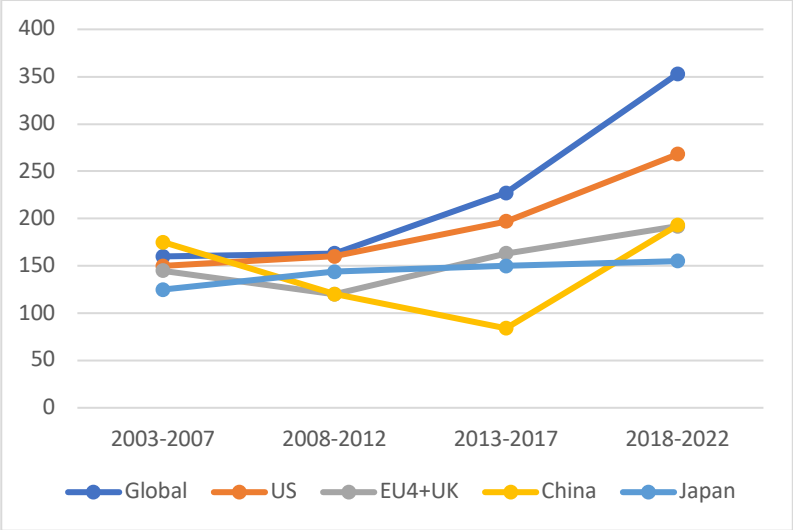
With these goals in mind, there is a growing consensus in Japan on the need to reform the pricing system to ensure that the most innovative, effective pharmaceuticals are available in a timely manner. The last full drug pricing reforms in April 2022 were adopted with the intention to promote innovation, instill transparency in the pricing process, and mitigate the risk of "drug lag." Measures included adjustments to the cost-calculation method to determine price when no comparative product exists in the market and expansion of eligibility for the PMP, intended to defer price adjustments on eligible patent-protected products.

However, instead of awarding innovation, certain detailed measures like the "co-factor zero" rule and the PMP corporate status tiers have penalized both Japanese and foreign products, as well as small and startup companies that could successfully develop innovative products in Japan.

These policies are making Japan a much less attractive market for development and launch of new medicines, undermining progress toward the goals of the government's 2021 Pharmaceutical Industry Vision Plan.

According to a 2023 IQVIA report on the global trends of pharmaceutical research and development, Japan had over 30 launches of novel active substances (NAS) over five consecutive years, but it is not keeping pace with other markets (*Figure I*).

Figure I: Novel Active Substances (NAS) Launched, 2003-2022



Source: IQVIA Global Trends in R&D 2023: Overview through 2022

The United States had over 50 NAS launches over four consecutive years, with a total high of 268 launches over five years. China overtook Japan with a five-year total of 193 NAS launches, driven by innovative policies introduced by the National Medical Products Association (NMPA).

Following the December 2022 off-year repricing decisions, this year's deliberations on important FY2024 drug pricing reforms will have major ramifications for the pharmaceutical industry. Policy decisions made in the fall of 2023 on the National Health Insurance (NHI) pricing framework for pharmaceutical products by MHLW, the Ministry of Finance, and the Chief Cabinet Secretary will shape Japan's ability to attract innovative products to the market

going forward and to achieve the goals set out in the 2021 Vision Plan and 2022 *honebuto*. Changes to two specific pricing policy issues would reinforce the Japanese government's focus on innovation and growth in the market.

2. KEY POLICIES THAT CAN BE TARGETED FOR FOCUSED CHANGE

TAG has identified that the "co-factor zero" rule of the cost-based pricing method, and the PMP's corporate status criteria, directly undermine the government's objectives of promoting startups and bringing innovative new products to market.

These policies most seriously impact companies and products that are new to the market, as well as on-patent, well-established drugs, both important categories for innovative drug supply in Japan.

Figure II: Pros and Cons of Co-Factor Zero Rule and PMP

	PROS	CONS
Cost-Based Method: Co-Factor Zero Rule	• Rewards transparency regarding overall costs provided by the manufacturer • Graduated system allows for some variability in cost disclosure	• Effectively wipes out premiums awarded for innovation in pricing, including *sakigake* premiums • Severe impact on startup companies that cannot afford to lose premiums; established companies with products expected to achieve a high base price may forego a premium in favor of claiming high costs while disclosing a low percentage • In many cases, low cost-disclosure rates are inevitable due to the difficulty of determining cost of materials, operations, etc.
Price Maintenance Premium: Corporate Status Criteria	• Provides buffer against NHI price revisions for eligible products until the end of the patent protection period • Updated rule allows for consideration of products with new indications	• Unfavorable to emerging biopharma companies, particularly foreign companies • Criteria used to decide premium ranks companies based on history in Japan (i.e., clinical trials, launches, and products developed in response to government requests)

Use of the "Co-Factor Zero" Rule in the Cost-Based Pricing Method: The 2022 addition of a "co-factor zero" rule to the cost-based pricing method most severely affects new market entrants (both foreign and Japanese companies) and is particularly impactful to patients'

access to the most advanced and effective drugs, particularly for rare diseases, as well as limits the overall advancement of an innovative pharmaceutical ecosystem.

The cost-based method – also known as cost calculation method – is used to determine the prices of novel, innovative products when no comparator drugs exist in the Japanese market at the time of launch. The method requires companies to disclose information regarding the costs of manufacturing, research and development (R&D), sales, operations, and distribution, as well as consumption tax. Premiums are then added based on certain criteria including innovativeness, usefulness, marketability, and designation for *sakigake* review.

Companies have in the past also referenced the prices of their products overseas (transfer prices); however, MHLW officials cited frustration with the use of these references, arguing that a lack of visibility into pricing methods overseas made it more difficult to justify the addition of premiums. In 2018, a new premium rule to encourage transparency was introduced, with co-factor tied to cost disclosure rates added to reduce premiums granted for innovation.

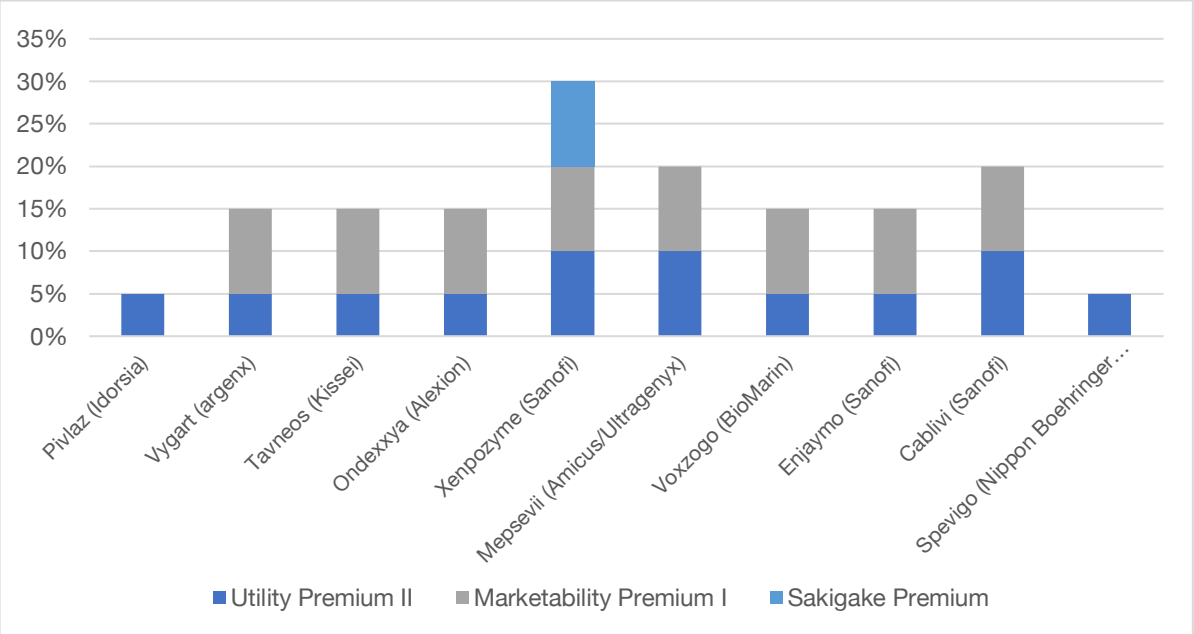
In an attempt to further improve price transparency and capture the most appropriate pricing level, the co-factor was reduced from 0.2 to zero in 2022 for cost disclosure ratios of less than 50 percent. While premiums could be slashed up to 80 percent under the previous framework, partial rewards remained for innovative products. However, the co-factor now cancels out many premiums granted to innovative products, even if gained through the successful and well-received *sakigake* program.

From April to November 2022, 13 products were priced using the cost-based method, of which 10 products gained a launch premium ranging from 5 to 30 percent (*Figure III*). However, the "co-factor zero" rule was applied to all 10 of those products, effectively removing any premiums granted to these products. Two of the products were designated as orphan drugs, and nine were produced by foreign drug manufacturers.

Notable among these cases was Sanofi's Xenpozyme, which saw the "co-factor zero" rule wipe out three premiums, including one from its *sakigake* designation.

The Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) has pointed out that there are cases where low disclosure rates are inevitable because of difficulties in obtaining detailed cost information on such a wide variety of business transactions, manufacturing and operational costs, and import processes.

Figure III: Premiums Nullified by Co-Factor Zero Rule in 2022



Source: Pharma Japan (2022)

At a December 9 meeting of MHLW's expert panel, Takuma Sugahara, Professor of the Faculty of Economic, Hosei University, argued that due to the complexity of the pharmaceutical value chains, the current pricing mechanism does not fit the current state of the industry. Industry representatives have also expressed concern that the rule "would completely prevent innovation from being reflected in NHI prices and interfere with efforts to increase disclosure."

In practice, the addition of this strict disclosure ratio has done little to encourage transparency. A 2018 study presented at the International Society for Pharmacoeconomic and Outcomes Research (ISPOR) examined whether the cost-based method and then-new transparency co-factor rule had any effect on Cost of Goods (COGs) transparency. The study examined seven drugs priced under the cost-based method that received premiums in April and May 2018. Of the seven products, one company disclosed 80 percent or more and received the highest ratio (1.0). The other six reported less than 50 percent and received an 80 percent reduction in premium. The researchers found that the 2018 changes did not "appear to sufficiently incentivize transparent disclosure of manufacturing costs."

The 2022 reduction of the lowest co-factor to zero continued this trend, as all ten products granted launch premiums under the cost-based method had those premiums nullified, suggesting that the co-factor rule is not an effective means to incentivize transparency. There is little reason for sponsors that receive low or no premium to disclose costs, while drugs with low costs themselves benefit enough from a higher reported transfer price to outweigh even significant penalties.

Impact of PMP Corporate Status Criteria on Emerging Biopharmas: First introduced in 2010, the PMP is a pricing mechanism intended to incentivize and reward innovation to companies through deferred NHI price revisions during a drug's patent period if specific criteria are met. The 2022 reforms extended the scope of the PMP to include drugs with new indications that would have been eligible for the premium at launch – a welcome adjustment. However, the PMP eligibility criteria introduced in 2018 implicitly leaves out emerging biopharmas. PMP is granted to on-patent drugs that meet certain product criteria and adjusted in accordance with corporate status criteria. Eligible companies are ranked into three tiers, in which only the top tier receives the full premium. Rates for the middle and bottom tiers are reduced by 10 and 20 percent, respectively. In 2022, tier 2 and 3 ranked drugs - 75 percent of new drugs - contributed more to the Japanese market than tier 1 ranked drugs – only 24 percent (*Figure IV)*.

Figure IV: 2022 Price Maintenance Premium Data

Current Status of Price Maintenance Premium (PMP) (FY2022 Drug Price System Revision)

VII Premium to promote the development of new drugs and eliminate off-label use (PMP)

1. Premium

Note: If applicable to multiple requirement categories, a drug is counted in higher category (Other requirements are 6) pioneering drugs, 7) drugs for specific uses, and 8) AMR medicine, but no products fall under 7.)

Requirement	Number of Ingredients	Number of Products
1) Orphan Drugs	187	277
2) Publicly Invited Development Products	13	23
3) Premium Applied Products	86	162
4) Standard-met New MOA Drugs	42	69
5) MOA drugs listed within 3 years & 1st among three listings is PMP applicable or meets the standard	20	40
Total	348	571

Number and Percentage of Companies Receiving Premium By Category

	Category I	Category II	Category III	Total
Number of Companies	22 (24 %)	47 (52%)	21 (23 %)	90 (100%)

- Total PMP Premium: Approximately JPY 52 billion

2. PMP Deduction Cumulative Amount

- Deductible
  Number of Ingredients: 65
  Number of Products: 145
- PMP Deduction Amount: Approx. JPY 86 billion

Source: MHLW Reference materials for 6th Expert Review Committee on Comprehensive Measures for Prompt and Stable Supply of Pharmaceuticals (unofficial translation)

As these criteria rank companies on legacy and experience in Japan, based on factors such as their record of in-country clinical trials and the number of products developed in response to government requests, three quarters of the drugs ranked in tiers 2 and 3 are small or start-up companies based on the PMP eligibility status. As a result, emerging biopharmas and overseas companies that lack an established track record of development and business activities in Japan are unfairly relegated to a lower premium tier.

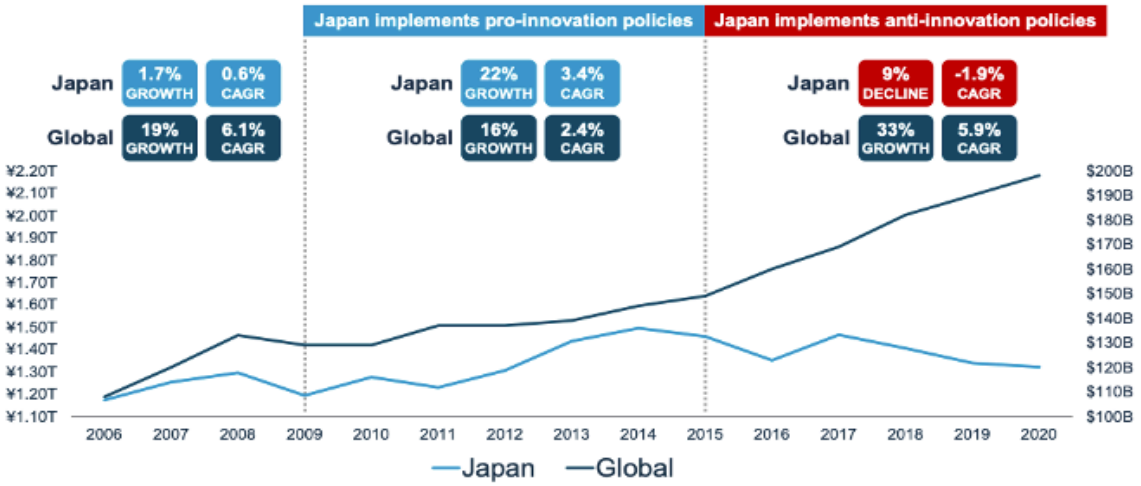
Pharmaceutical stakeholders in the government, academia, and private sector are now focused on developing Japan's biopharmaceutical industry in light of its diminishing market share and fears over the return of drug lag. Experts participating in MHLW's panel on comprehensive pharmaceutical policies have called for the product and corporate status criteria to be reviewed and possibly abolished, due to their disincentivizing effect on emerging biopharma companies. According to Kitasato University Graduate School for Pharmaceutical Sciences Professor Mamoru Narukawa, "[the criteria] is either rewarding past efforts or focusing on the value of new medicines," and "given the recent developments, we should focus on the value of medicines itself without having company criteria." Other experts said

that criteria favoring existing companies will disincentivize biotechs from conducting R&D in Japan.

3. CONTEXT OF DRUG LAG AND DRUG AVAILABILITY

Likely Impact on Drug Lag: While Japan was previously successful in reducing its drug lag, policy changes since 2016 have heralded its potential return and decline in Japan's biopharmaceutical industry growth (*Figure V)*. Key factors deterring new product launches in Japan include the lack of transparency in pricing decisions and predictability in the pricing system, as well as strict clinical trial regulations and limited domestic investment in biopharma. The new limitations on launch premiums for innovative products may add to this trend by disincentivizing companies from bringing groundbreaking therapeutics to the Japanese market. These trends go directly against the guidance set out in the 2021 Vision Plan, which states that "predictability for appropriate rewards commensurate with investments is important, given that the research, development, manufacturing, and distribution of pharmaceuticals are undertaken by private companies."

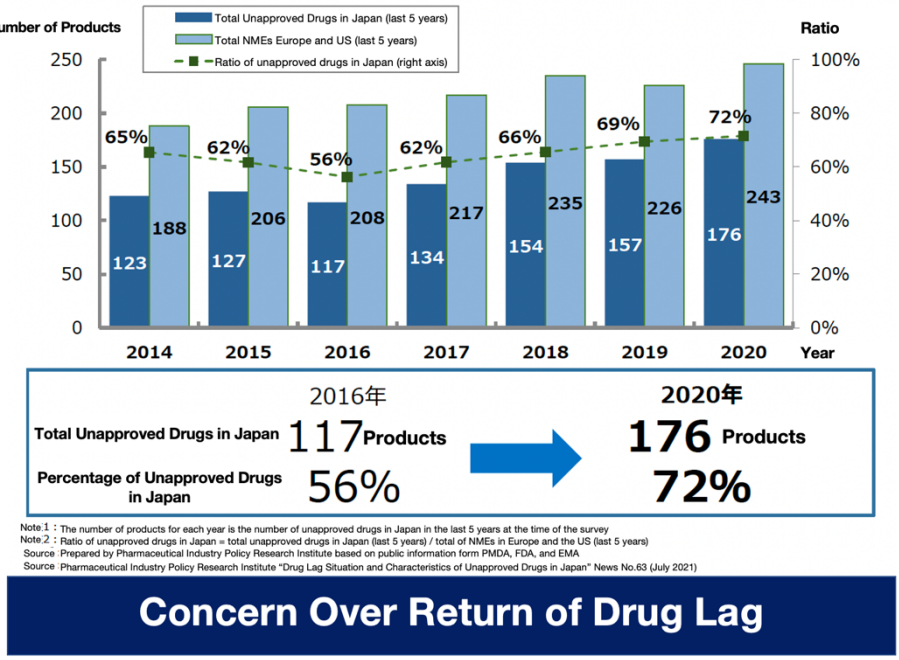
Figure V: Japan vs. Global Growth in Biopharmaceutical Industry R&D Investment



Source: PhRMA Analysis of World Health Organization, U.S. Food and Drug Administration, European Medicines Agency and Japan Pharmaceuticals and Medical Devices Agency data, January 2022.

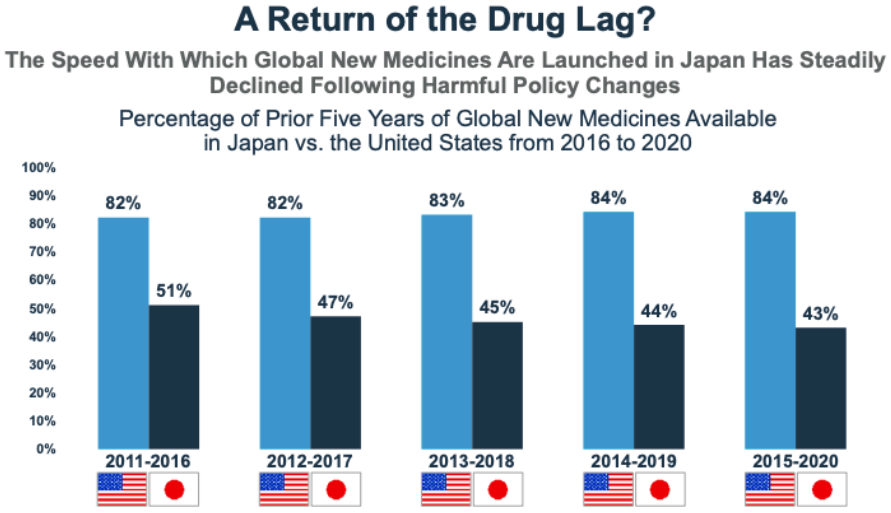
Figures VI and *VII* show the effect of anti-innovation policies on the growth of the pharmaceutical market in Japan. According to a 2022 survey by the Japan Pharmaceutical Manufacturers Association (JPMA) the number of unapproved drugs in Japan has been steadily increasing since 2016 (*Figure VI*). The Research and Pharmaceutical Manufacturers Association of America (PhRMA) has also pointed out the delay in launching globally marketed new drugs in Japan, adding further evidence of the possible return of the drug lag (*Figure VII*).

Figure VI: Unapproved Drugs in Japan, 2016 vs. 2020



Source: JPMA Materials for September 22, 2022 "Expert Review Meeting on Comprehensive Measures for Rapid and Stable Supply of Pharmaceuticals" (unofficial translation)

Figure VII: Japan vs U.S. Global New Medicines Available, 2016-2020

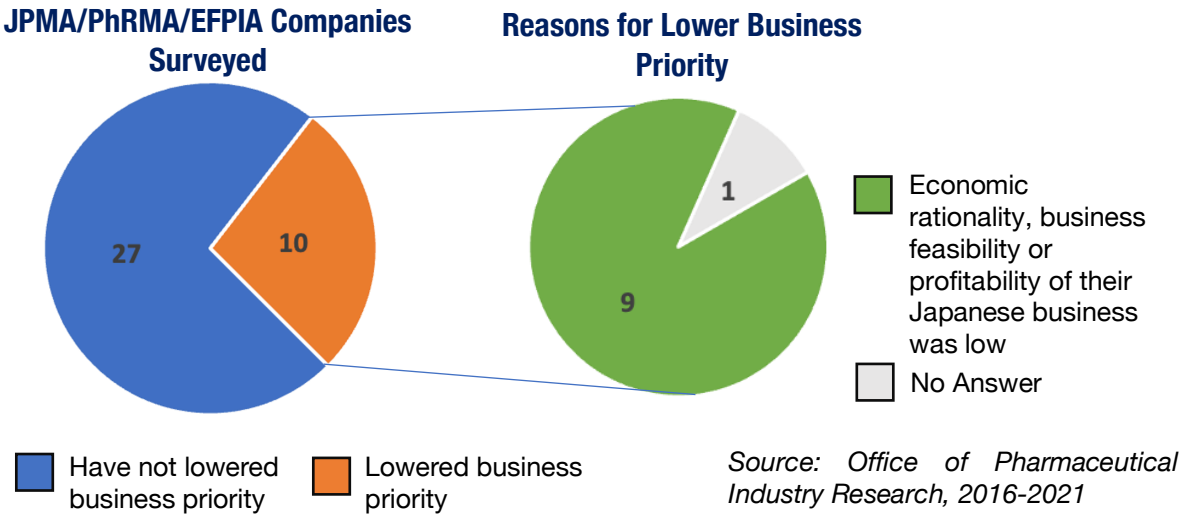


Source: PhRMA Japan

If pricing policies such as the co-factor zero and PMP corporate status criteria stay in place, the attractiveness of the Japanese pharmaceutical market will continue to decline. Japan's pharmaceutical market remains the third largest in the world, with a 7 percent market share, and it is expected to grow 1.1 percent in 2022 to JPY9.498 trillion (USD 68.08 billion). However, a report by IQVIA projects that Japan's pharmaceuticals market will decline at a rate of 0.2–1.2 percent each year through 2025, creating less attractive market conditions for international pharmaceutical companies.

Companies' Views of the Japanese Market: Since the extensive 2016 drug pricing reforms were adopted, companies have already been reevaluating their positions in the Japanese market (*Figure VIII*). JPMA President Yasushi Okada said in a 2021 interview that 117 drugs were approved in Japan from 2016-2020, whereas 176 new drugs were approved in the United States and Europe during the same time. Separately, according to an Office of Pharmaceutical Industry Research (OPIR) survey of 37 companies belonging to JPMA, PhRMA, and the European Federation of Pharmaceutical Industries and Associations (EFPIA), 11 companies (27 percent) have made Japan a "lower priority" market due to "low economic rationality, especially low drug prices and assumed drug prices." OPIR research further suggests that about 40 percent of major global companies are deprioritizing the Japanese market for investment.

Figure VIII: Pharmaceutical Firms De-Prioritizing Japanese Market



Source: Office of Pharmaceutical Industry Research, 2016-2021

These dynamics have even disincentivized domestic investment. JPMA reported in a survey of 34 domestic companies, just seven companies (17 percent) increased the number of products developed and introduced for the Japanese market between 2016 and 2021. Eleven companies (26 percent) reported plans to increase product launches in the future – totaling only 18 companies that have or plan to increase. JPMA's research also found that 16 companies (38 percent) plan to decrease the number of launches in the future.

4. RECOMMENDATIONS

In TAG's estimation, the two policies analyzed in this paper worsen existing pressure on new products and startups. They also undermine the Japanese government's initiatives to support innovative drug discovery while developing the industry and economy through medical research and technological advancements, as well as ensure access to high-quality healthcare by securing the quality and stable supply of medicines.

Squeezing these companies, especially startups and new market entrants, via these pricing mechanisms is gradually creating an unfavorable environment for innovative products. Product launches have become a do-or-die scenario in the Japanese market, and disincentivizing and penalizing policies make the situation even more difficult for startup companies that cannot afford to lose as a first entrant into Japan. Such companies must be successful for further innovation and launches in the market. If this pattern continues, Japan

will be pushed lower and lower in the ranks as companies prioritize where to sell their new medicines and treatments.

Therefore, TAG recommends the elimination of **both** the transparency co-efficient system (and the "co-factor zero" rule), and the corporate status criteria for the PMP.

The transparency co-efficient system has not successfully promoted transparency, but rather – via the "co-factor zero" rule – has effectively canceled out most premiums for innovation. This disproportionately penalizes the emerging biopharma companies that most value such incentives. Industry leaders, including PhRMA, have shared their concerns with "co-factor zero" and have recommended broadening the scope of eligibility for the comparator method to allow for more drugs to be priced under this scheme, rather than the cost calculation method. TAG further recommends the full elimination of the co-efficient system, to ensure that products receive the entire premium amount for which they are eligible. This will ease the way for such firms to enter the Japan market and promote more significant R&D of innovative drugs.

Likewise, the elimination of corporate status criteria for the PMP will boost a key incentive for new and emerging biopharma companies to launch innovative products in Japan. Instead of criterion favoring established firms, the MHLW should focus on product profiles from innovative points of views based on successfully developed and commercialized products.

These two changes would be reasonably low-cost to Japan, but greatly ease the process of market entry for new players, while more effectively spurring growth and fostering a dynamic innovation ecosystem.