EMERGING FROM DRUG LOSS:
A NEW DAWN FOR BIOTECH IN JAPAN

KYBORA

SWANIELLE

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Recent reforms to pharmaceutical and medical device regulations in Japan are creating greater opportunities for foreign drug developers to market their products in Japan, and deliver the latest medicines to Japanese patients.

Introduction

For a number of years, strict regulations and unfavorable market access conditions for new medicines have led to a phenomena in Japan known as drug lag or even drug loss. This is where foreign companies delay (in the case of drug lag) or even abandon (drug loss) developing and launching their products in Japan, as the barriers to market entry are too high.

Drug loss presents a serious issue for Japanese patients who are unable to access new medicines that have already been approved in other markets. For example, the drug avrapritinib - manufactured by US firm Blueprint Medicines Corporation - is the only treatment available for a type of gastrointestinal stromal tumor (GIST), and was approved in Europe and the US in 2020. However, avrapritinib has still not been approved and therefore is still not available to patients in Japan[1].

The complex drug development environment and pharmaceutical market has deterred many non-Japanese companies, particularly smaller biotech companies without Japanese affiliates, from entering the Japanese market. This is despite Japan being the world's third largest pharmaceutical market, with a value of $88 billion in 2024, and a projected value of $92 billion by 2029[2].

In recent years however, the Japanese government and the private sector have begun to address the issue of drug loss and drug lag in Japan with a series of measures designed to ease market entry for non-Japanese drug developers and incentivize innovative drug development in Japan, and signs of improvement are beginning to show.

This article will briefly look at the origins of the problem of drug loss in Japan, before exploring a number of recent reforms that have been made to address the issue, and finally present some examples of non-Japanese companies that have begun to capitalize on the improved market conditions.

Origins of Drug Loss in Japan

DRUG PRICE CUTS

As with other markets around the world, Japan has faced increasing pressure to reduce spending on healthcare and drugs. This has led to Japan's National Health Insurance (NHI) implementing strict drug pricing policies, with yearly downward price revisions and premium adjustments on drugs and medical devices. Such pricing controls have undoubtedly deterred some life science firms from marketing of their products in Japan.

MANDATORY JAPANESE PHASE I DATA

Until late 2023, Japan's regulators required phase I data from trials conducted in Japanese patients before allowing Japanese patients to enter later phase global, registrational trials.

This regulation effectively added at least $1M in costs (typical minimum cost for a phase I trial) and one additional year to the development timeline of any drug being launched in Japan.

IMPLICATIONS FOR DRUG LAUNCH IN JAPAN

[1] Japan to scrap rule requiring testing of new drugs on Japanese (2023) Nikkei Asia. Available at: https://asia.nikkei.com/Business/Pharmaceuticals/Japan-to-scrap-rule-requiring-testing-of-new-drugs-on-Japanese (Accessed: 15 November 2024).

[2] Japan Pharmaceutical Market Size: Mordor Intelligence (2024) Japan Pharmaceutical Industry Analysis | Market Growth, Size & Forecast Report. Available at: https://www.mordorintelligence.com/industry-reports/japan-pharmaceutical-market (Accessed: 04 November 2024).

Given that development of new drugs today increasingly comes from emerging biopharma companies, primarily based outside Japan and with no Japanese affiliate, as opposed to large multinational pharmaceutical companies, the requirement for phase I data in Japanese patients is likely to have contributed to drug lag and drug loss.

Reforms Addressing Drug Loss

The Japanese government has recognized the challenges faced by foreign pharmaceutical firms wishing to market their products in Japan, and appears to be taking the issue of lagging drug discovery seriously.

In fact, the Prime Minister of Japan himself, Fumio Kishida, has described the delivery of the latest drugs to Japanese patients as one of his government's "most important policies". At a Drug Discovery summit in Tokyo in July of this year, Kishida even promised to make Japan a "land of drug discovery", with a plan to attract global investment and encourage greater private sector involvement in drug development. The plan includes pledges to start clinical trials on the most urgently needed drugs by 2026, and establish 10 new drug discovery startups by 2028[3].

The Japanese government has also been implementing numerous reforms and new initiatives over the last 15 years to address drug lag and drug loss, in an effort to make Japan a more attractive market to foreign drug and medical device firms.

DRUG PRICING REFORMS

Price Maintenance Premiums (PMP) were first introduced in 2012, with the aim of protecting prices of innovative drugs from frequent price reductions, to encourage investment in new drug development, and help counter drug loss. PMPs apply specifically to drugs that are designated as innovative, which may include those with unique mechanisms of action, orphan drugs, and therapies with high clinical value.

The initial impact of PMPs was positive, with the percentage of new drugs being approved in Japan within a year of overseas approval increasing from just 18% before PMPs to 71% after the introduction of these premiums[4].

Recent updates to drug pricing policies, including updating PMP eligibility to allow more small and mid-sized life science firms to benefit, have further improved conditions for drug developers interested in marketing their products in Japan. The new policies, introduced by Japan's main government advisory body that sets prices for medicines and medical devices - the Chuikyo - in April of this year[5], can be summarized as follows:

Expanded Eligibility for Premiums for New Drugs

- Previously, new drugs had to apply for marketing approval in Japan within 30 days of filing to US or EU regulatory bodies (FDA and EMA respectively) to be eligible for Sakigake, or pioneer drug designation (see below) and the associated 10%-20% premium. Now, sponsor companies have up to three months from the date of their overseas filing to file a new drug application (NDA) in Japan and still be eligible for Sakigake designation.

- Additionally, a new 'rapid introduction' premium, set at a rate of 5%-10%, has been introduced for drugs launched in Japan within six months of US or EU approval. Unlike the Sakigake designation, there is no need for drugs to meet particular conditions of innovativeness, efficacy or therapeutic area to be eligible for the premium.

Revisions to Eligibility for Price Maintenance Premiums (PMPs)

- PMPs have traditionally been awarded on the basis of a company's level of R&D in Japan, effectively penalizing smaller biotech companies and startups. This so-called 'company index' method for awarding PMPs has now been abolished, to ensure that all companies with PMP-designated products can receive price protection, regardless of their size.

- As well as relaxing PMP company criteria, PMP product criteria have also been expanded, to allow pediatric and rare disease drugs to benefit from price protection.

Additional Premiums for Multiple Drug Indications

- Previously, a drug could only qualify for a post-launch price premium for one indication. This limited the incentives for developers of drugs with multiple applications. Under the 2024 reform, drugs can now earn multiple premiums for each different indication approved, allowing for price protection across several therapeutic areas. This change incentivizes the development of new uses for existing drugs.

Post-listing Upward Price Adjustment for Imported Drugs

- This measure has been introduced to shield imported drugs from drastic price drops during Japan's annual price revisions, and in doing so help make Japan a more attractive market for foreign companies. Drugs whose active ingredients and formulations are imported, and that did not receive a foreign price adjustment when first listed, will now get a one-time upward price adjustment based on the drug's average price in other major markets.

[3] Gate opening summit for Innovative Drug Discovery (2024) Prime Minister's Office of Japan. Available at: https://japan.kantei.go.jp/101_kishida/actions/202407/30souyaku.html (Accessed: 15 November 2024).

[4] Kobayashi, N. (2020) *Japan: Balancing cost and innovation through pricing, PharmExec*. Available at: https://www.pharmexec.com/view/japan-balancing-cost-and-innovation-through-pricing (Accessed: 15 November 2024).

[5] Gist of FY2024 Drug Pricing Reform (2023) PHARMA JAPAN. Available at: https://pj.jiho.jp/article/250145 (Accessed: 04 November 2024).

FLEXIBLE CLINICAL TRIAL REQUIREMENTS

In late 2023, Japan's Ministry of Health, Labor, and Welfare (MHLW) announced that it was relaxing the requirement for early-phase clinical data from Japanese subjects before allowing Japanese patients to enter later stage, global multicenter trials[6]. The notification explained that if existing clinical data supports the safety and tolerability of dosages being used in late-stage trials, and shows the safety of an investigational product to be clinically acceptable for Japanese participants, a standalone phase I trial in Japan is no longer necessary.

By eliminating the additional costs and timelines of conducting separate Japanese phase I studies, this new reform removes a significant obstacle for non-Japanese companies wishing to incorporate Japan into their development plans, and also opens up the theoretical opportunity for simultaneous Japanese drug approval with the US and Europe.

SAKIGAKE DESIGNATION FOR BREAKTHROUGH DRUGS

In an effort to counter drug lag, Japan's MHLW launched the Sakigake designation system in 2015[7]. Meaning 'pioneer' or 'forerunner', the Sakigake program aims to fast-track the development and approval of innovative treatments for serious, unmet medical needs in Japan. It is similar to other accelerated pathways, such as the Breakthrough Therapy Designation (BTD) in the US and Priority Medicines (PRIME) in the EU.

To qualify for Sakigake designation, a drug must demonstrate strong early clinical data in terms of safety and efficacy, be submitted for market approval first in Japan, or at least simultaneously with other markets, and be a novel therapy for a disease with high unmet need.

Companies whose innovative products gain the Sakigake designation are eligible for a range of advantages. Prioritized and comprehensive consultations with the Pharmaceuticals and Medical Devices Agency (PMDA) - Japan's regulatory agency - (within one month versus two months in the standard process) allow companies to receive guidance and submit materials to the agency for review before applications, with a PMDA manager even assigned as a 'concierge' during the process. An accelerated review process for Sakigake-designated products aims to shorten the approval timeline from 12 months to 6 months. If approved under the Sakigake designation, drugs may also qualify for higher price premiums, as well as extended market exclusivity, further rewarding companies for bringing new drugs to market in Japan.

INVESTING IN DRUG DISCOVERY

In addition to regulatory reforms to encourage more non-Japanese firms to develop and launch their products in Japan, the Japanese government and some pharmaceutical companies have implemented a number of financial incentives to boost the country's biotech 'engine'.

To encourage investments in Japan's biotech sector, the government offers subsidies, tax breaks, and startup funds. For example, the 'Strengthening Program for Pharmaceutical Startup Ecosystem' provides up to $60 million per project, as well as collaboration with venture capital firms throughout the program to support startups during early stage drug development[8].

Japanese pharmaceutical companies have also created dedicated research funds to encourage partnerships and invest in new drug development. For instance, Astellas, Shionogi, and Daiichi Sankyo have all launched funds aimed at supporting innovative research both domestically and internationally[9].

Finally, with the long-term goal of building 'clusters' of biotech innovation in a similar style to the technology hubs of Silicon Valley, innovation centers such as the Shonan iPark - opened by Takeda in 2018 - and the SakuLab-Tsukuba - opened by Astellas in 2023 - have been set up to promote collaborations between academia, startups, and major pharmaceutical companies[10]. Similarly, The Greater Tokyo Biocommunity (GTB) and Biocommunity Kansai (BiocK) are biotech hubs created to support Japan's '2030 Bioeconomy Strategy" by attracting significant private investment and encouraging collaboration across industry, academia, and international partners. The GTB alone has already attracted over $3.3 billion in investment[11].

[6] (2024) Regulatory updates in Japan. Available at: https://www.pmda.go.jp/files/000269411.pdf (Accessed: 04 November 2024).

[7] Tanaka, M. et al. (2021) 'Achievements and challenges of the designation system in Japan', British Journal of Clinical Pharmacology, 87(10), pp. 4027–4035. doi:10.1111/bcp.14807.

[8] *Strengthening program for pharmaceutical startup ecosystem* (2024) Japan Agency for Medical Research and Development (AMED). Available at: https://www.amed.go.jp/content/000131506.pdf (Accessed: 15 November 2024).

[9] Pharmaceuticals in Japan (2014) The Government of Japan. Available at: https://www.japan.go.jp/letters/medical/pharmaceuticals/Pharmaceuticals%20in%20Japan.pdf (Accessed: 04 November 2024).

[10] Siddiqui, A. (2024) *Rebooting Japan's Biotech Growth Engine, BioSpectrum Asia*. Available at: https://www.biospectrumasia.com/analysis/25/24797/rebooting-japans-biotech-growth-engine.html (Accessed: 15 November 2024).

[11] *Government initiatives: Life science - industries - investing in Japan - Japan external trade organization* (2023c) *Japan External Trade Organisation (JETRO)*. Available at: https://www.jetro.go.jp/en/invest/attractive_sectors/life_science/government_initiatives.html (Accessed: 15 November 2024).

English Language Registration

In another effort to ease the application process for non-Japanese firms seeking marketing approval for their products in Japan, the MHLW also announced in September 2024 that, under certain conditions, it would accept filing documents to be submitted in English. Provided that a drug contains a new active ingredient, is a new combination of (prescription) drugs, or has a new route of administration, and that its parent company has no offices in Japan, all documents for approval filing will be accepted in English. It is hoped that by removing hurdles for more innovative foreign products to enter the Japanese market, this new measure will contribute to addressing the drug gap between Japan and the global market.

Impact of the Changes

Foreign biotech companies are now taking advantage of the recent reforms, with a growing number of firms conducting drug development and launches in Japan in recent years.

For example, this year Gossamer Bio, a San Diego-based biotech company, was one of the first companies to take advantage of the changes allowing Japanese patients to enter global phase 3 studies without the need for a bridging study in Japanese patients. This allowed Gossamer to include Japanese patients in its global phase 3 PROSPERA study of seralutinib, a treatment for pulmonary arterial hypertension.

Similarly, Mannkind Corporation, a biopharma company from the US, received clearance from the PMDA in September this year to include Japanese patients in their global phase 3 trial of their Clofazimine Inhalation Suspension, targeting nontuberculous mycobacteria (NTM) lung disease. This allows the company to move towards launching their product on the Japanese market despite having no previous data in Japanese patients.

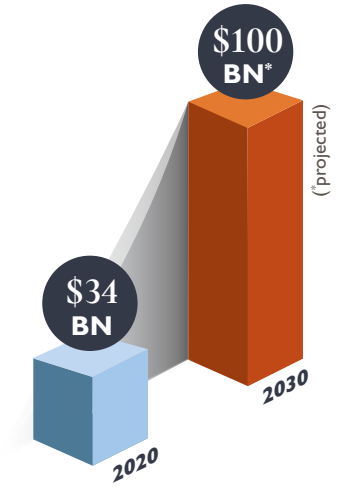
Meanwhile Belite Bio's efforts to bring its vision loss product tinlarebent to Japanese patients were boosted earlier this year following Sakigake designation and orphan drug designation for the product in Japan. These privileges mean Belite Bio will benefit from a streamlined registration process, as well as potential price premiums and price protection if tinlarebent is approved.

Another company that saw commercial success in Japan recently was the Swedish biotech firm Calliditas. It chose partnering as a route of entry to the Japanese market, teaming up with Japan's Viatris to bring Nefecon, a treatment for IgA nephropathy, to the Japanese market. The deal was successful, with Nefecon now in phase 3 trials. It also caught the eye of Japanese conglomerate Asahi Kasei, who acquired Calliditas for $1.1BN in June this year.

Following the introduction of incentives to boost drug development in Japan such as Sakigake designation and PMPs, the average drug lag has also decreased by approximately three years. since new reforms introduced[12].

Today, Japan's biotech market is growing, valued at $34BN in 2020 and projected to reach a value of $100BN in 2030.

RAPID GROWTH OF JAPAN'S BIOTECH MARKET



[12] Tanaka, M. et al. (2020) 'Evolving landscape of new drug approval in Japan and lags from international birth dates: Retrospective Regulatory Analysis', *Clinical Pharmacology &Therapeutics*, 109(5), pp. 1265–1273. doi:10.1002/cpt.2080.

Conclusion

The Japanese government has clearly recognized the need to address the issues of drug lag and loss. For too long, patients have had to wait for, or simply gone without the latest drugs available in other markets.

Recent reforms to the regulatory system have created new opportunities for non-Japanese companies to establish a foothold in the world's third largest pharmaceutical market.

Many of the reforms specifically benefit companies developing innovative treatments for rare diseases and diseases with a high clinical need. That means these reforms can particularly help smaller and mid-sized companies from the biopharma sector, where many of the most innovative therapies are being developed nowadays.

A number of US and Europe-based firms have already started to make use of the improved conditions, whether through enjoying an accelerated review process, more sustained price protections for their products in Japan, or simply by being able to include Japan in global registrational trials without having to conduct bridging studies in Japan.

Significant recent investment into life science innovation projects also underline how serious Japan is about building drug discovery infrastructure for the long term. The products of these initiatives will also enable more access to the Japanese market for foreign drug developers through partnerships and collaborations with an invigorated domestic market.

A large and important market that was effectively isolating itself from the rest of the world with restrictive regulatory barriers is now opening its doors to foreign drug developers, easing access and creating a more favorable environment for them.

This could bring significant rewards for companies that bring their products to the Japanese market, and for Japanese patients.

ABOUT KYBORA

KYBORA is a global advisory firm and investment bank whose mission is to guide transformative healthcare companies to enduring success globally. We provide M&A, licensing, fundraising, and strategic advisory services to the global healthcare industry, creating value for our clients worldwide. With offices in the US, Switzerland, and China, and a direct presence in all key biopharma markets around the world, KYBORA offers unparalleled global reach and local knowledge. Contact us to explore how we can help you address your most pressing challenges.

Email: info@kybora.com
www.kybora.com

ABOUT SWANIELLE

Swanielle is a Japanese consulting company that accelerates medicine access through strategy and partnerships. The company's mission is to eliminate "Drug Loss" in Japan, thereby ensuring that patients have prompt access to essential medicines. Swanielle supports companies in strategically planning and executing partnerships, from co-development to commercial collaborations within Japan/Asia.

Email: hiroshi.yamabe@swanielle.com
www.swanielle.com