European Federation of Pharmaceutical Industries and Associations

Building sustainable Pharmaceutical Innovation Ecosystems through effective Health Technology Assessment (HTA) review in Japan

EFPIA Japan

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In collaboration with EY Strategy and Consulting

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Summary

- Since its official implementation in 2019, the HTA system in Japan has rapidly evolved with biennial updates enhancing its robustness. Although the latest revisions in 2024 have advanced the system's transparency, the system still faces several challenges such as sub-optimal process clarity and predictability, incomplete scientific basis for cost-effectiveness determination, fragile balance of HTA adjustment scope and innovation reward, and insufficient patient stakeholder involvement. As such, further optimisation is warranted.
- We believe the public and private sector can further contribute to improving the system via enabling patient-centric regulation development, regular payer-industry dialogue, and better stakeholder engagement through public-private partnerships with academia.
- Further optimisation of the HTA system in Japan has the potential to drive long-term innovation by balancing patient, payer, and industry interests in a sustainable manner.

1 Introduction to HTA in Japan

To effectively and sustainably drive the Pharmaceutical Innovation Ecosystem, it is crucial that the interests of patients and payers are balanced in a predictable manner. This allows patients to receive optimal care at a fair value, whilst pharmaceutical industry players are being sufficiently incentivized to invest in developing future treatments. Health Technology Assessment (HTA) can enable this process by systematically evaluating the cost and impact of health technologies via different methodologies such as cost-effectiveness assessment and comparative clinical benefit assessment.

Cost-effectiveness assessment was adopted as the HTA system in Japan, complementing the drug pricing system and used for post-launch price adjustment. First piloted in 2016 and officially introduced in 2019, it is still in its early stages with only 50 drugs having been selected as assessment candidates to date. Japan is fundamentally different to other major markets in that HTA results do not inform reimbursement decisions, as all approved drugs in Japan are made available to patients under universal healthcare coverage without exception. The unique implementation of HTA in Japan means that it does not add delays to patient access to drugs.

Since its 2019 launch, HTA in Japan has been the topic of numerous discussions as it holds an important role in shaping the future healthcare landscape; one which has been under substantial pressure due to the super aging and declining population in Japan. This has resulted in the government looking for ways to reduce the financial burden as there are less people paying into the healthcare system while costs keep increasing. However, at the same time there is a need to promote further innovation, as the pharmaceutical market growth in Japan has been projected to lag severely behind other major markets (0.3% in Japan as compared to 2.5-5.5% globally between 2023 and 2027)[1]. As a result, Japan's current position as the third largest pharmaceutical market with ~5% global share is likely to be lost to Germany by 2026. In view of this, we believe it is crucial to seek out opportunities to continuously improve the HTA system such that both cost and innovation are well balanced to ensure a sustainable and thriving healthcare landscape in the long term.

2 Challenges with the current system

- **Sub-optimal process transparency and predictability**

A key challenge of the current HTA implementation is the lack of transparency and predictability. Identifying the latest set of rules is not straightforward, and certain criteria definitions within the rules lack clarity[2]. It is also unclear how certain seemingly conflicting definitions will be addressed, making it hard for industry players to predict whether their products will be subjected to the HTA system.

An example of rule ambiguity is where HTA is applicable to drugs of considerable market value (>5 billion JPY forecasted revenue at peak year) and/or that are "significantly high-priced", but the precise definition of "significantly high-priced" is not specified and is subject to the decision of the Chuikyo (Central Social Insurance Medical Council)'. The fact that decisions to subject a treatment to HTA can be made on a case-by-case basis at Chuikyo's discretion negatively impacts the transparency and predictability of the HTA process.

Another example that illustrates seemingly conflicting definitions is that while current HTA rules exempt drugs treating diseases for which there is no other cure or drugs approved only for paediatric indications, the rules do not elaborate on what would happen if these exempted drugs are also considered to be of considerable market value and/or "significantly high-priced". 2024 guideline updates saw the removal of "drugs for diseases which are rare" from HTA exemption, and it can be speculated that the omission is partly due to the fact that this category includes Orphan Drugs that are in general highly priced.

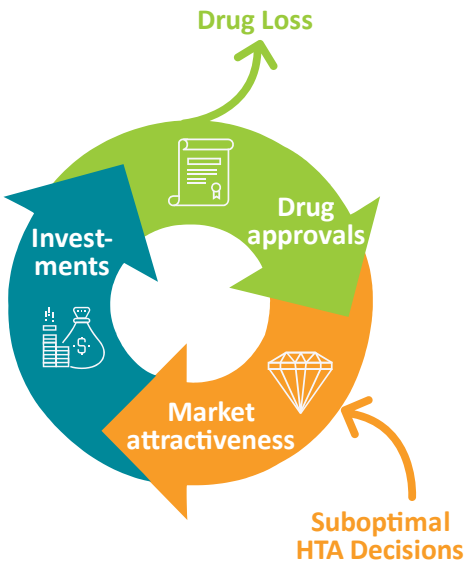
The apparent prioritisation of NHI price in HTA eligibility decisions can be illustrated with the case of the first treatment to have its price reduced as a result of HTA[3]. The subject, a cell therapy, is a Designated Orphan Regenerative Medicine priced at 32.6 million JPY (as of Apr 2024; one-off usage), causing it to be classified as being "significantly high-priced" and thus subjected to HTA, despite treating Orphan Diseases where there are no other indicated drugs.

It would appear that despite the ambiguity on whether non-indicated treatments (chemo-therapy in this case) are considered as a

"cure", it was nonetheless subjected to HTA seemingly based on its price tag.

This is a potential cause for concern for the industry, especially for smaller biotechs focused on innovative therapies and treatments for orphan diseases. Ambiguous rules that leave room for interpretation mean that there is a considerable amount of uncertainty on how and when future innovative treatments for Rare Diseases will be subjected to HTA. This presents a risk to investors assessing investment returns that potentially translates to lower market attractiveness and thus reduced investments, resulting in the exacerbation of the 'drug loss' problem and directly affecting patients. (Figure 1)

Figure 1. How suboptimal HTA decisions can exacerbate the Drug Loss problem



Drug Loss occurs when innovative treatments approved in the US and Europe are not available to Japanese patients (usually due to delays in regulatory submission, or Japan not being included in global clinical trials). As of Nov 2023, 86 drugs are 'lost' in Japan, including 39 indicated for diseases without existing treatment locally.

Suboptimal HTA decisions can contribute to the Drug Loss problem by negatively impacting marketing attractiveness, thus decreasing the confidence of investors to include Japan in the clinical development stage.

- **Incomplete scientific basis for cost-effectiveness determination**

Once a drug is selected as an HTA candidate, its cost-effectiveness is calculated as the Incremental Cost-Effectiveness Ratio (ICER) against a designated comparator. The validity of ICER calculations depends heavily on comparator choice, and in addition, a scientifically robust method for analysing unquantifiable parameters of treatment value improvement such as productivity gain and reduction in caregivers' burden, and continuous dialogue is warranted in order to determine if and how these social benefits can be incorporated into the cost-effectiveness calculation.

While there are no set rules, in practice the cheapest treatment within the indication or drug class can be selected with insufficient consideration of clinical data and actual usage and comparability. As an example, the HTA of an GLP-1 agonist was conducted using the cheapest therapy in all analysis groups within the indication. The fact that the comparator is the cheapest but also only represents 2% of the market share highlights the limited clinical relevance of the chosen comparator[4].

The 2024 HTA guideline updates[5] partly address these concerns with minor specifications added to the comparator choice criteria (such as defining 'widespread clinical use' not only according to total patient numbers but that the drug in question is the recognised Standard of Care). While this potentially facilitates better decision making for choosing the most appropriate comparator, concerns remain that the lack of scientific evidence and rationale for comparator choice compromises scientific validity of the cost-effectiveness assessment outcome, as voiced by Health Economics and Outcomes Research (HEOR) experts[6] and also

touched upon in a previous whitepaper from EFPIA[7].

As the value of HTA lies in securing the balance between the cost to the healthcare system and benefits to society with life-improving treatments, addressing these concerns to establish a solid scientific basis for analysing cost-effectiveness is vital.

- **Fragile balance between HTA repricing scope and innovation premiums**

Recent discussions on expanding the scope of HTA price adjustments raises potential issues. HTA is currently applied to the premium portion of the drug price, and Chuikyo intends to expand this scope for extremely highly priced drugs (> 150 bil. JPY market size), and adoption of this new rule as a 'Special Provision HTA' for a new drug for Alzheimer's Disease[8] has been announced. Under this measure, a reference price point corresponding to an ICER of 5 mil. JPY/QALY will be used to determine whether the drug price should be decreased (down to 85%) or increased (up to 110%). While positioned as a special provision, the Chuikyo has not ruled out broader applications in the future.

If broadly adopted in the future, the new rule potentially allows HTA to erode into the base price, and may even result in a drug ending up with a price lower than a less innovative competitor that was not selected for HTA. As drug price is calculated based on multiple factors including clinical efficacy, while HTA assesses cost-effectiveness, these two systems should be separate but complementary, rather than interfering with each other. More discussions must be conducted on how to ensure fair HTA without negating the value of a drug and hampering innovation.

- **Limited patient involvement**

Involvement of key stakeholders to contextualize health technologies is crucial for properly assessing the value of health technologies, thus substantially reducing the risk of mis-assessment. Patients in particular give meaning to new treatment technologies, being the direct beneficiary of innovative treatments. Within this context, updates were made to the 2024 HTA guidelines recommending QOL (Quality of Life) value estimation to be based on patient responses rather than proxy ones by HCPs, and to prioritise patient voices from Japan. However, the effectiveness of this on patient inclusion remains to be seen, and the issue remains that insufficient patient perspectives in HTA decisions risk compromising the relevance of the cost-effectiveness assessments. If patients are not directly engaged and involved, the HTA system will run the risk of a mismatch with unmet needs and stray way from a patient-centric system that is the heart of an innovative market.

3 Towards the optimisation of HTA in Japan

Having a clear view of current challenges facilitates an effective review of the HTA system, and we believe that the following efforts from both the public and private sector can contribute to optimising the system to drive cost-effectiveness and innovation.

- **Increase transparency of the rules and decision-making processes**

EFPIA regularly and actively work together

with other industry bodies in Japan such as JPMA (Japan Pharmaceutical Manufacturers Association) and PhRMA (Pharmaceutical Research and Manufacturers of America) to advise the Chuikyo, providing highly relevant and significant feedback on HTA. These input and insights have so far been effective in pointing out gaps within the system from both local and global perspectives to help shape HTA rules (as seen in some of the 2024 updates to the HTA guideline)[4,6], and continued involvement of the industry will be invaluable to evolve HTA in Japan.

Legislators and payers can also drive HTA changes by enhancing assessment criteria clarity by clearly outlining the scope and rules for HTA candidate selection. Scenarios where exceptions to the rule can be expected should be clearly defined to improve consistency and predictability in the process.

- **Invite patients, industry, and academia voices to shape regulations**

While recent HTA guideline updates demonstrated an appetite of the government for taking industry opinion into account, the positive changes are coupled with remaining issues, where continued engagement of all stakeholders will be crucial to ensure that future policies do not hinder innovation and access.

Being the center of the Pharmaceutical Innovation Ecosystem, the involvement of patients and patient organizations in multi-stakeholder dialogues is crucial. Public-private partnerships with academia involvement can facilitate the selection of the most valuable and relevant patient voices to be given the appropriate weight to address unmet needs in the best way, and patient engagement can be encouraged by providing accessible and inclusive education.

Industry bodies can provide platforms for patients and other stakeholders to exchange ideas, drawing on successful examples to improve the system. The government can also initiate and embrace public-private partnerships to secure stakeholder involvement in building a compelling logic for HTA that maximizes value for patients, and reference best practices from other markets such as IMI[9], the world's largest public-private health partnership funded by the EU and industry in Europe through EFPIA.

4 Conclusion

To shape future assessments and decision-making, Japan should build on current strengths including the short duration till reimbursement, and address challenges that may hinder long-term innovation. Tackling the technical and scientific challenges with current HTA will contribute to an optimised system. In particular, increased transparency, more careful deliberation of the HTA adjustment scope, and the involvement of patients as facilitated by private-public partnership can not only drive a patient-centric Pharmaceutical Innovation Ecosystem that benefits all stakeholders involved, but also allow the healthcare system to remain affordable with demographic and social changes and continue to sustainably provide true value to patients.

References

1. The Global Use of Medicines 2023: Outlook to 2027. IQVIA Institute for Human Data Science, January 2023 (link)
2. Cost-effectiveness Assessment Subcommittee meeting materials. (See slide 4-5 for rules and selection criteria). Chuikyo, Sep 2023 (link, Japanese version only)
3. Report on Kymriah HTA and resulting price adjustment. Chuikyo, April 2021 (link, Japanese version only)
4. Industry opinion towards the HTA system. Chuikyo, November 2023 (link, Japanese version only)
5. Cost-effectiveness Assessment Subcommittee meeting materials. Chuikyo, January 2024 (link, Japanese version only)
6. Shiroiwa, T. (2023) 'Selection of a comparator and population for cost-effectiveness evaluation', *J. Natl. Inst. Public Health*, 72 (2), pp. 152-160 (link)
7. Fundamental Observations on Cost-Effectiveness Assessment of Drugs – Issues surrounding scientific validity. EFPIA Japan, August 2021 (link, Japanese version only)
8. Cost-effectiveness Assessment Subcommittee meeting materials. Chuikuo, December 2023 (link, Japanese version only)
9. Innovative Medicines Initiative (link)

European Federation of Pharmaceutical Industries and Associations, Japan

EFPIA Japan was established in 2002 and represents 23 R&D-based European pharmaceutical companies operating in Japan, occupying 31% of the local pharmaceutical market altogether in 2022. We actively engage in dialogue with policy makers, and our mission is to contribute to the welfare of the Japanese population through the provision of innovative pharmaceuticals and vaccines without delay.

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Contact EFPIA Japan at info@efpia.jp

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EY Strategy and Consulting K.K.

Health Sciences & Wellness Consulting

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