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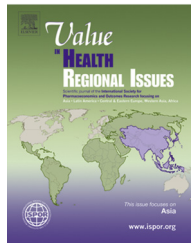

Themed Section: Drug Policies in Asia

Role of Health Technology Assessment in Drug Policies: Korea

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ABSTRACT

South Korea is the first Asian country to mandate the submission of pharmacoeconomic data for reimbursement decision making. For a new drug to be listed, it must demonstrate its value in terms of comparative effectiveness and cost effectiveness. The Health Insurance Review and Assessment Service (HIRA) judges the submitted drug's value and decides whether its coverage is appropriate on the basis of the recommendation of the Pharmaceutical Benefit Coverage Assessment Committee. Once the drug has been accepted by HIRA, the National Health Insurance Service and the sponsoring company negotiate the price and expected sales volume. Even if HIRA acknowledges the value of the drug, it cannot be listed if the negotiation fails. In the off-patent market, generic and original branded drugs are treated equally in terms of pricing. Once generics enter the market, both drug prices should be lowered to 53.55% or less of the on-patent price. Since the current system was implemented, concerns have been raised about a decline in the accessibility of new drugs, especially for high-priced drugs used to treat serious diseases. In 2013, several measures had been introduced aimed at improving the accessibility of these drugs. A risk-sharing scheme and an increase in the maximum acceptable cost-effectiveness ratio were subsequently initiated. Although these schemes have been successful in improving access to high-priced drugs, they are often criticized for reducing transparency in pricing. Finding a balance between accessibility and efficiency is still a challenge in Korea.

Keywords: coverage, drug policy, health technology assessment, South Korea.

Introduction

National Health Insurance

In 1989, Korea's National Health Insurance (NHI) coverage was expanded to the entire population, only 12 years after it was first introduced for large-scale workplace workers. Currently, about 97% of the population is covered by the NHI except for those who are eligible for medical aid. Medical aid, financed by tax revenue, mainly targets low-income groups and those in need of social protection.

Although the entire population is covered by the public health security system, there is still room for improvement in terms of the depth and height of coverage in Korea [1]. Some medically necessary services are excluded from the benefit basket, and the co-insurance rate for covered services is relatively high—20% for inpatient services and 30% to 55% for outpatient services. To improve the coverage of NHI, the Korean government has been continuously expanding the benefit basket and has lowered co-insurance rates for patients who suffer from severe diseases (5% for cancer and rare diseases). The current government also announced that it intends to increase service coverage and the level of protection for vulnerable people.

In addition to coverage issues, financial sustainability is an important challenge facing the Korean society. In 1990, total health expenditure was 3.68% of the gross domestic product (GDP), which was estimated to be 7.67% in 2016 [2]. Given that Korea's population is aging rapidly, it is necessary to control the rise in health expenditure in some way.

Pharmaceutical Market

Korea's pharmaceutical market was the 13th largest in the world in 2015 [3]. Although pharmaceutical expenditure per person is slightly lower than the average of the member countries of the Organization for Economic Co-operation and Development, the proportion in terms of total health spending is relatively high. In fact, it was between 20% and 28% during the last decade. Moreover, it has increased very rapidly. In particular, during the first half of the 2000s, per capita pharmaceutical expenditure increased by more than 10% per annum [2].

Because pharmaceutical expenditure has been increasing rapidly since 2000, the government has begun to actively look for policy alternatives to control it, and finally, in 2007, announced comprehensive cost control measures in the form of the Drug Expenditure Rationalization Plan (DERP). The DERP

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includes the introduction of a positive list system (PLS), price negotiation, price reduction after patent expiry, and incentives for rational drug use [4]. In addition to DERP, the government has made several price cuts in the off-patent market.

In this article, the details of the Korean drug policy and how health technology assessment (HTA) is used in this process will be elaborated upon. The challenges facing the Korean society today will also be discussed. It is hoped that this will provide implications for Asian countries considering the introduction of similar policies.

Market Authorization

The Ministry of Food and Drug Safety (MFDS) is a governmental regulatory body that ensures pharmaceuticals and medical devices are safe and efficacious and meet all the necessary quality standards. The manufacturers who wish to launch new products in the Korean market should prepare a dossier and submit their application for market authorization to the MFDS, which will then review the submitted evidence of the safety and efficacy of the drugs and make a market authorization decision. Depending on whether the submitted drugs are new, modified, or generics, the types of data that need to be submitted vary. Market approval is valid only for 5 years, and so manufacturers must renew the approval every 5 years. Detailed guidelines for processing the submission are published by the MFDS.

To facilitate early access to innovative drugs used to treat life-threatening diseases or orphan drugs, some policies have been suggested to accelerate approval, such as conditional approval and rolling review. Conditional approval is granted for drugs that show probable innovation in phase II clinical trials, subject to the submission of phase III clinical trials. A rolling review is a kind of adaptive review process in which the reviewer continues to engage in a dialogue with the sponsors during clinical trials and reviews the safety and efficacy of the drugs from an early stage in the trial only if the case shows the possibility of being innovative, which can shorten the time required for approval [5]. There is, however, concern over this process because there is uncertainty about the safety and efficacy of drugs that have limited evidence to support this. In practice, there are cases that fail to demonstrate their superiority as opposed to earlier expectations. Early decisions based on immature data can accelerate the introduction of probable new drugs, but it runs the risk of introducing ineffective or unsafe drugs.

Another issue is the cooperation of market authorization and reimbursement process. Patient groups complain that the listing decision is delayed for too long after the market authorization decision is made. The delay is inevitable to some degree because different types of evidence are required in the reimbursement decision. For market approval, safety and efficacy are central factors, but comparative effectiveness and cost effectiveness are also important in reimbursement and pricing decisions. Nevertheless, there is room for shortening the time gap between approval and listing. If the review process starts before the market approval process is finalized, the time required for listing will be shortened. Therefore, the Korean government decided to link the two processes to shorten the listing time [6].

Reimbursement and Pricing

New Drugs

Since 2007, the drug listing system in Korea has changed from negative to positive. In the past, all drugs had to apply for listing within 30 days after market approval, and the Health Insurance Review and Assessment Service (HIRA) determined the price according to a predetermined formula. Only drugs used to alleviate minor symptoms were excluded from the list (negative list). Under the PLS, however, sponsoring companies have been able to decide whether to apply for listing.

The listing process begins when the sponsor submits a dossier to HIRA with supporting evidence about the comparative effectiveness and cost effectiveness of the drug (Fig. 1). HIRA staff reviews the submitted evidence and assesses its scientific soundness. Then, the Pharmaceutical Benefit Coverage Assessment Committee (PBCAC) deliberates on the value of the case on the basis of the submitted evidence and HIRA staff's review comments. HIRA is a public agency that is commissioned by the Ministry of Health and Welfare to review the comparative effectiveness and cost effectiveness of any new drugs submitted for listing and to determine the price for generic drugs. The PBCAC is an independent advisory committee whose role is to make recommendations on benefit coverage for HIRA.

If the new drug is similar to its comparators in terms of effectiveness, its price is compared with the prices of existing drugs and accepted only when it is lower than the average price

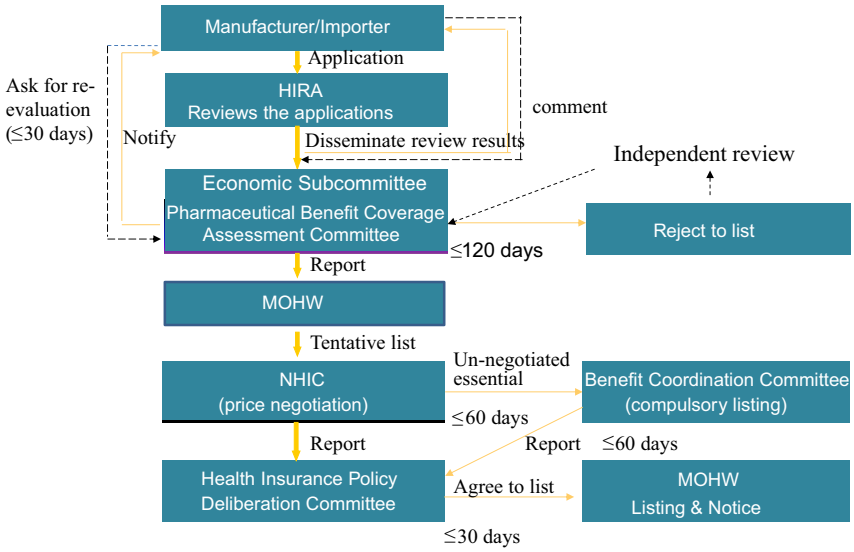
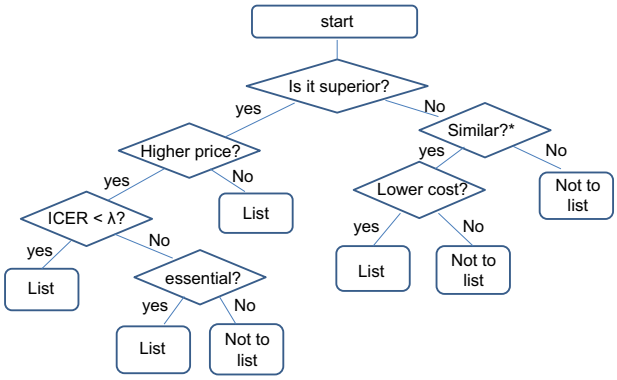


Fig. 1 – Process of new drug listing. HIRA, Health Insurance Review and Assessment Service; MOHW, Ministry of Health and Welfare; NHIC, National Health Information Center.



*'Similar' includes the cases which are equal or non-inferior compared to the alternatives.

Fig. 2 – Flow of reimbursement decision making. *"Similar" includes the cases that are equal or noninferior compared with the alternatives. ICER, incremental cost-effectiveness ratio.

of the existing comparators. In case the drug is superior to the alternatives, cost effectiveness is judged on the basis of the incremental cost-effectiveness ratio (ICER) (Fig. 2). In addition to comparative effectiveness and cost effectiveness, other social values, such as the severity of disease and the existence of substitutable drugs, are also considered in reimbursement decisions [7].

Once the PBCAC accepts the case, the sponsor and the National Health Insurance Service (NHIS) begin price negotiations. The negotiated price cannot exceed the level accepted by the PBCAC. To negotiate the price, the NHIS checks the prices in other member countries of the Organization for Economic Co-operation and Development and considers the budget impact. Once a negotiation agreement is reached, the NHIS and the company sign a contract on the basis of price and expected volume. Price negotiation was implemented from 2007 as a part of DERP.

When price negotiation was introduced, some stakeholders criticized it for being redundant with the process done by HIRA. Some, however, appreciated it in the respect that it maximized the insurer's bargaining power. In fact, prices have fallen considerably during the price negotiation process.

Generics

In Korea, generics account for more than 40% of the total pharmaceutical market, which is not as low compared with other countries [8]. Nevertheless, there is no active price competition in the generic market. According to Kim et al. [9], the weighted average price of drugs with the same molecule is higher than their simple average price, which means that higher priced products are preferred in the market.

Entry prices of generic products are regulated by the government. Before 2012, the first generic drug should have been priced lower than 68% of the price of the original branded drug. Furthermore, upon entry of the first generic drug, the original branded drug's price should have also been lowered by 80% of its original price. This pricing system was, however, criticized in Korea in that it was not reasonable to reimburse different amounts for the same molecules despite the fact that the generics and the originals were not different in efficacy.

In 2012, the differential pricing system was abolished. All drugs with the same molecules were to be priced at a minimum of 53.55% of the original drug, 1 year after the first generic's entry into the market [10]. This contributed a lot to reducing the proportion of pharmaceutical expenditure in total health spending. Nevertheless, the new pricing system still does not allow for price competition; that is, there is no incentive to lower the price below the regulated maximum price. After the change to the pricing formulae, the market share of generics has decreased, which may be because there is no difference between the prices of original and generic drugs.

Essential Drugs

There is no list of essential drugs in Korea. Instead, there is a list of drugs that are guaranteed at a certain price to prevent them from exiting the market. Most of these drugs are cheap and have few substitutes, and so it can cause problems with patient care if they are unavailable in the market.

In 2016, the Korean government introduced the concept of "national essential drugs" in the amended Pharmaceutical Affairs Act, which aims to ensure a stable supply of drugs that are essential in patient care but maintaining their stable supply is difficult in the market [11]. If a drug is selected as an essential drug, its supply is monitored, and measures are taken to prevent an interruption in supply. This is to safeguard a stable supply, which is the key to this policy.

Role of HTA in Drug Policies

HTA: Current Status

Organizations involved in HTA

HIRA is an organization that plays a key role in reimbursement decision making on the basis of scientific assessment of submitted evidence and value judgment. Whenever a sponsoring company submits a dossier with supporting evidence, HIRA staff reviews it and assesses whether it has adhered to the guidelines.

The PBCAC makes a recommendation on whether to list the submitted drug. Even though the role of the committee, as specified in the act, is to provide advice to HIRA, it can be regarded as a decisive role because HIRA does not make decisions that differ from the committee's recommendations. The committee is composed of experts in medical subspecialties, pharmaceutical science, statistics, and health economics. In addition, representatives from consumer advocacy groups, patient groups, and government officials are also included.

In case full economic evaluation data are submitted, the Economic Subcommittee reviews the submitted data and the HIRA staff's assessment results before the PBCAC deliberates on the case and provides technical advice to the PBCAC. The PBCAC is expected to respect the Economic Subcommittee's technical advice on cost-effectiveness studies, but the final decision is solely PBCAC's responsibility. The PBCAC considers not only comparative effectiveness and cost effectiveness, but also severity of disease, the availability of substitutes, rarity of disease, budget impact, and the benefit status of the drug in other countries as well. These criteria are specified in the committee's operating rules [12].

The National Evidence-based healthcare Collaborating Agency (NECA) is the representative HTA agency in Korea. It evaluates new or existing technologies in terms of comparative effectiveness and cost effectiveness and publishes the results on its Web site to disseminate them widely. New technologies, other than drugs, are to be assessed by the new medical technology assessment committee to determine their safety and effectiveness before any reimbursement decisions are made. Currently, NECA supports the new medical technology assessment committee by producing supporting evidence. It is, however, not involved in the process of market approval or reimbursement decision making for the new drug.

Capacity of conducting HTA

Pharmacoeconomic guidelines were developed in 2005 for the voluntary submission of economic evaluation studies by pharmaceutical companies. These guidelines became official when the PLS implemented them in December 2006. In addition to the pharmacoeconomic guidelines, guidance for indirect comparisons and checklists for reviewers have been continuously published by HIRA since 2007 [13]. Moreover, reference materials for systematic reviews and costings were published by NECA [14].

When the government announced that new drugs had to show their cost effectiveness if they were to be priced higher than existing drugs, there was a concern over the lack of expertise in both the industry and HIRA. Nevertheless, according to a survey of the stakeholders conducted a few years after the introduction of the system, expertise was not a significant problem, although there was still a lack of expertise on both sides. That is because the number of submissions requiring full economic evaluations was not high, and most of them were submitted by global pharmaceutical companies where the headquarters prepared the economic model and local branches modified the basic model to reflect the situation locally [15].

Lack of local data was also a cause for concern for many stakeholders in the early days of the PLS. In the survey, stakeholders responded that lack of local data is the most problematic for utility and disease epidemiology [15]. Cost data are also insufficient, but have improved with enhanced access to claim data over the last decade. Currently, HIRA and the NHIS provide sample data, which link the years of claim data at patient levels.

Use of HTA in Decision Making

After the introduction of the PLS, HTA has officially been used in reimbursement decision making. All submitted drugs must demonstrate their value, and the methodology of HTA has been used to assess the comparative effectiveness of a drug. For drugs that are superior to and more expensive than existing drugs, a full economic evaluation is required to support their cost effectiveness.

The selection of comparators and the method of base-case analysis are specified in the pharmacoeconomic guidelines. Regarding the selection of the comparator, the most prevalent one among substitutable drugs is recommended. If two or more drugs with similar market shares are competing with each other, multiple comparators may be selected. Cost-utility analysis is the preferred type of analysis when the submitted drug is superior to comparators, and changes in resource use and outcomes from the perspectives of the society are expected to be included in the analysis (limited societal perspective). For outcome estimates, a head-to-head comparison with the specified comparator is preferred, but an indirect comparison is also allowed when there are no, or few, direct comparisons. In most cases, there is substantial uncertainty in the structure and parameters of the model used, and so extensive sensitivity analysis is an essential requirement [16,17].

At the time of introduction of the PLS, the government mainly focused on improving transparency within the system. More opportunities to appeal the applicant's view on HIRA's assessment were permitted to pharmaceutical companies. In case the submitted drug is rejected by the PBCAC, an independent review can be requested from a member of the independent review panel, which is independent from the government or any decision-making bodies that are involved in the reimbursement decision-making process [15]. Nevertheless, after the system was stabilized to a certain degree, the issue of accessibility became more intense than that of transparency [15].

Compared with the previous period, the rejection rate has increased, because some new drugs failed to demonstrate their value. From January 2007 to December 2014, 69.2% of submitted drugs were accepted by the PBCAC, and 65.6% were finally listed after successful price negotiations. It is comparable with the number observed in other countries where the HTA-driven reimbursement decision-making system is implemented [18–20]. Accordingly, not only pharmaceutical companies but also clinicians and patients insisted that their accessibility to new drugs has deteriorated after the introduction of the PLS [15]. In particular, there were concerns about lowering accessibility to new treatments used to treat severe diseases, such as cancer. For reference, the acceptance rate for anticancer drugs stood at 51.6%, which is lower than that for other drugs. The low acceptance rate of anticancer drugs is due to most of them being submitted at much higher prices than their comparators [21].

Responding to stakeholders' arguments, the government announced a series of measures to improve accessibility to high-priced new drugs that are used for severe life-threatening diseases. One of them is the introduction of a risk-sharing scheme. This is a system in which the applicant and the insurer share the financial risk and the risk of uncertain treatment effects. There are four types of risk-sharing plans in Korea: refund the gap between the listed price and the contracted price, a mixture of conditional treatments based on response and refund, global expenditure cap, and per patient expenditure cap. Except for coverage with evidence development, all risk-sharing plans are intended to meet the cost-effectiveness criteria by decreasing the effective price in a way that the pharmaceutical company refunds the gap between the listed price and the cost-effective price, or pays the drug cost of nonrespondents [22].

Pharmaceutical companies can suggest a risk-sharing plan if the submitted drug is used for life-threatening cancer or rare diseases, and there are no substitutes or no alternatives with the same therapeutic position. Drugs with risk-sharing plans go through PBCAC deliberations and price negotiations with the NHIS, which is identical to other drugs. Until 2017, most drugs that applied for listing with risk-sharing plans chose to refund the price gap [23]. Both industry and patient groups agreed that accessibility has improved after the introduction of risk-sharing schemes and are asking for a wider range of medicines to apply for risk-sharing plans.

In addition to risk sharing, the government announced an increase in the upper threshold of the ICER in 2013. The Korean government denied the use of a fixed cost-effectiveness threshold, but the PBCAC is known to consider per capita GDP. This means it is difficult to get positive recommendations from the PBCAC if the ICER is higher than the per capita GDP. Nevertheless, even before 2013, some drugs were accepted despite their ICER being higher than the per capita GDP, in cases in which they are used to treat severe diseases and have few substitutes [15]. The government's announcement does not mean an overall increase in threshold, but an allowance for higher ICER than before for some drugs used to treat very severe diseases.

In addition, some drugs used to treat ultrarare diseases are exempt from submitting economic evaluation data. Instead, their price must be lower than the lowest price among the A7 countries (France, Germany, Italy, Japan, Switzerland, the United Kingdom, and the United States) to be accepted by the PBCAC [7].

All these policies were introduced after 2013, following the government's plan to extend coverage for several severe diseases. Industry and patient groups admit that accessibility has improved after 2013, when risk-sharing schemes and other measures were implemented; nevertheless, there are still complaints that it takes too long to reach a final listing decision.

Challenges

Since HTA has officially been used in reimbursement decision making, many issues have been highlighted. First, the biggest controversy was the balance between quick access to expensive

new drugs and efficient use of the limited NHI budget. This is more of a problem when it is used for serious diseases. Patients often complain about the delay in reimbursement decision making after market approval. As the voice of patient groups grows, this issue has become even more important. According to HIRA, the average time from application to listing was 348 days for oncology drugs, 260 days for orphan drugs, and 249 days for other drugs [24]. This has occurred even though the due dates for reviews are fixed. If the time from market approval to final listing is considered, it will be much longer. There are several factors that attribute to the cause of such delays: delay in applications, repeated applications, delay in the process of repeated dismissals and re-applications, and delay in data supplements. Even though the government has announced that it would link the market approval and the listing process and allow companies to apply for listing before the market approval process has been finalized, it has not been especially effective in reducing listing delays.

How to incorporate social values in the decision-making process is another important issue. According to decision criteria, the PBCAC should consider the severity and rarity of a disease and the availability of substitutes, in addition to clinical effectiveness and cost effectiveness. Nevertheless, it has been criticized that social values other than clinical effectiveness and cost effectiveness are reflected only in implicit ways, and so cost effectiveness is too heavily weighted in the final decision. Some argue that a more explicit way of incorporating social values needs to be implemented to make reimbursement decisions more consistent and transparent, and suggest multicriteria decision analysis as one of the alternative approaches. Others, however, insist that the PBCAC is already considering other social values in the decision-making process, and it is better to leave it to the committee's deliberation rather than use a questionable formula. A current study suggested that multicriteria decision analysis methodology has many issues both in theory and in practice [25].

The third issue is related to stakeholder involvement. Currently, the committee is mainly composed of experts in medicine, pharmacy, and HTA methodology. Even though representatives from citizen activist/consumer groups participate in the committee, the number of seats for them is relatively low, and so it is difficult for them to represent public views at meetings. From the time the current committee was formed, the patient group had the right to nominate one member. There is, however, some controversy about the involvement of patient groups in the committee, because patient groups have direct interests in the decisions, and many of them are supported by pharmaceutical companies.

In addition to the involvement of members who can reflect public views, more information needs to be opened to the public to improve the transparency of the system. Currently, evaluation results and summarized evidence on submitted drugs are published on the HIRA Web site, but these are not detailed enough for stakeholders to understand the reasoning behind the committee's decision.

Finally, uncertainty surrounding evidence is another challenging issue. According to previous studies, there is a difference in recommendations from different institutions, even for the same drug, which is considered to be due to a difference in the attitudes of institutions regarding the uncertainty of the data [19]. At entry, there is great uncertainty in terms of safety, efficacy, and cost effectiveness of the drug. Thus, after time has passed, and the uncertainty of the data has been somewhat removed, it is necessary to correct early decisions by re-evaluating the comparative effectiveness and cost effectiveness of the drug. Nevertheless, after giving up the re-evaluation project, there was no systematic re-evaluation of the listed drug in Korea [26]. Recently, the necessity of re-evaluation has been raised again, mainly by researchers and policymakers.

Conclusions

Over the past two decades, Korea's drug policy has undergone many changes. The biggest change was the introduction of a PLS in 2007. From this time on, the new drugs had to demonstrate their value to be listed on the NHI formulary, and HTA was mobilized to support the submitted drugs' value.

During the introduction of the PLS, the Korean government focused on strengthening the transparency of the decision-making process. In fact, there have been many improvements in the transparency of the system compared with previous years. Nevertheless, once the system had settled to a certain extent, accessibility to new drugs emerged as an important issue. In Korea, 65.6% of submitted drugs are eventually listed on the formulary, which is not as low compared with other countries using HTA in reimbursement decision making. Nonetheless, because some drugs used to treat serious diseases were not listed, industry and patient groups demanded improved access to new drugs. The government responded to this demand by introducing several policies that could improve accessibility to specified drugs—a risk-sharing scheme is one such policy.

Even after these measures have been implemented, there is a continuing claim that accessibility needs to be further improved. There is, however, a need to balance accessibility and efficiency, and social discussions and consensus are needed to find a suitable balance.

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