

Pharmacoeconomic Guidelines and Their Implementation in the Positive List System in South Korea

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ABSTRACT

This article reviews the change in the reimbursement and pricing system in South Korea, which was the precursor to the eventual implementation of evidence-based decision-making. There has been pressure on Korea's National Health Insurance system to control its skyrocketing expenditures on drugs. As a result, a series of cost-containment policies have been implemented. The idea of economic evidence-based decision-making was first introduced in Korea in 2001 when the government announced cost-effectiveness as one of the criteria for reimbursement decisions. After this announcement, the Health Insurance Review and Assessment Service (HIRA) developed guidelines, which became the standard for economic evaluations.

In 2006, the drug listing system for reimbursement was changed from a negative to a positive system under the drug expenditure rationalization plan. Under this new system, only drugs that are proven economically and

clinically valuable can be listed, and applicants have to submit economic evaluation studies to support the cost-effectiveness of their drugs. Once new applications are submitted, HIRA reviews them, and the Drug Reimbursement Evaluation Committee (DREC) decides whether or not to recommend the submitted drugs. In its reimbursement decisions, the DREC considers not only cost-effectiveness but also the availability of therapeutic alternatives, the severity of the condition treated, and the impact on the budget, among other measures. After the introduction of the positive list system, 56% of drugs were determined to be appropriate for reimbursement by the DREC. Despite limited human resources, experience, and quality local data, Korea is continuing to make efforts to establish a system of evidence-based decision-making.

Keywords: drug reimbursement, economic evaluation, PE guidelines, positive list.

Background

According to Organization for Economic Co-operation and Development (OECD) health data, the share of drug expenditures from total Korean health expenditures was around 26% in 2006 [1]. This figure places South Korea as the fourth highest among OECD countries and is the main reason why the control of drug expenditures has surfaced as a social issue.

In 2000, South Korea initiated reforms that separated the role of prescribing and dispensing. Nevertheless, contrary to expectations, drug expenditures did not decrease despite the fact that the use of certain drugs such as antibiotics and some injected drugs fell. This is attributable to the fact that some drugs that were previously purchased outside of the health insurance system now require a prescription. In addition, physicians who used to prescribe generic drugs in the past because of the higher margin of those drugs switched to brand name drugs when the financial incentive was eliminated. As a result, pharmaceutical expenditure per capita, which was actually US\$158 in 1998, increased to US\$236 in 2001, which was a higher rate of increase than other medical expenditures [1].

South Korea's National Health Insurance system, which had experienced deficits for a considerable length of time, requested a more fundamental change in drug reimbursement and pricing policies [2]. This led to the introduction of a series of cost-containment policies in late 2001. These policies included a triennial price revision policy and drug use monitoring. A reference price system was also considered but was ultimately rejected because of objections from industry, physicians, and patient groups.

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In addition to these policies, the government announced a new regulation at the end of 2001, which, for the first time, introduced the idea of economic evidence-based decision-making to South Korea. The new regulation states that decisions on the reimbursement of newly submitted health technologies should consider the economic aspects, that is, the cost-effectiveness of the new technology. In accordance with this new regulation, the Health Insurance Review and Assessment Service (HIRA) decided to formulate a methodological standard of economic evaluation and began to draft the South Korean version of the pharmacoeconomic guidelines in 2003.

Nevertheless, despite many attempts at countering it, drug expenditures continued to rise. In May of 2006, the government announced the drug expenditure rationalization plan (DERP), which focused on the introduction of a "positive list system (PLS)" [3]. According to the announcement, companies that wanted to list a new drug on the national formulary had to submit an economic evaluation to verify its value. Only those drugs acknowledged as valuable or necessary by the system could be reimbursed at the price negotiated with The National Health Insurance Corporations (NHIC). In addition to new drugs, currently listed drugs are also scheduled to be reevaluated over a 5-year period. Products that do not prove their clinical or economic value are to be eliminated from the national formulary in the future, even if they were already listed.

Although the pharmaceutical industry strongly opposed the DERP, the South Korean people agreed to the principle that only clinically and economically valuable drugs be listed, leading to the announcement of the regulation at the end of December 2006 and to the initiation of the new system in 2007. The South Korean policy stems from an environment that differs substantially from those of other countries such as Australia, UK, and Canada, where the listing system did not change when the government decided to use pharmacoeconomic (PE) data to support

evidence-based decision-making. This article intends to review how drug insurance policies have changed through the evidence-based decision-making process. The focus will be given first to the development process and contents of South Korean pharmacoeconomic guidelines and then to the detailed process and the main issues surrounding the new PLS of South Korea.

Development Process and Contents of HIRA Guidelines

Development Process

As mentioned earlier, HIRA began formulating the South Korean version of the pharmacoeconomic guidelines in 2003 after the announcement of the new regulations at the end of 2001.

The guideline development team at HIRA first reviewed existing international guidelines, academic journals, and other related literature. The main issues to be considered in establishing the direction and scope of the guidelines were then screened. When the main issues became clear, HIRA created an advisory committee consisting of prominent Korean scholars within the field and discussed those selected issues. Based on literature review and the consensus of the expert group, it drafted its first version of the guidelines. Experts in epidemiology and statistics and key figures in industry, along with the existing advisory committee members, reviewed the contents of the first draft. In addition, HIRA held an open workshop in June of 2005, at which time the public could comment on the guidelines [4]. The draft guidelines were revised to reflect public comments and were presented to the Drug Reimbursement Evaluation Committee (DREC) for endorsement. They were officially published by HIRA in June of 2006.

In South Korea, stakeholders participated in the discussion process in the later stage because there were few experts in the industry in the period from 2003 to the beginning of 2004. Because PE experts are active in the industry at present, however, they will likely play a more prominent role in any future guideline revision processes.

When HIRA formulated the guidelines, many countries around the world were already using their own pharmacoeconomic guidelines, of which several were known internationally. Because most of them were similar in content, we could have adopted one of them rather than developing one of our own [5]. Nevertheless, HIRA formulated its own guidelines out of the awareness that South Korea did not have enough research experience and that the quality local data available in South Korea were not the same with those in other countries such as the UK, Australia, and Canada. There was thus a need to formulate guidelines that reflected the local situation. It was also taken into consideration that discussions of methodological issues among researchers could be facilitated through the guideline development process and that the process could also contribute to the establishment of an academic infrastructure.

Contents of Guidelines

The HIRA guidelines comprise two parts: guidance and explanatory notes. The full version of the HIRA guidelines is posted on the HIRA Web site (<http://www.hira.or.kr/>). Nevertheless, only the Korean-language version is available as of this writing. Therefore, some of the important components are summarized here in a comparison with other international guidelines [6].

The selection of a comparator. With regards to the selection of a comparator, the HIRA guidelines demand that in cases in which there are comparable drugs, the most prevalent drug should be selected as a comparator. Comparable drugs are drugs that have

been used to treat or control a target disease or an indication of the submitted drug, and that can be substituted for the submitted drug. Nevertheless, comparable drugs are not limited to those that have the same therapeutic mechanism. As for the unit cost of the selected comparator, the price of the generic version should be considered in cases where a generic version of a comparator has been released. That is, the weighted average price of each molecule should be reflected as the unit cost of the selected comparator.

Data sources. A less biased data source for costs and effects, such as a randomized controlled trial, is recommended. The use of head-to-head trials that directly compare the proposed drug with comparators is also strongly preferred. If a head-to-head trial is not possible, however, an indirect comparison is acceptable. The details of the data search procedure and the rationale for the selection should be clearly described.

Analytic perspective. HIRA guidelines recommend that the analysis should adopt a societal perspective. Therefore, all costs that are appropriate, from a societal perspective, should be included. Nevertheless, the guidelines have reserved opinions on several items. It recommends that productivity costs not be included in base case analysis but be presented separately or in a sensitivity analysis. In addition, the future medical cost of any unrelated disease is open for theoretical debate, but the guidelines recommend that it not be included in base case analysis to secure comparability.

Final versus surrogate outcome. A final intended outcome, rather than a surrogate outcome, is recommended for the outcome indicator because there is uncertainty in the relationship between the surrogate and final outcomes. Moreover, it is difficult to judge the economic implication of an increase of one unit in a surrogate outcome.

Handling uncertainty. Uncertainty in the analysis should be examined by executing a sensitivity analysis. The HIRA guidelines currently state that at least a one-way sensitivity analysis should be executed for all uncertain variables, but presenting results using a more advanced method such as probabilistic sensitivity analysis is also encouraged.

Discount rate. Costs and outcomes should be discounted at 5% per year. In addition, sensitivity analyses with 0%, 3%, and 7.5% should also be presented.

Adapting data from a different setting. If there is quality local data for an evaluation, the use of such data is the best means of reflecting the local situation. Nevertheless, this is not always possible. When adapting data from a different setting, the HIRA guidelines state that the price and medical utilization data must be domestic, even though HIRA will permit citations from foreign studies if they are related to clinical effects or disease epidemiology. Of course, in the case that South Korea's treatment pattern for the disease is different from that of the country of origin of that particular data, it is suggested that a sensitivity analysis of the domestic situation be carried out. In the case of multinational trials involving local participation, a sensitivity analysis with specific domestic samples should accompany the base case analysis.

Reporting results. The pharmacoeconomic evaluation report should be described in such detail that interested readers can follow the background and procedure of the evaluation and

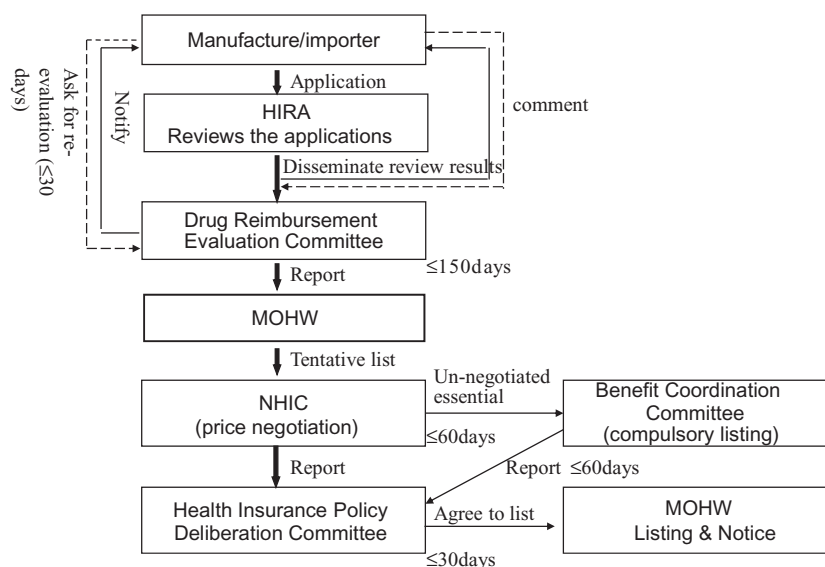


Figure 1 Process of the listing of a new drug in South Korea. HIRA, Health Insurance Review and Assessment Service; MOHW, Ministry of Health and Welfare; NHIC, National Health Insurance Corporations.

reviewers can replicate the entire analysis process. To enhance the clarity and to facilitate communication among researchers and reviewers of the pharmacoeconomic studies, the final report should be written using a structured format.

Prospects for Revision

A variety of issues have surfaced during the more than 3 years since the announcement of the first draft, and some have pointed out the need for an update to the guidelines.

The most important issue regarding the guidelines is the controversy related to the selection of comparators. The guidelines currently suggest that the most prevalent among comparable drugs should be selected as the comparator. The problem is that because the guidelines are not prescriptive enough, they occasionally lead to cases in which the comparator selected by the pharmaceutical companies and that considered appropriate by HIRA are different. Therefore, companies demand more transparent guidelines, but it is difficult to set clear and detailed criteria for the range of comparable drugs. For instance, some drugs are used as substitutes for other drugs despite the fact that the two drugs have different therapeutic mechanisms, whereas some others cannot substitute for other drugs because of the difference in the mechanism. HIRA is currently attempting to approach this problem by initiating a prior-consultation system.

The next issue is the standard of indirect comparison. The guidelines state that an indirect comparison is possible in cases where there is no head-to-head trial with a comparator, but it states nothing further on the subject. There are no guidelines for the method of indirect comparison. Because the relative effectiveness of comparative drugs has a large effect on cost-effectiveness, more specific guidelines pertaining to indirect comparisons are needed.

Lastly, the point has to be made that there is a gap between the perspectives of the guidelines and the perspectives that applicants are actually using. Most submitted economic evaluation studies include only direct medical costs. HIRA has not raised this issue because it is a more conservative approach. Nevertheless, if some studies are executed from a societal perspective and some are executed from a narrower perspective, problems of inconsistency can arise. Therefore, there is a need to review

whether the guidelines will maintain a societal perspective or permit the use of a narrower perspective reflecting the actual study perspectives of current submission documents.

Introduction of the PLS and Economic Evaluation of New Drugs

Process of New Drug Listing under the PLS

With the introduction of the PLS in 2007, pharmacoeconomic evaluations were formally used to answer policy questions regarding drug reimbursement. Under the negative list system, all drugs that were approved by the Korea Food and Drug Administration could automatically be listed for reimbursement, with only a few exceptions [7]. Nevertheless, with the change from the negative to the PLS in 2007, only clinically and economically valuable drugs can be listed based on the presented evidence of comparative cost-effectiveness.

Figure 1 shows the entire process of listing under the PLS. Once a company submits the application documents for a drug, in-house staff at HIRA reviews them. Health economists in the research department and experts outside of HIRA are sometimes invited for consultations for more professional and high-level reviews. The DREC, composed of 18 members, has a mandate to review submissions and make recommendations on listings [8]. After a period of deliberation, one of three reimbursement decisions is made: positive recommendation, rejection, or restriction by indication. The NHIC negotiates the price of drugs with a positive recommendation with the manufacturer.

If an agreement cannot be reached through drug price negotiations, patient treatment is guaranteed for necessary drugs through compulsory listing by the Benefit Coordination Committee (BCC), which can mediate and determine the price [8]. The Ministry of Health, Welfare and Family Affairs has provided a legal basis to secure the accessibility of necessary drugs. By law, even if a pharmaceutical company does not apply for listing or if price negotiations fail, drugs evaluated as being necessary for treatment can be directly listed. For example, cancer drugs (dasatinib, imatinib), and an anti-HIV agent (enfuvirtide) went through the BCC after the failure of price negotiations. Nevertheless, it remains up to pharmaceutical companies to determine whether they will supply the drugs at the price mediated by the BCC.

Table 1 PE studies submitted to HIRA

Period	No. of submissions	Submissions with PE studies		
		MNC	Local	Total
June 2005–December 2006	—	—	—	13
2007	129	20	6	26
2008 (–June 30)	58	3	2	5

Source: Health Insurance Review and Assessment Service, 2008.
HIRA, Health Insurance Review and Assessment Service; MNC, multi national countries.

In addition, to strengthen stakeholder involvement and transparency, pharmaceutical companies are given the opportunity to participate in the hearing process and to request a reevaluation. The development of PE guidelines has incorporated consistency and transparency throughout the review, and HIRA also prepares checklists for reviewers to ensure the consistency of reviews by minimizing variations between reviewers, which enhances the transparency of the system. Once a detailed evaluation standard for each case is determined through deliberation by the DREC, they are posted on the HIRA Web site. HIRA has also implemented conflict-of-interest guidelines. Committee members are not expected to attend meetings where submissions in which they have a conflict of interest are being considered.

PE Study Submission and Decision-Making

Table 1 shows the number of PE studies submitted to HIRA. In 2007, a total of 26 PE studies were submitted. Nevertheless, there were 129 new drug applications, a fact that indicates that many of the submitted drugs did not include PE data [9]. This occurred because submitted drugs with lower prices relative to that of an existing drug were exempt from providing PE data and because companies chose a strategy of lowering the price instead of submitting PE data if the products were not proven to be effective to an extent that justified the price. Considering that PE data submission became mandatory in 2008, it is puzzling that the number of submissions in 2008 was lower than that of 2007, although the 2008 submissions reflect only the first half of the year. It can be conjectured that companies only submit PE studies when they are confident of cost-effectiveness. When they are not, they choose a strategy of preparing for price negotiations at an early stage instead of going through the complex and costly process of ensuring a premium price.

Under the PLS, the DREC considers various factors for reimbursement decision making, including the cost-effectiveness, the availability of therapeutic alternatives, the severity of the condition treated, clinical effectiveness, the budget impact after the introduction of the drug, the listing conditions in other countries and the uncertainty in the evidence presented. In order to evaluate whether the cost-effectiveness of a submitted drug is acceptable, the maximum willingness to pay for a QALY (Quality

Adjusted Life Year) can be an important reference. It, however, has not yet been officially designated in South Korea. The DREC decision-making process results over the years show that per capita GDP was referred to as a threshold for the incremental cost-effectiveness ratio (ICER) in decision-making; nevertheless, reimbursement decisions have been made with flexibility by considering social values as well [10].

Regarding decisions made for reimbursement and pricing, 56.0% of items evaluated by the committee, comprising a total of 47 items, were determined as being appropriate for reimbursement after the introduction of the PLS in 2007. Ten of these have completed price negotiations. The reimbursement rate is lower than that of the previous years, 62.0% in 2005 and 76.0% in 2006, respectively (Table 2).

Reevaluation of Listed Drugs

The South Korean government has announced that all listed drugs will be reevaluated by the same standard of cost-effectiveness under the PLS. In 2007, when the PLS was first introduced, nearly 20,000 drugs were already listed for insurance under the negative list system; thus, a plan was set to reevaluate the list over 5 years, by 2011 [3]. In the 1st year, a pilot project on migraine and hyperlipidemia drugs was initiated.

As a result of the reevaluation, drugs that were not considered to be cost-effective were eliminated from the list. Nevertheless, drugs remained on the list if pharmaceutical companies accepted the evaluation results and made voluntary price cuts. The pilot project results show that out of 11 ingredients for migraine, 8 remained on the list, 2 lowered their prices, and 1 was listed with restrictions [11]. Evaluations of hyperlipidemia drugs are still in progress, but it is predicted that there will be up to a 30% price cut.

Since the initiation of the pilot project, many issues related to reevaluations of listed drugs have been raised. One significant issue is the debate about the purpose of the PLS. The results of the reevaluations of migraine and hyperlipidemia drugs show that drugs eliminated from the list are comparatively few and that most remain on the list through price cuts. The debate involves whether the results correspond with the basic purpose of the PLS [12]. The second issue is whether the reevaluations can be adequately and thoroughly completed by 2011. Listed drugs have a great deal of supporting evidence, which requires a considerable amount of manpower, time, and money to evaluate. At this point, there is not yet a well-established solution to this problem.

In the interim, there was also controversy regarding several methodological issues, including the method of indirect comparison, the selection of an outcome indicator, and the precision of medical costs calculated through claims data. In addition, the fact that the assessment and appraisal processes are not clearly separated and that decision-making is too dependent on the

Table 2 Decisions made for reimbursement and pricing in South Korea

Decision	2007 (Jan 2007–April 2008)		2006*		2005*	
	No. of drugs	%	No. of drugs	%	No. of drugs	%
Reimbursement and pricing complete	10	11.9	79	76.0	31	62.0
Reimbursement complete but price negotiation in process	26	31.0	—	—	—	—
Reimbursement complete but price negotiation fails	11	13.1	—	—	—	—
Delisted (fail)	25	29.8	14	13.5	14	28.0
Request for reevaluation	12	14.3	11	10.6	5	10.0
Total	84	100.0	104	100.0	50	100.0

*There was no price negotiation process before 2007.

assessment report reduces the likelihood of a thoughtful decision based on various social values [13].

Major Barriers for Economic Evaluation

The limited availability of human resources with expertise is one of the most important barriers in conducting economic evaluations. Pharmacoeconomics education has made significant advances since the introduction of the PLS, but there remains a lack of experts who can actually perform the studies. Academia has gradually shown an interest in PE studies, but there has not been enough accumulated knowledge and experience to go through the controversial issues. This situation has arisen partly because for now, most research demands in academia are adaptation studies based on core models developed by the headquarters of pharmaceutical companies, which are under pressure to complete them in a short period of time. This can be a limitation in capturing the attention of the academic world. There are also some experts currently working at pharmaceutical companies. Nevertheless, instead of directly conducting pharmacoeconomic evaluations in-house, companies prefer to outsource to universities or private consulting companies. This actually limits their opportunities for pharmacoeconomic evaluation experience.

The lack of local data is another challenge. It is not always possible to find quality local clinical or epidemiological data. In this regard, PE guidelines permit the use of international data to acquire clinical efficacy and disease progression-related estimates. It requires local data only on the price and medical utilization. Nevertheless, there are cases in which the incidence or prevalence of a disease differs from that of other countries (especially Western countries). This influences the absolute benefit of the drug. Furthermore, genetic differences and differences in medical practices affect the clinical benefit. Therefore, there is a need to establish patient registries and to promote the use of the claims databases that are available in South Korea [14].

There is yet limited social consensus on bridging the gap between the ICER value for pharmacoeconomic studies and decision-making. First, the fundamental problem is that no official definition of an explicit ICER threshold for decision-making in South Korea exists. Nevertheless, even if there were a threshold, it would be difficult to connect it directly to decision-making because first, there is uncertainty and limits in data sources and study method, and second, there are many factors that are considered in reimbursement decisions in addition to cost-effectiveness. Unfortunately, there is no fixed decision rule to reflect the qualitative aspects of social values.

Therefore, there must be a more formative discussion regarding the gaps that inevitably exist between pharmacoeconomic evaluations and decision-making. It is currently necessary to accumulate domestic decision-making experience and comprehensively reflect the various factors considered in decision-making processes to generate a more detailed evaluation standard. Such efforts will contribute to a soft landing of the PLS by reducing the uncertainty in decision-making and improving the degree of predictability.

Conclusion

South Korea is the first Asian country to formulate PE guidelines and require the submission of economic evidence when applying for a listing for insurance. Nevertheless, the system has to operate in a challenging environment in many ways compared with those

of other countries with established evaluation systems because it lacks local data, experience in evidence-based decision-making, and experts who can conduct pharmacoeconomic analysis. Occasionally, there are conflicts in the process of executing policies because of the lack of shared experience among the government, stakeholders, and academia. Nevertheless, because the current situation is not simply an addition of one standard, pharmacoeconomics, but is a fundamental change in the listing system from negative to positive, a debate might be inevitable in the process of adapting to the new system.

A considerable amount of effort is required from both the government and industry to strengthen the transparency of the system and establish a solid base for evidence-based decision-making through that process. More active solutions such as the introduction of a prior-consultation program being reviewed by HIRA need to be continuously considered. In addition, communication between the government and stakeholders should take place more frequently and in more diverse ways. On the international level, more effort is needed in networking. There may be differences in prices, medical utilization patterns, or the basic epidemiology of a population according to the country, but data on the treatment effects of drugs can be used similarly in many countries. Sharing the clinical effectiveness-related data accumulated in each country can make evaluations more efficient. In particular, networking among health technology assessment (HTA) agencies in the Asia region is important because there are some similarities in epidemiology and policy contexts in the region. Recently, Thailand and Taiwan set up units that conduct health technology assessments to support an insurer or government decisions. Significant collaboration between HTA agencies in the region is expected in the future.

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