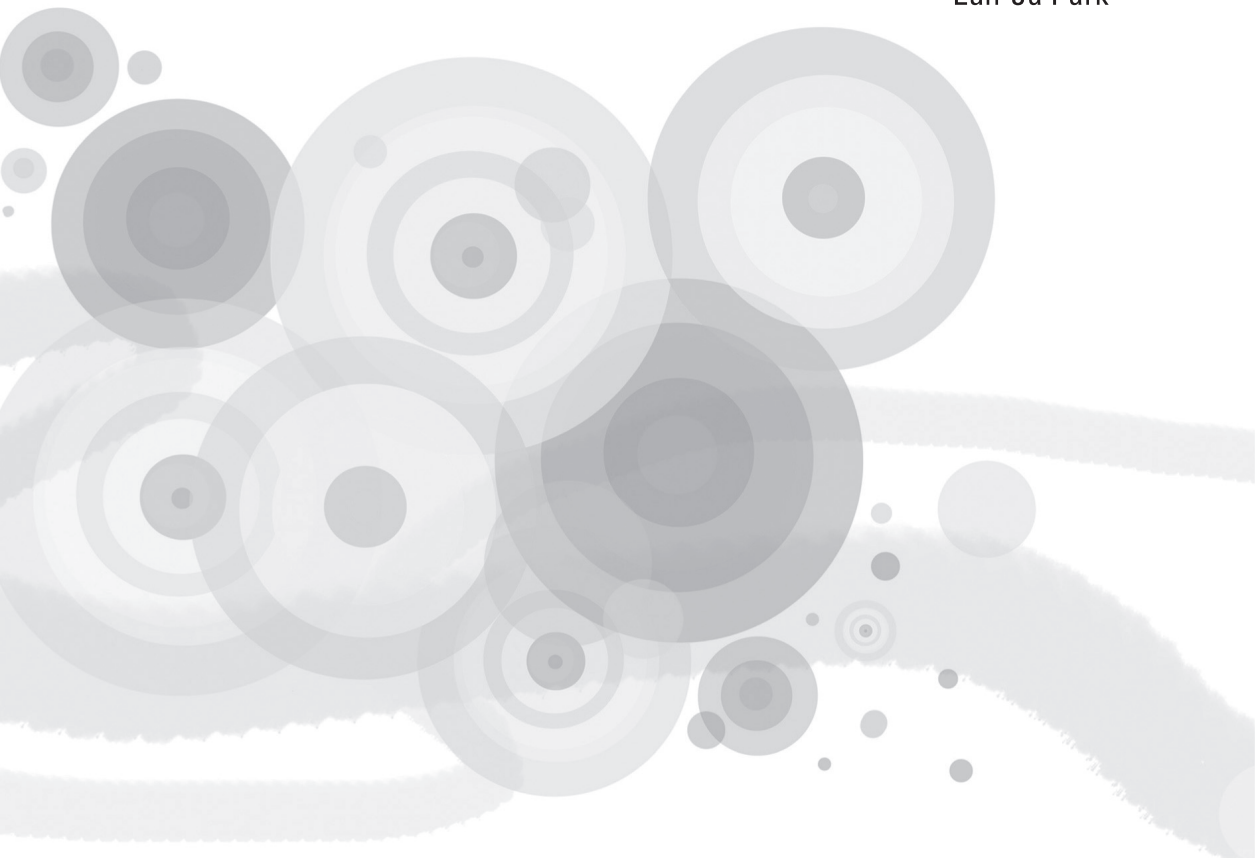




# Future Directions for Pharmaceutical Policy in the New Era of High Cost Medicines

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Future Directions for  
Pharmaceutical Policy in the New  
Era of High Cost Medicines

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Chapter

01

# Introduction







## Chapter 1

# Introduction

### Section 1. Background

As a number of new drugs introduced since 2000 become more expensive, the number of drugs with large therapeutic cost is increasing. Drugs costing from tens of millions of won to hundreds of millions of won per patient per year continue to enter the pharmaceutical market for the treatment of serious medical conditions such as cancer. Drug costs and efficient utilization of these new drugs are raised as important issues in drug policies worldwide. The same is true of Korea, where the growing use of expensive new drugs is cited as a major cause of rising drug expenditures.

New drugs that are far more expensive than existing medications are mostly for the treatment of cancers, AIDS, rheumatoid arthritis, and asthma that greatly affect lifespan or the quality of life of patients. Not only are these drugs important from the aspect of people's health, but they are also significant from the health care policy perspective in the context of insurance coverage and expenditures due to high costs. Yet there has been a lack of sufficient analysis and understanding of the current state of these high-cost medicines, as well as studies on policy issues and implications associated with high-cost medicines.

With biotechnology-based drug development becoming more

vigorous, the market entry of new drugs having these characteristics is expected to increase. Therefore, there is a need to assess the current state of new drugs such as high-cost biological products that are increasingly developed for the treatment of serious medical conditions and analyze associated policy issues in order to identify policy implications for proper utilization of drugs and for efficient cost management.

## **Section 2. Purpose**

This study aims to observe the current state of high-cost medicines and associated major policy issues and then identify policy implications pertaining to high-cost medicines for facilitating rational utilization of drugs and for efficient management of pharmaceutical spending.

## **Section 3. Contents and Methods**

This study consists of five chapters.

Chapter 2 describes the current state of high-cost medicines, along with definitions and main characteristics of high-cost medicines, developments in the pipeline in the global drug market, market outlook, and associated policy issues. For this, domestic and foreign literature as well as Internet sources have been researched and analyzed.

Chapter 3 analyzes the current state of high-cost medicines in Korea. It includes high-cost medicines approved and covered under the National Health Insurance (NHI), and observation of related systems related to reimbursement, utilization management and enhanced evidence development. With regard to the research methodology employed in this chapter, drug approval databases of the Korea Food & Drug Administration and NHI's drug price list have been analyzed to understand the current state of high-cost medicines in Korea. For the analysis of related diseases, health insurance statistics data of the National Health Insurance Corporation has been used. With regard to the current systems, research has been conducted through analysis of relevant laws and regulations, interviews with clinical specialists in health conditions concerned, and in-depth discussions with policy experts concerning policy implications.

Chapter 4 provides policy recommendations for sensible utilization of high-cost medicines and efficient cost spending. Based on the understanding of the current state of high-cost medicines in Korea and other countries, policy recommendations concerning reimbursement, utilization management, and enhanced evidence development have been provided.





Chapter

02

# **Current State of High-Cost Medicines**





## Chapter 2

# Current State of High-Cost Medicines

## Section 1. Definition of High-Cost Medicines

### 1. Definition

Advances in biotechnology and medical science have been accompanied by advances in technologies for disease diagnostics and drug development. Noticeable from the recent drug development trend is the growing number of biological products and drugs designed to treat rare, intractable or serious ailments. Whereas new drugs developed in the past largely focused on primary treatment of common diseases like hypertension, hyperlipidemia, and diabetes that have a large pool of patients, more recently developed drugs that use innovative technologies like biotechnology tend to target diseases with a high degree of severity such as cancers, asthma, multiple sclerosis, rheumatoid arthritis, pulmonary hypertension, and osteoporosis that are mostly treated by health care facilities involved in special care. These drugs, due to their bio-technical characteristics, higher cost of research and development, and enhanced market power, tend to be very expensive. Drugs having these characteristics are known as specialty drugs.

Initially, the term specialty drugs applied only to high-cost injectable drugs. More recently, the term is more often used to

describe biological drugs. However not all drugs that are classified as specialty are biologic in origin (Stern and Reissman, 2006). Some drugs classified as specialty also include oral drugs, so it is not appropriate to confine the definition to injectable drugs.

Specialty drugs were initially developed for the treatment of rare medical conditions. Their treatment scope has then steadily expanded to include broader types of diseases such as cancers, autoimmune disorders, multiple sclerosis, AIDS, asthma, pulmonary hypertension and osteoporosis, among others.

Specialty drugs cannot be defined only at the therapeutic class level. Not all drugs within the oncology class are considered specialty drugs. The same is true of other classes.

Specialty drugs are generally considered high-cost injectable, infused, oral or inhaled drugs that require "close supervision and monitoring" (Fontanez, 2005).

As such, it is hard to make a definite or exclusive definition of specialty drugs. While it is true that specialty drugs generally require high treatment cost, it is not only difficult to make a definition of what "high-cost" exactly means, but people's perception of "high-cost" also changes with time or in different situations.

The high-cost medicines covered in this study will mostly relate to specialty drugs described so far. For the purpose of this study, the following definition of specialty drugs will be used: Specialty drugs are generally considered high-cost medicines, mostly biological drugs, that are developed for the treatment of serious medical conditions such as cancer and autoimmune disorders with high drug costs relative to existing medications.



## 2. Products available

In 2010, Forbes released a list of the nine most expensive drugs in the world, each of which costs over \$200,000 annually. Most of them are designed to treat rare diseases. Because drugs for rare diseases have no alternative therapies, pharmaceutical companies that have market dominance can charge high prices for these drugs. Soliris is the world's single most expensive drug at over \$400,000 per patient per year. The drug is used to treat paroxysmal nocturnal hemoglobinuria (PNH). PNH hits only 8,000 Americans, but sales of Soliris were as much as \$295 million in 2009 (Table 2-1).

〈Table 2-1〉 Examples of the Most Expensive Drugs in the World

Product Name	Ingredient	Manufacturer	Annual Cost	Indication
Soliris	Eculizumab	Alexion Pharmaceuticals	\$409,500	PNH (paroxysmal nocturnal hemoglobinuria)
Elaprase	Idursulfase	Shire Pharmaceuticals	\$375,000	Hunter syndrome
Naglazyme	Galsulfase	BioMarin Pharmaceutical	\$365,000	Maroteaux-Lamy syndrome
Cinryze	C1 esterase inhibitor	ViroPharma	\$350,000	hereditary angiodema
Myozyme	Alglucosidase alpha	Genzyme	\$300,000	Pompe disease
Arcalyst	Rilonacept	Regeneron	\$250,000	Cryopyrin-associated periodic syndromes
Fabrazyme	Agalsidase beta	Genzyme	\$200,000	Fabry disease
Cerezyme	Imiglucerase	Genzyme	\$200,000	Gaucher disease
Aldurazyme	Laronidase	Genzyme, BioMarin Pharmaceutical	\$200,000	Hurler syndrome

Source: [http://www.pharmaceuticalcommerce.com/frontEnd/1383-Forbes\\_rare\\_disease\\_orphan\\_drug\\_Genzyme\\_Biomarin.html](http://www.pharmaceuticalcommerce.com/frontEnd/1383-Forbes_rare_disease_orphan_drug_Genzyme_Biomarin.html)

IMS Health, a global company that provides market intelligence on pharmaceuticals, released the top ten global specialty pharma categories in 2008: Oncologics; antivirals (HIV/AIDS), immunosuppressants; erythropoietins; autoimmune biologics; immunostimulants; autoimmune modulators; immunoglobulins; blood coagulants; and interferons for Hepatitis C (MM&M, 2010). Most of these drug classes are among the global top 20 therapy classes. Spending on autoimmune modulators, HIV antivirals, and multiple sclerosis drugs has grown year-on-year more than by 10% in 2010 (Table 2-2).

〈Table 2-2〉 Leading Therapy Classes in 2010

Rank	Therapy Class	2010 Sales (US\$ million)	YoY Growth (%)	Share in Total Drug Market (%)
1	Oncologics	55,972	6.7	7.1
2	Lipid Regulators	36,400	2	4.6
3	Respiratory Agents	35,926	7	4.5
4	Antidiabetics	34,429	12.2	4.4
5	Anti-ulcerants	27,972	-6.5	3.5
6	Angiotensin II Antagonists	26,630	4.5	3.4
7	Antipsychotics	25,412	9.0	3.2
8	Autoimmune agents	20,710	14.7	2.6
9	Antidepressants	20,216	3.4	2.6
10	HIV Antivirals	15,432	13.2	1.9
11	Platelet Aggr. Inhibitors	15,244	1.8	1.9
12	Vitamins & minerals	12,971	6.1	1.6
13	Anti-epileptics	12,553	-3.3	1.6
14	Narcotic analgesics	12,011	6.4	1.5
15	Cephalosporins & combs	11,466	6.1	1.4
16	Non-Narcotic Analgesics	10,986	0.0	1.4
17	Vaccines	10,972	2.8	1.4
18	Erythropoietins	10,596	-2.3	1.3
19	Anti-Rheumatics, Non-Steroidal	10,152	3.6	1.3

Rank	Therapy Class	2010 Sales (US\$ million)	YoY Growth (%)	Share in Total Drug Market (%)
20	Multiple Sclerosis	9,844	13.8	1.2
	Global Market	791,449	5.2	100.0

Source: IMH Health, 2011.

High-cost drug development is most vigorous in oncology. The research paradigm for new cancer drugs is moving from cytotoxic oncologic drugs to targeted therapies, and advances in DNA sequencing techniques are enabling the development of therapies based on genetic properties of patients. Working in ways that are different from traditional pharmaceuticals, most of these new drugs are used in patients who have not shown improvement with existing therapies, or who have no alternatives. As a result, the drugs are being sold at very high prices.

The number of oncology drugs among the global top 200 drugs was 23 in 2008, a more than two-fold increase from 10 years earlier (Loewenberg, 2010). The oncology drug market grew at a rate of over 20% during the mid-2000s and became the biggest therapeutical group in the world in 2007 (IMS, 2011).

## Section 2. Characteristics of High-Cost Medicines

### 1. Biological products

The rise in specialty drugs has come with the advances in biotechnology in pharmaceutical research and development. Many

specialty drugs are biological products and distributed in injectable form. The nine most expensive drugs in the world shown in Table 2-1 are all injectable biological products.

Unlike chemical synthetic drugs, development of biological generics is difficult. An approval process for generic versions of biologics was not in place until the mid-2000s, so even if they were generic, they had to go through the new drug approval process. As a result, new biological products could enjoy market dominance for a long period of time compared to chemical synthetic drugs. Pharmaceutical companies globally have shown a keen interest in the development of bio-pharmaceuticals, recognizing that this will be a major area of research in which to gain competitiveness in the future.

Most bio-pharmaceuticals are developed in injectable form. Injectable drugs are usually more expensive than oral drugs and, as they are administered in hospital settings by care providers, are often accompanied by service cost. Unlike oral drugs prescribed to patients for use at home, injectable drugs have an impact on the places where the drugs are used as they are mostly administered in providers' offices.

## **2. Targeted therapies**

A recent trend in development of drugs including oncologics and rheumatoid arthritis drugs is that the drugs target cells or substances directly related to the disease through research on the diseases. Particularly in oncology, targeted therapies are expected to represent a major share of cancer therapies and their

market share is projected to steadily grow. Existing cytotoxic agents attack both cancer cells and normal cells. Targeted therapies on the other hand show relatively superior effects and fewer side effects by selectively attacking cancer cells only.

Yet it doesn't mean that these new drugs are used in place of existing drugs. Targeted therapies tend to be used for patients as secondary treatment when existing therapies do not show therapeutic effect. Use of expensive targeted therapies as second-line treatment may be due to medical evidence, but it may also be because of cost. Patients are first given lower-priced existing medications and if there is no therapeutic outcome, they are given the option to use the costly therapies.

### 3. High drug prices

High-cost medicines are fast entering the market especially with the evolution of new drug development technologies. Among others, the rise in genetic mapping technology has ushered in a new era for drug development. Research and development of new drugs such as oncologics for serious medical conditions has rapidly expanded. High-cost medicines are mostly biological, so costs associated with production, keeping and management are high. Most of these drugs are new drugs with high market power, so they tend to be very expensive.

Pharmaceutical companies can charge very high prices for these new drugs. Even if the drugs show limited efficacy or can be administered in only certain patients suffering from rare cancers for instance, the rising drug cost per patient is known

to result in considerably high profitability. For example, there are only 15,000 chronic lymphocytic leukemia patients in the United States, but ofatumumab used to treat the disease costs each patient as much as \$98,000 for six months. Pralatrexate for peripheral T-cell lymphoma costs \$30,000 per month, and clofarabine for childhood leukemia costs \$34,000 per week (Loewenberg, 2010).

Soliris (which costs \$409,500 per patient per year), selected as the most expensive drug in 2010, was initially researched as a drug therapy for rheumatoid arthritis but failed. As many as one million Americans suffer from rheumatoid arthritis. If Soliris had been launched as a drug for rheumatoid arthritis, the drug's manufacturer would have had to lower the price to the extent that it would cost approximately \$20,000 per year in order to compete with existing drug therapies (Herler, 2010). That is, the high drug price can be largely attributed to smaller groups of patients and the lack of therapeutic alternatives.

Specialty drug costs per patient in the United States run \$18,000 per year, which is very high compared to \$550 for traditional medications (Towers Perrin, 2008).

### **Section 3. Current State of High-Cost Drug Market and Outlook**

Beginning in the 2000s, the number of new drugs launched in the market began to decline. In the mid-2000s, the growth of the global pharmaceutical market began to slow due to the

patent expiry of blockbuster drugs. On the other hand, development and marketing of specialty drugs has continued, with blockbuster drugs increasingly entering the market. New blockbuster drugs that target primary care in such diseases as hypertension, diabetes and hyperlipidemia are disappearing from the market due to patent expiry of existing drugs and the lack of successors, whereas the number of blockbuster drugs in specialty treatment is increasing (Table 2-3). Accordingly, trends in the new drug market are being led by specialty drugs (Table 2-3).

〈Table 2-3〉 Global Top 20 Drugs in 2010

Rank	Product Name	Indication	2010 Sales (US\$ million)	YoY Growth (%)
1	Lipitor	Hypertension	12,657	5.2
2	Plavix	Hyperlipidemia	8,817	-6.2
3	Seretide	Asthma	8,469	-3.4
4	Nexium	Gastric ulcer	8,362	4.4
5	Seroquel	Schizophrenia	6,816	1.3
6	Crestor	Hyperlipidemia	6,797	13.2
7	Enbrel	Rheumatoid arthritis	6,167	24.0
8	Remicade	Rheumatoid arthritis	6,039	5.2
9	Humira	Rheumatoid arthritis	5,960	10.3
10	Zyprexa	Schizophrenia	5,737	19.7
11	Avastin	Colorectal cancer	5,532	6.6
12	Singulair	Asthma	5,466	11.1
13	Abilify	Schizophrenia	5,430	9.2
14	Mabthera	Non-Hodgkin's lymphoma	5,034	16.3
15	Lantus	Diabetes	4,686	7.8
16	Aricept	Dementia	4,432	16.7
17	Actos	Diabetes	4,317	8.5
18	Lovenox	Thrombosis	4,282	3.9
19	Herceptin	Breast cancer	4,165	-5.3
20	Diovan	Hypertension	4,157	6.7

Source: IMS Health, 2011.

R&D-centered pharmaceutical companies see opportunities from the specialty drug market for technological and other important reasons. Unlike medicines largely used in primary care, specialty drugs are administered to smaller groups of patients, mostly in tertiary care hospitals. Extensive marketing or promotional efforts are therefore not required. On top of this, if a specialty drug is the only therapy option for serious medical conditions, it is likely to be covered by insurance. Because pharmaceutical companies can enjoy reimbursement at high prices, they view specialty drugs as a key strategic market in the future at a time when governments and payers globally are stepping up efforts to reduce costs.

The top 10 products by sales projected for 2014 are mostly monoclonal antibodies and recombinant drugs for serious medical conditions such as cancers and rheumatoid arthritis. Monoclonal antibodies and recombinant drugs are from the new technology field of new product development. From this, it can be anticipated that high-cost medicines developed with new technology for the treatment of serious medical conditions will lead the drug market (Table 2-4).

〈Table 2-4〉 World’s Top Ten Products by Projected Sales for 2014

Rank	Product Name	Indication	Drug Type	Projected 2014 Sales (US\$ billion)
1	Avastin	Colorectal cancer	Monoclonal antibody	9.2
2	Humira	Rheumatoid arthritis	Monoclonal antibody	9.1
3	Rituxan	Blood cancer	Monoclonal antibody	7.8
4	Enbrel	Rheumatoid arthritis	Recombinant drug	6.6
5	Lantus	Diabetes	Recombinant drug	6.4
6	Herceptin	Breast cancer	Monoclonal antibody	5.8



Rank	Product Name	Indication	Drug Type	Projected 2014 Sales (US\$ billion)
7	Crestor	Hyperlipidemia	Small-molecule compound	5.7
8	Spiriva	Chronic obstructive pulmonary disease	Small-molecule compound	5.5
9	Remicade	Rheumatoid arthritis	Monoclonal antibody	5.2
10	Gleevec/Glivec	Leukemia	Small-molecule compound	5.1

Source: FierceBiotech, EvaluatePharma.(Bilotech Policy Research Center, 2010 Bioln Special Issues. 2010. op. cit., p.10)

In US employers' pharmacy spending for 2006, specialty drugs accounted for 10.4%, still representing only a small market share. Annual growth of specialty drugs, however, was considerably high at 16.1%, compared to the 5.8% growth for other drugs in 2006 (Towers Perrin, 2008). By 2013, revenue from specialty products is expected to exceed \$160 billion globally (MM&M, 2010).

The oncology drug market, a major high-cost drug market, has been growing fast in recent years. The US oncology drug market is expected to grow at a rate of 10% annually through 2013. There are more than 900 oncology products in the pipeline, and some products with superior efficacy are chronically used by patients as they are known to better control cancers. This in turn is contributing to rising drug spending (Krauskopf, 2011).

Major pharmaceutical firms facing patent expiry of their chemical synthetic drugs are striving to secure a pipeline for their future through the acquisition of existing biologic drug companies. The French multinational pharmaceutical company

Sanofi acquired a US specialty drug maker Genzyme in 2010, and another multinational company Teva acquired a medium-sized specialty drug developer Cephalon in 2011 when Teva's key generic products were facing competition.

With the paradigm shift in the new drug development technology and with specialty products comprising a major share in the drug development pipeline, development of new drugs from this field is expected to accelerate, thereby driving the growth of the pharmaceutical market.

## **Section 4. Policy Issues Related to High-Cost Medicines**

### **1. Rising financial burden due to high drug prices and fast growth**

High-cost drug spending is growing much faster than spending on traditional drugs, and high-cost medicines are expected to play a bigger role in the increase in pharmaceutical spending. As high-cost medicines are mostly designed to treat patients with chronic diseases, the number of patients using them is increasing with demographic changes. This phenomenon, coupled with the increasing number of products, will become an important policy issue.

The US and some European countries, where high-cost medicines are widely used, have been striving hard to address the drug spending issues through improvement in their drug approval systems. Many of the high-cost medicines are biological products, but there was no generic approval system for biological

drugs under the current drug approval system. Unlike chemical synthetic products, biological products cannot be copied through synthesis. Even products developed with reference to existing products were approved as new drugs, further increasing drug spending. As cost burden from biological products rose, there was a growing need to approve generic equivalents of biological drugs upon patent expiry to allow relatively cheaper generic drugs to enter the market. Against this backdrop, important steps were taken in the United States and Europe in the development of scientific guidelines for the approval of biosimilars (MM&M, 2010).

Under the new guidelines, the EU made the first approval for biosimilars in 2006. The 2010 Patient Protection and Affordable Care Act of the United States defines procedures for approval of similar biologic drugs and grants biologics manufacturers 12 years of exclusive use for purposes of containing spending on high-cost medicines while facilitating use of lower-priced biological drugs through expedited development of competing products. The 12-year exclusive use of new biologics is a quite long period of time compared to the five-year exclusive period for ordinary new drugs. When the legislation was debated in the United States, there was intense tension between new drug developers who advocated 14 years of exclusive use and generic developers who demanded seven years. Eventually, 12 years of exclusive use agreed and incorporated in the law. But when the health care system was under intense pressure from rising costs, the US president made a proposal to shorten the period to seven years, which met with opposition from Congress

members. Debates on the exclusive use period for new biological drugs continue today. Such a dispute is a good example that shows the considerable impact of new biologic drugs on the increase in health care expenditures.

Traditional interventions insurers have used to contain rising drug costs include encouragement of prescribing according to clinical guidelines, prior authorization, step therapy, and encouragement of the use of generic drugs. Currently, there are no effective generic drugs that can replace or compete against specialty drugs. Therefore, there is less room to contain drug costs from the use of specialty drugs.

Therefore in the case of high-cost medicines that have relatively big financial impact with just one administration, health outcomes become an important consideration. That is, there is a growing demand for evaluating effectiveness or cost effectiveness of these drugs relative to other means of treatments when used in actual medical practice.

There are increasing instances where high-cost medicines such as oncologics are excluded from coverage in countries like the United Kingdom that conduct health care technology evaluation. In response, pharmaceutical companies are proposing "pay-for-performance" that involves reimbursement only when drugs show intended clinical effect, or a "risk sharing scheme" that involves reimbursement under limited quantity used or spent as a way to include their drugs in the pharmacy coverage while mitigating the budget risk of payers. Risk sharing schemes have been employed by the United Kingdom, Italy, Australia and the United States since the 2000s in their reimbursement and pricing

decision-making for certain high-priced drugs. Benefits offered by these programs include access to expensive new drugs that have good therapeutic value with insufficient evidence for reimbursement, as well as shared risks generated from reimbursement. Yet not sufficient experience or evaluation of these programs are available, and it is difficult to accurately determine costs incurred from such a reimbursement method.

High prices impose a financial burden not just on the payer but on the patient also. According to a report released by the United States, 10% of outpatient prescriptions for life-saving oral oncology drugs were not filled due to patent's cost sharing. When out-of-pocket cost exceeded \$500, 25% of patients gave up the prescription, and when the cost was around \$100, 6% of patients gave up the prescription.<sup>1)</sup>

## 2. Importance of evidence for reimbursement decision-making

Many high-cost medicines are used for cancers or rare diseases. New drugs in this class have been approved without published phase 3 clinical trial evidence, often making it difficult to assess a drug's safety and efficacy relative to other new drugs due to insufficient amount of evidence. Oncology drugs are often approved for their intermediate effects known as "surrogate outcome" like tumor shrinkage, rather than effects on life extension. Cases have been observed in clinical trials conducted after product launching, which showed that the drugs do not

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1) 「Study: 10% of oral cancer prescriptions go unfilled due to cost burden」SCRIP 2010. 6. 3.

necessarily help patients live longer.

For example, bevacizumab was approved for marketing in Korea, the United States, and Europe as a treatment for breast cancer based on clinical data on tumor shrinkage, but the drug failed to demonstrate effects in prolonging patient life. The drug is even known to cause serious side effects leading to death. Controversies remain over whether the drug is effective in treating breast cancer. Despite such controversies, this drug costs up to \$4,000 per treatment (Sinha, 2008). In 2010, the therapeutic value of bevacizumab in breast cancer was globally a debate issue. An FDA advisory committee recommended that the federal agency withdraw its approval of bevacizumab for breast cancer indication, and the FDA finally withdrew approval of the breast cancer indication for the drug in November 2011. The EU on the other hand recognizes the drug's therapeutic value for breast cancer and keeps the approval for the drug. The same is true in Korea.

As such, different decisions made by different regulatory agencies for the same drugs mean that there is a lack of transparent evidence on the efficacy and safety of new drugs. In other words, due to the coexistence of evidence that shows drug effectiveness and evidence that does not, experts can make different interpretations on the same data set and may come to different conclusions.

Use of high-cost medicines has a big financial impact. Hence, the size of clinical effectiveness and existence of evidence are particularly required. As seen from the example above, in reality, evidence is often insufficient compared to other new drugs.

These drugs are mostly designed to treat serious medical

conditions for which treatment is difficult or greatly affects life or the quality of life of patients. For this reason, patients strongly demand coverage for new drugs. Some high-cost medicines work in mechanisms different from traditional drugs and offer new and innovative opportunities to treat patients who could not continue treatment. However some drugs cost as much as tens of millions of won just to prolong life by a few more months. Still prolonging life of patients with end-stage diseases by a few more weeks or months can be a big benefit and some patients will be willing to pay for such high medical bills.

However, it is difficult to justify coverage for all high-cost medicines under limited health insurance resources that aim to ensure health for all members of society. Because coverage decisions are based on the cost-benefit analysis, it is difficult to include high-cost medicines in coverage. Even if drugs are included in coverage, it doesn't mean that all approved indications are fully reimbursed; the level of reimbursement is determined by the level of evidence required under the reimbursement scheme and financial impacts. If there are existing drugs, high-cost medicines can be classified as a second-line treatment and reimbursed accordingly.

In cancers and autoimmune disorders targeted by high-cost medicines, if patients show different responses to different drugs, and traditional drugs are not proven effective, there can be an increased need to turn to high-cost specialty drugs. Even if patients want to use high-cost medicines, they can still face difficulties in using the drugs if the specialty drugs they want are not covered or only partially covered.

high-cost medicines not covered due to the lack of proven clinical superiority or cost effectiveness not only limit access to health care services, there are far limited opportunities to assess utilization and outcomes of the drugs.

Evaluation of clinical usefulness and cost effectiveness to determine health insurance coverage is conducted for different demographic groups, so outcomes from different patients do not always match. Even if a drug is to be covered, it may not produce therapeutic value in some patients, and even if a drug is not covered, it may be the only drug therapy for other patients. Therefore, it is important to gather evidence on clinical and cost effectiveness from correctly targeted patient groups. Recent advances in drug technology to optimally identify target patients using genetic information are increasing the possibility of producing such evidence.

Yet covered drugs may produce different degrees of therapeutic value and side effects in different patients. Also, there is need for evidence as to the right one among a set of replaceable high-cost medicines. However it is not easy to motivate pharmaceutical companies to conduct comparative effectiveness analysis between competing drugs that are already marketed and reimbursed.

When the use of a high-cost drug is an economic burden and a lower-priced version of the same therapeutic effect is available, off-label use of the lower-priced drug is widely practiced in some cases. Because off-label use is rather based on experience or cases than on strict clinical data, some drugs may benefit patients but also may expose them to risks. That is, successful



clinical cases are not enough to justify off-label use. Instead, assessment of the safety and effectiveness of off-label use for the indication concerned must be made under soundly designed research settings. As far as high-cost medicines are concerned, information on effectiveness and high price all warrant evidence development.

### 3. Importance of appropriate utilization and management

As high-cost medicines are used in a long course of treatment for patients with serious medical conditions, they have considerable impacts on patients' health. High-cost new drugs developed with new technology in recent years may be superior to traditional medicines in efficacy. But this may not be the case for all patients; some patients may experience side effects.

Especially because even one administration of a high-cost drug is costly, there is a need to proactively identify patients who are likely to benefit from the treatment and who are not. This is to enable timely medical interventions to ensure that the drug is not administered in patients in whom the intended effect is not likely to occur.

For instance, if a patient who has been prescribed a cancer drug for a three-month supply has to stop the medications due to severe side effects, the prescribed drug cannot be re-used. This will be a waste of out-of-pocket expense paid by the patient as well as a waste of budget of the national health insurance that paid a much bigger amount of money than the patient did. Especially for oncologic and orphan drugs, the patient cost share

is very low at 5% and 10%, respectively, so prescriptions can be easily filled for a long period of time due to the small copayment. On the other hand, the actual cost incurred on society is considerable as the national health insurance is responsible for 95% or 90% of total drug cost. The low out-of-pocket expense structure implemented to improve access to expensive drugs must not be used as a tool for frequent or excessive prescription.

Patients with serious conditions have a keen interest in treatment and sometimes want to use drugs currently being tested. Off-label use can occur when newly developed drug therapies are no longer effective or when there is no appropriate therapy available. As off-label drug use occurs without sufficient amount of research results or evidence required for application in clinical practice, adequate control procedures in the drug administration process are needed to assure patient safety and maximized effects.

#### **4. Change in focus of drug utilization and cost management**

Traditional strategies taken by the payer to control use of drugs have focused on promoting use of generic drugs or lower-priced drugs. To contain use of drugs that are not essential or urgent, patient copayment levels have been increased or restrictions have been imposed on drug use. These strategies were targeted at both health care providers and consumers.

To promote prescribing or dispensing of generic drugs or lower-priced drugs, health care providers are required or recommended to use international non-proprietary names or generic substitution. Total drug cost is also pre-determined to

reduce drug spending. To make consumers aware of cost and reduce drug use, out-of-pocket expense rates are also raised.

However, these strategies are not appropriate in the management of drug utilization for high-cost medicines used for serious conditions. Many of the high-cost medicines began to be marketed after 2000, so there are no generic equivalents. Especially biological drugs have no generic concept and biosimilars that can be considered as follow-up versions of biological drugs are still in development phases with few commercial versions available. It is possible that patients began to use high-cost medicines because there were no cheaper alternatives or after they found that lower-priced traditional drugs they had first tried had no effect or had side effects. In this case, use of high-cost drug would be an inevitable choice.

Cost containment through copayment can also result in unexpected outcomes. Studies found that the increase in copayments has an impact on patient decision to use high-cost medicines, but once patients begin to use the drugs, they don't reduce drug use despite copayment increases (Goldman et al, 2006). That is, patients are largely insensitive to cost sharing for high-cost medicines, and copayment increases end up putting more economic burden on patients.

high-cost medicines are often supplied as injectables to be administered in providers' offices, most likely in general hospitals or upper-tier health care facilities. That is, high-cost medicines are distributed through different channels from outpatient drugs used for primary care. Therefore the main focus of policies regarding drug quality management and cost improvement will be on selective groups of patients requiring special care, not

primary care intended for the general population. The main policy focus will be health care providers, not consumers, and among health care providers, hospitals will be the main focus. When policy focus changes, its content is likely to change compared to previous policies, and the content will need to be consistent with the related service delivery environment.



Chapter

03

# **High-Cost Medicines and Relevant Systems in Korea**





## Chapter 3

# High-Cost Medicines and Relevant Systems in Korea

## Section 1. High-Cost Medicines in Korea

When a new drug is launched in the global market, it gets quickly approved and launched in the Korean market also. The same is true of new high-cost medicines. Table 4-1 shows super expensive global drugs launched in the Korean pharmacy market as of 2010. Of the nine drugs, seven were approved between 2002 and 2010 and are currently sold in Korea. Although these drugs cost several hundreds of millions of won per patient, they are all covered under the national health insurance scheme except for one approved in 2010 because they are mostly orphan drugs with no alternatives.

Imports of the covered six drugs totaled \$27 million in 2010. Even if the unit price or per patient cost of individual drugs is very high, the total annual cost is not significant due to a small group of patients. Yet the small total annual cost does not mean that its impact on health insurance budget is also small.

After the drug formulary system changed to a positive system and drug pricing system based on price negotiations was implemented in 2007, listing high-cost medicines in the national health insurance coverage was not easy and often hotly debated. Table 3-1 shows three drugs among those approved since 2007

whose coverage inclusion was not easy. A special step was taken to remove import duties for Elaprase to increase acceptance by pharmaceutical companies regarding the price. Naglazyme and Myozyme were not first included in the coverage due to failed price negotiations. Distribution of these drugs finally began after a refund system was implemented on a trial basis.

As seen from above, there has been growing appearance of new drugs that are expensive to the extent that it is difficult to determine drug prices or include in coverage under the existing system. In some cases, new systems had to be put in place as the drugs had essential or irreplaceable therapeutic value, or providers had significant market power. Most of these drugs are orphan drugs and there is a quite significant amount of demand from patients for coverage for these drugs.

〈Table 3-1〉 World's Most Expensive Drugs Marketed in Korea, 2010

Product Name	Ingredient	Year Approved	Insurance Coverage	Price (Won)
Soliris	Eculizumab	2010	Not covered	-
Elaprase	Idursulfase	2008	Covered	2,790,000
Naglazyme	Galsulfase	2008	Covered	1,900,000
Cinryze	C1 esterase inhibitor	Not released	-	-
Myozyme	Alglucosidase alpha	2008	Covered	957,000
Arcalyst	Riloncept	Not released	-	-
Fabrazyme	Agalsidase beta	2002	Covered	5,067,626
Cerezyme	Imiglucerase	2002	Covered	1,180,000
Aldurazyme	Laronidase	2004	Covered	963,075



Most new drugs developed for the treatment of serious medical conditions such as cancer, rheumatoid arthritis, and multiple sclerosis are high-cost medicines, approved for sale in Korea and reimbursed under the national health insurance. However, not a few new high-cost medicines approved since 2007 failed to receive coverage as a result of the economic evaluation.

〈Table 3-2〉 Major High-Cost Medicines in Korea

Condition	Ingredient Name	Product Name	Year Approved	Reimbursement	Price	Size
Cancer	Rituximab	Mabthera	2003	Reimbursed	1,346,170	50ml/vial
	Erlotinib	Tarceva	2005	Reimbursed	62,761	150mg tablet
	Temozolomide	Temodar	2005	Reimbursed	102,527	100mg capsule
	Sunitinib	Sutent	2006	Reimbursed	157,508	50mg capsule
	Bortezomib	Velcade	2006	Reimbursed	1,030,205	1 vial
	Bevacizumab	Avastin	2007	Not covered	-	25mg/1ml
	Trabectedin	Yondelis	2008	Not covered	-	0.1mg/vial
	Lenalidomide	Revlimid	2009	Not covered	-	5,10,15,20mg capsule
Rheumatoid arthritis	Etanercept	Enbrel	2007	Reimbursed	201,474	50ml/vial
	Adalimumab	Humira	2006	Reimbursed	457,146	40ml/vial
	Infliximab	Remicade	2005	Reimbursed	595,640	50mg/vial
	Abatacept	Orencia	2010	Reimbursed	354,000	250mg/vial
Multiple sclerosis	Interferon beta-1a	Revif	2007	Reimbursed	112,058	44mcg
	Interferon beta-1b	Betaferon	2008	Reimbursed	83,398	300mcg/vial
	Glatiramer acetate	Copaxone	2003	Reimbursed	30,000	1 vial

## Section 2. Relevant Systems

### 1. National health insurance coverage

Reimbursement and pricing decisions for high-cost medicines are made using the same criteria applied to other new drugs. Unlike other new drugs, high-cost medicines are typically expensive due to adoption of the latest technologies, so reimbursement and pricing decisions on these drugs are more likely to involve complex review process and heated debates.

Often at the center of debates are oncology and other drugs used for the treatment of serious medical conditions. Reimbursement is warranted when drugs target the right segments of patients, increase the rate of survival or extend survival, or when alternative therapies are not available and innovative therapeutic value is shown. Reimbursement is not likely to be warranted when existing drugs are available and when drugs are not dramatically effective in increasing survival rates or survival period, or have low cost-effectiveness.

high-cost medicines recently introduced to treat cancer, rheumatoid arthritis, among others, are mostly targeted therapies, and reimbursement is given only when the drugs are used as second-line treatment in patients who have not responded to existing therapies. Especially in the case of oncology drugs, a list of Class 2 anti-cancer drugs specifically sets criteria for the use of drugs covered for each type of cancer. These criteria, including those for approval, are based on clinical effectiveness and can be considered as decision-making that considers high

drug prices in resource allocation.

Such reimbursement criteria are judgments made from the societal perspective. Yet there are certain situations where drug use for individual patients is required outside of the criteria. Some also argue that certain high-cost medicines classified as second-line must be classified as first-line agents. The scope of reimbursement is determined by the national health insurance from the societal point of view, but it doesn't mean that a full consensus exists across society.

In the meantime, national health insurance runs special copayment criteria for rare and intractable diseases under which copayment rates for drug costs and professional services have been lowered to 5% or 10%. Eligible conditions are mostly severe medical conditions that include many indications targeted by high-cost medicines.

The low copayment rates lead to greater access to health care as well as increases in health care utilization. The out-of-pocket maximum limits the amount paid by patients per year to KRW2-4 million based on income levels. As a result, there is a limited amount of cost including drug cost borne by patients for covered services.

Medical costs excluding the out-of-pocket portion for covered services are borne by the payer. The less payment burden patients feel owing to the special copayment criteria and the out-of-pocket maximum, the more patients are motivated to use health care. This will result in more amount of medical expenses the payer has to shoulder. Moreover, the ever-rising prices of newly introduced drugs will have more impact on the budget of the

national health insurance if drugs for cancers, rare and intractable diseases are reimbursed.

Due to the rising cost sharing from the payer, it becomes more important for the payer to make rigorous judgment when determining coverage scope for serious medical conditions and manage expenditures as effectively as possible.

## 2. Utilization management

Utilization of drugs covered by the national health insurance scheme is monitored and managed under the reimbursement guidelines. Activities designed to promote the appropriate use of drugs are made on an ex post basis through medical claims review of the payer organizations, and health care providers use drugs according to the reimbursement guidelines to get reimbursed for their services. Other activities designed to improve the quality of drug utilization include care benefits adequacy review, drug reimbursement adequacy review, and drug utilization review (DUR) of the Health Insurance Review & Assessment Service, and other quality management activities voluntarily carried out by certain health care facilities. That is, most activities for the appropriate drug utilization focus on drugs covered by the national health insurance scheme.

Likewise, covered high-cost medicines are also reviewed and managed according to the reimbursement guidelines, which can be considered as a tool for appropriate utilization of drugs for covered drugs. On the other hand, high-cost medicines approved for sale but not covered are not managed at all under the national

health insurance scheme, and it is therefore difficult to track and manage the utilization and the quality of these drugs. A bigger problem in view of appropriate drug utilization can occur when uncovered high-cost medicines that do not meet cost effectiveness due to high price are used for serious medical conditions with slightly better efficacy and fewer side effects. The reason is that these drugs cannot be managed under the current utilization management scheme although they are highly likely to be used in real care. Therefore, to facilitate appropriate utilization of high-cost medicines under the current system, it is necessary to include them in the benefit coverage to ensure that both quality and cost of health care services can be managed. However due to the high payer cost-sharing rates, set to 90% or 95%, for high-cost medicines, it is difficult to include these drugs in benefit coverage.

This can make it even more difficult to manage appropriate utilization of high-cost medicines, and may result in unnecessarily aggravating economic burden for patients. To address this problem, some experts argue that high-cost medicines such as those for cancer must be included in benefit coverage even at low reimbursement rates to provide greater access to therapies and to allow the payer to manage utilization.

Recently, reimbursement for Sorafenib, known as the only therapy for liver cancer, began at a 50% copayment rate, easing patients' financial burden. This is a relatively low reimbursement rate compared to other oncology drugs whose copayment rate is only 5%, but it has greatly contributed to increasing access to therapies compared to those days when patients had to pay

for the full amount of drug costs. On the part of the payer, it is also meaningful. Now that the payer is only responsible for 50% of costs, it will face less budget burden while being able to manage appropriate utilization of drugs.

Therapies for serious medical conditions covered under the health insurance scheme have relatively detailed guidelines as to the target patients and the scope of use. Especially for oncology drugs, the payer organization and a cancer review committee formulate disease-specific drug utilization guidelines. Despite the guidelines, however, there are instances where judgment on utilization appropriateness is difficult to be made due to the variety of clinical cases, and there may be differences between the committee's judgment and clinical doctors' views.

Even if cancer drugs meet review criteria, they have a high probability of generating side effects due to high toxicity. In some cases, side effects are so serious that drug therapy itself cannot be attempted. However, it is impossible to predict every single patient who is likely to suffer from side effects. In fact, some patients are not able to continue medications prescribed for a several-month supply because of side effects. This is not desirable in view of proper selection and utilization of drugs. It also increases unnecessary expenditures of national health insurance.

With the copayment rate for cancers lowered to 5%, financial burden even for a several-month supply of prescription may not be big for patients even if the cancer drugs are expensive. But there is also a possibility that doctors prescribe drugs for a long-term supply without carefully thinking whether the

prescribed drugs are appropriate for patients. Even if a patient's financial burden for purchasing drugs is not significant, total drug cost paid by national health insurance is not small at all. Therefore with regard to drugs that incur high cost and that may produce toxic side effects, efficacy and side effects must be carefully considered for each patient to ensure that the optimal drugs are selected.

In the meantime, conditions targeted by high-cost medicines are in many cases cancers, rare or intractable diseases. In these disorders, treatment is very complex due to varying degrees of response to treatment from patient to patient, or no response at all to existing therapies at certain stages of disease. For this reason, these medical conditions tend to require off-label use relative to other conditions.

Off-label use is not eligible for reimbursement and patients must therefore pay for full medical costs. While the insurance payer is not responsible to be involved in the reimbursement, appropriate drug use based on evidence is very important because clinical and economic outcomes are directly passed on to patients. For this reason, Korea has approval procedures for off-label use of drugs to manage minimum levels of quality.

When a health care facility needs off-label use, it can submit an application to the Health Insurance Review & Assessment Service for approval. Only health care facilities designated as clinical trial organizations can submit such applications, and applications can be submitted only when the Institutional Review Board (IRB) within the health care facilities have reviewed and accepted off-label use prior to the submission. Submitted

applications for off-label use is reviewed by the Health Insurance Review & Assessment Service and the Korea Food & Drug Administration. Health care facilities whose applications have been approved must submit utilization reports to the Health Insurance Review & Assessment Service no later than May 31 and September 30 each year.

With regard to oncology drugs, if a health care facility designated as a clinical trial organization also runs a multidisciplinary board, it can use drugs off label with approval from the cancer review board of the Health Insurance Review & Assessment Service<sup>2)</sup>.

Medical evidence used for approval of off-label use include textbooks, domestic and foreign clinical guidelines, clinical research papers published on authorized academic journals, and drug authorization regulations in other countries. Clinical research papers are classified into four categories based on research type, and evidence of two or more categories below are needed to get approval for off-label use. When off-label use is for rare diseases, up to the fourth category is accepted<sup>3)</sup>.

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2) Health Insurance Review & Assessment Service. Care benefit application criteria for drugs prescribed or administered to cancer patients. December 2010

3) Criteria and procedures for non-reimbursable off-label use of drugs. Notification No. 2010-43 of the Ministry of Health and Welfare (July 1, 2010)



- Category 1: Systematic literature review for randomized controlled trial
- Category 2: Randomized controlled trial or systematic literature review on Category 3
- Category 3: Quasi-randomized controlled trial, case-control study, cohort study, and other observational studies
- Category 4: Cross-sectional study, before-and-after study, case reports, case series study, non-analytic study

Currently, off-label use applications submitted by health care facilities are first reviewed and approved by the Health Insurance Review & Assessment Service, and then drug safety and effectiveness is reviewed by the Korea Food & Drug Administration. In some cases, the two organizations come to different conclusions. Once approved by the Health Insurance Review & Assessment Service, a drug can be used off-label, but if the Korea Food & Drug Administration reverses its assessment decision, use of the drug must be stopped, which can cause confusion in decision-making during treatment. Different opinions on off-label use between the Health Insurance Review & Assessment Service and the Korea Food & Drug Administration can reflect different standpoints of the payer and the approval authority regarding approval for drug use. However, reversal of any decision due to such different standpoints creates confusion in patient treatment, and it is not desirable in view of the appropriate utilization of drugs. Measures are needed to enhance balance and consistency in decision-making.

### 3. Evidence enhancement

Initial reimbursement decisions on drugs are made based on clinical test data before product launching. Decisions are made to determine the therapeutic value and cost effectiveness of drugs expected from the course of treatment. When drugs are administered to patients under varying conditions, new evidence on efficacy and safety is produced.

In fact, as a result of the reassessment of listed drugs conducted following the implementation of the positive list system, 296 drugs were found to be lacking in clinical usefulness and were removed from coverage. Coverage for 156 drugs remained with conditions attached for 2.6 years, and studies and paper publications demonstrating clinical usefulness were requested.

Scientific evaluation on these drugs concluded that it is difficult to demonstrate clinical usefulness of the drugs although the drugs completed phase 3 clinical test, are used in other countries, and even are recommended for use from professional medical societies.

The lack of evidence is more apparent in high-cost medicines. As drugs for cancers and rare conditions that make up a large portion of high-cost medicines can be approved only with phase 2 clinical test results, evidence on clinical effectiveness of these drugs is very weak. Nevertheless, there is a relatively high possibility for drugs used for serious medical conditions to be reimbursed despite high prices when there are no alternative therapies available and owing to strong demand for coverage.

Still it doesn't mean that evidence-gathering for clinical value or cost effectiveness for covered high-cost medicines is no longer

needed. Evidence required by the insurance payer can be better produced in real world than in clinical tests conducted under limited conditions.

Under the current drug reimbursement scheme, there is no tool with which to reassess the adequacy of reimbursement using additional evidence. Not only is there no tool to obtain additional evidence on therapeutic value and cost effectiveness of covered drugs that incur high costs, there is also a lack of a system under which socially required evidence can be produced for non-reimbursed high-cost medicines.

The Health Insurance Review & Assessment Service makes some assessment for off-label use using patient outcome data. As off-label use increases, there is also a growing need to establish the safety and effectiveness regarding use of these drugs. The Korea Food & Drug Administration is stepping up efforts to implement rigorous research and evaluation systems to gather evidence related to off-label use.

However, efforts to establish systems to gather evidence on clinical and cost effectiveness are still insufficient compared to efforts to control and manage off-label use. Moreover, there is no system in place under which decisions made regarding approval or reimbursement can be reassessed based on reliable data.





Chapter

04

# **Policy Recommendations in the High-Cost Drug Era**





## Chapter 4

# Policy Recommendations in the High-Cost Drug Era

## Section 1. Insurance Coverage

### 1. Reimbursement within the current national health insurance

Drug reimbursement under the national health insurance scheme in Korea was changed to the positive list system in 2007 to make reimbursement and pricing decisions based on clinical value and cost effectiveness and to determine final drug prices through price negotiations. As described in this paper, a majority of the world's most expensive drugs have entered into the Korean market. Due to high costs of these drugs, drug listing and pricing decision-making did not go smoothly, and new systems like a pilot refund system had to be implemented.

Given the high prices of high-cost medicines, reimbursing the drugs is not easy unless innovative therapeutic value or cost effectiveness is expected from clinical application. When these drugs are needed for the treatment of serious medical conditions, high costs can be an issue in terms of patients' access or right to choose drugs. For this reason, particularly for purposes of securing access to orphan drugs, some experts are supportive of exceptional financial assistance programs instead of existing reimbursement principles.

Emergence of high-cost medicines has been brought by the paradigm shift in new drug development technology. The number of high-cost medicines is therefore expected to further grow over time. If high-cost medicines are not covered by the national health insurance and put under separate programs, it will become difficult to cope with the ever-increasing number of high-cost medicines. It will be more desirable to reimburse the drugs at reasonable levels within the national health insurance scheme, which is the key health security system in Korea.

Clinical value and cost effectiveness currently used as the criteria for drug reimbursement need to remain regardless of drug price levels because they are the principles for the effective utilization of limited health care resources. Therefore, it is desirable to also assess high-cost medicines based on clinical value and cost effectiveness and determine reimbursement and prices within the current health insurance scheme.

## **2. Flexible decision-making on reimbursement**

The current health insurance scheme employs a binary drug reimbursement decision-making: whether a given drug should be reimbursed or not. When it comes to high-cost medicines, reimbursement greatly affects patient access due to their high prices. As the copayment rate for serious medical conditions is very low at 5% or 10%, patients don't feel burdened when they use covered drugs. Use of uncovered drugs, however, can be seriously burdensome.

Although patients' co-sharing burden has been substantially



reduced with expanded coverage for serious medical conditions, overall coverage will decrease if patients have to use uncovered drugs. In this case, the coverage level felt by patients will not be so high.

If coverage includes as many drugs as possible, it will greatly increase cost burden on the payer, so this option is not desirable from the perspective of insurance budget management. Therefore, there is a need to include drugs even at low reimbursement rates and improve access to drugs to some degree if alternative therapies are extremely limited. Another option worthy of exploring to mitigate the excessive financial burden is making agreements on the gross reimbursement amount with pharmaceutical companies.

## **Section 2. Appropriate Utilization**

### **1. Enhanced management of drug supply**

High-cost medicines are mostly developed to treat serious medical conditions. If used improperly, they can have a serious impact on patients. In cases where there are already available drugs to treat such ailments, an optimal choice needs to be made between these existing drugs and newer and more expensive drugs. Even when clinical guidelines or reimbursement criteria are available, judgment by a specialist is very important when administering medications in patients because progression of disease differs from patient to patient.

For this reason, some countries are using a limited number of providers that can prescribe or dispense certain high-cost medicines to ensure that drugs are properly and safely used. In addition, drugs are only dispensed to patients who meet certain criteria.

Korea has reimbursement criteria for drug use but does not place restrictions on health care providers that can prescribe. Applications for off-label use submitted by health care facilities that have IRB are reviewed and approved, but any physician or health care facility is allowed to prescribe drugs as long as the drugs are covered.

Under the current fee-for-service system that does not motivate restricted medical practice, physicians are very unlikely to voluntarily contain the use of high-cost medicines if there is no limit on prescribing physicians. Controlling use of high-cost medicines that show clinical value but that have been excluded from coverage due to the lack of cost effectiveness is even more difficult. Clinical experts would want to use a new drug in treating their patients in anticipation of therapeutic effect, and patients would also want to try high-cost medicines even if they have to pay for the full amount of costs, hoping that the drugs will treat them. If out-of-pocket expense can be reimbursed through private health insurance plans, use of high-cost medicines can be further stimulated. This may result in increasing access of patients to therapies, but considering the potential side effects from the highly toxic high-cost medicines and high social costs, a mechanism with which to determine whether the high-cost medicines are inevitable and to control their utilization is needed.

For high-cost medicines with significant side effects and financial impact, prescription needs to be limited to health care facilities staffed with specialists that can voluntarily manage the quality of drugs to facilitate the appropriate drug utilization. In determining health care facilities allowed to prescribe high-cost medicines, adoption of separate approval procedures for each drug with prescribing qualifications for physicians and health care facilities can be considered, rather than designating prescribing facilities based on the type of health care facility.

## **2. Promotion of appropriate utilization through coverage inclusion**

Since the implementation of the positive list, an increasing number of high-cost medicines is excluded from coverage. This coverage exclusion may result in market shrinking if pharmaceutical companies carry out passive marketing strategies. On the contrary, it may result in increased use of certain drugs.

If high-cost medicines excluded from coverage due to the lack of clinical value or cost effectiveness are frequently used in clinical fields, management of these drugs can be difficult. As there is no price limit, among others, pharmaceutical companies can charge high prices using their ability to exercise dominant market power, and this in turn will directly affect patients. Health care providers will be motivated to use new uncovered drugs more freely due to the lack of regulatory restrictions. Coverage exclusion decisions made for efficient utilization of resources of the national health insurance scheme can result in inefficient utilization of resources across the society.

Therefore, for high-cost medicines that are not deemed sufficiently qualified for coverage but that need to be used given the risk vs benefit, coverage needs to be gradually expanded so that patients can have more access to drugs and appropriate utilization can be managed. However, because these drugs come to be covered despite insufficient evidence, their reimbursement rates need to be limited to certain levels, which can be gradually revised upward as more evidence on clinical value and cost effectiveness is collected.

## **Section 3. Enhanced Evidence Development**

### **1. Coverage with evidence development**

When a drug has superior therapeutic potential but there is not enough evidence with which to decide coverage, coverage with evidence development (CED) can be considered. Under CED, coverage is warranted to the extent that the drug is used with conditions to gather additional evidence. CED can be viewed as a middle ground between coverage and no coverage and a tool to secure a minimum level of appropriateness of drug use by allowing for drug use under controlled conditions while ensuring patient access to new drugs. Adequacy of reimbursement can also be reassessed using further evidence on clinical usefulness and cost effectiveness.

When coverage is warranted with insufficient evidence on clinical usefulness or cost effectiveness, drug use can quickly

spread. Once the drug use is widely practiced, it becomes very difficult to restrict drug use under research settings to produce evidence. On the contrary, if no coverage is decided, there is a risk of limiting patient access to a drug that may deserve to be reimbursed.

One of the determinants of success or failure of CED is research designs for collecting evidence data. Research conducted under CED involves a variety of stakeholders such as insurers, pharmaceutical companies, technology assessment organizations, health care providers, patients and experts. As costs are also shared publicly, stakeholders need to agree up to detailed levels of research designs. These agreements include parameter definitions and measures to be used in the assessment of outcomes as well as decision makers. A specialized organization to oversee across all stages of research is also needed. In essence, CED requires substantial infrastructure for clinical studies and analysis (Park, 2010).

As seen from above, CED requires considerable social costs in the course of evidence generation. Therefore, evidence cannot be the only value to pursue; there must be discussions and agreement as to the level of uncertainty and costs that can be accepted.

Conditions that qualify new drugs for CED can be summarized as below (Park, 2010).

First, there is a reasonable amount of evidence that the drug is of significant value for patients, and uncertainty exists about the drug's clinical usefulness or cost effectiveness. In addition, evidence can be generated within a given period of time to address

the uncertainty, and final reimbursement and pricing decisions can be made using the additionally generated evidence.

## **2. Evidence generation for off-label use**

Off-label use involves the use of drugs for ailments other than indications approved by the regulatory authority, based on cases or experiences without conclusive evidence on safety and efficacy. Off-label use is practiced when off-label use is inevitable due to the lack of available therapies for the indications, or when off-label use is more convenient or more beneficial compared to other approved therapies.

Whatever the situation, off-label use is not sufficiently supported by scientific evidence, and thus can jeopardize the safety of patients. Therefore, safety and efficacy of any drug used off-label must be eventually evaluated.

Clinical studies are currently conducted in Korea to evaluate the safety and efficacy of off-label use, but more systematic procedures are needed to generate evidence. To this end, priorities for currently used off-label drugs must be determined based on their impact on public health care and budget, and research design for gathering a sufficient amount of scientific evidence on safety and efficacy must be established. When evidence is collected to the extent sufficient to approve the drugs for new indications as a result of safety and efficacy assessment, the drugs can be added to the concerned indications and reimbursement decisions can be made. Guidelines must be developed so that discontinuation of off-label use can be instructed when safety and efficacy is

still found to be insufficient.

Especially in the case of off-label use that can replace use of high-cost medicines, if safety and efficacy evaluation suggests that the drug used off label can be assigned a new indication, it can contribute to reducing health care expenditures. If high-cost medicines can be replaced with cheaper ones, pharmaceutical companies can make half-hearted efforts to generate evidence. That is, motivations for evidence generation for off-label use can be different between pharmaceutical companies and the society as a whole. Therefore, there is a need to identify cases of off-label use for which evidence development is needed from the societal perspective, and research needs be conducted for the identified cases.







Chapter

05

# Conclusions





## Chapter 5

# Conclusions

With the paradigm shift in new drug development technology, the number of high-cost medicines is expected to increase and reimbursement and utilization of these high-cost medicines will need to be managed within the current national health insurance scheme. When high-cost medicines outside of benefit coverage are frequently used in clinical fields and there are no other drugs patients can choose, the high-cost medicines need to be included in benefit coverage even at low reimbursement rates based on the level of evidence to provide greater access and manage drug utilization. To mitigate impacts of increased drug coverage on the national health insurance budget, making total drug cost agreements with pharmaceutical companies can be considered for risk sharing. When a drug has a potential therapeutic value but there is not enough evidence to warrant reimbursement, coverage with evidence development can be applied to the extent that the drug is used with conditions for additional evidence generation.

Considering the impacts of high-cost medicines on patient health and health insurance budgets, there is a need to manage reimbursement, prices, as well as drug supply and utilization more rigorously. To prevent excessive or inappropriate use of drugs that may arise from coverage inclusion, prescribing rights can be given only to those health care facilities staffed with

specialists for the concerned diseases where the quality of drug utilization can be voluntarily managed for drugs whose utilization needs to be controlled. Once a drug is approved for sale, additional evidence on its clinical usefulness and cost effectiveness can be generated through application in various clinical fields. Efforts are needed to identify areas requiring evidence development in view of appropriate drug utilization and sensible pharmaceutical spending. For the identified areas for evidence development, research must be carried out and guidelines for drug utilization need to be developed.

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