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Future Prospects of Pharmaceuticals and Medium to Long-Term Strategies of Health Policy and Governance

People with People in Mind

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Introduction

I Introduction

1. Research Background and Purpose

The world of pharmaceuticals is expected to undergo dramatic changes in the coming years thanks to the radical progress being made in understanding diseases and developing pharmaceutical technologies. Not only will the range of treatable diseases expand, but the cost and methods of drug administration will also be transformed. Recent new drugs, particularly those for treating cancer, have been marketed at high prices, posing new challenges to public health systems that operate with limited fiscal resources. The rising cost of new cures for advanced and serious illnesses, and their governance by policy, present a growing global problem. As the cost of treatments for advanced and serious illnesses will continue rising, while the supply of new and innovative drugs also keeps growing, it is critical for governments to keep track of changes in technological trends, thereby allowing them to predict future pharmaceutical innovations and prepare policy and system resources for ensuring the sustainability of drug coverage and use.

The purpose of this study is to provide an international survey of the technological innovations that are underway in the world of new drugs, highlighting key characteristics of future

pharmaceuticals and related issues, and thereby revealing policy implications for the more sustainable governance of the health and drug coverage system in Korea. This study is intended to help the Korean health system better manage future pharmaceutical innovations and ensure the appropriate use of, and payment for, pharmaceuticals society-wide.

2. Research Structure and Method

The remainder of this study is divided into four sections.

Section II provides a survey of the latest trends and innovations in pharmaceutical technology and explores the implications of expected future drugs for health policy. Existing literature, both in Korea and around the world, on the pharmaceutical industry, research and development (R&D), technological trends, and policy trends is surveyed, as are the web resources provided by governmental authorities, such as the Korean Ministry of Food and Drug Safety (MFDS), U.S. Food and Drug Administration (FDA), and European Medicines Agency (EMA). The U.S. National Library of Medicine's website on information from clinical trials (ClinicalTrials.gov) is also surveyed to identify trends in the development of highly anticipated new treatments. Section III provides an analysis of new drugs authorized for marketing in Korea, their use and expenses in the National Health Insurance system. Specifically, all

pharmaceuticals that have been approved as new drugs or orphan drugs (ODs) in Korea from 2007 to 2018 have been sampled and subjected to analysis in light of the policy and other important issues identified in Section II. Section IV then analyzes the structure of governance on the introduction, evaluation, and coverage of new drugs in Korea. The authors developed structuralized and semi-structuralized questionnaires for this purpose, and used them to conduct in-depth, in-person interviews with stakeholders, including representatives of domestic and foreign pharmaceutical companies that have launched new drugs, Korean and international governmental agencies, and consumer and patient groups. Finally, Section V provides a summary of the findings of this study and identifies implications for improving health policy and governance for the purpose of strengthening the Korean health system's capability to manage future pharmaceutical innovations.

Ⅱ

Trend of Recent Pharmaceutical Developments and Health Policy Issues

1. Trend of Pharmaceutical Developments
2. Pharmaceutical Innovations in Progress
3. Future Pharmaceuticals and Health Policy Issues

Ⅱ Trend of Recent Pharmaceutical Developments and Health Policy Issues

1. Trend of Pharmaceutical Developments

The foremost trend in the global pharmaceutical industry today is the shift of focus from low-molecular chemical compounds to biotechnology (e.g., monoclonal antibodies). Although synthetic drugs still account for 51 percent of all existing pipelines, biotechnology-based cures have steadily crept up the ranks of important pipelines. Biologics, proteins, and antibodies account for 12.7 percent of all pipelines, but they have together been growing at an average rate of 12.8 percent a year (Pharmaprojects, 2019).

Anticancer drugs are leading the new drug pipelines worldwide. The percentage of anticancer drug pipelines under R&D grew sharply from 26.8 percent in 2010 to 35.2 percent in 2019, making cancer the most-invested type of illness on the pharmaceutical market today (Pharmaprojects, 2019). Anticancer R&D and pipelines continue to expand because cancer treatment is one area of medicine that still features a significant number of unmet medical needs, while recent progress in biotechnology research has significantly increased our knowledge of pathogenesis (Schmid and Smith, 2007).

2. Pharmaceutical Innovations in Progress

2-1. Immuno-oncology Therapeutics

Immuno-oncology therapeutics have changed our paradigm for cancer treatment, i.e., by targeting the natural human immune system. Whereas the earlier generations of cancer treatments specifically targeted the tumor itself, immune-oncology therapeutics enhance the ability of the patient's existing immune system to detect and attack cancerous cells (Lee, 2014, pp. 284-285). As of May 1, 2019, seven immune checkpoint inhibitors (CIs) had been authorized for marketing in Korea, the United States, and Europe.

ClinicalTrials.gov was searched for data on the latest clinical developments in immune-oncology therapeutics. Results with a status of terminated, completed, withdrawn, or unknown were omitted from the analysis, while clinical trial phases from zero to three were added as a search condition. Entering "cancer vaccine" as a keyword returned results on 114 clinical trials. Entering "checkpoint" (to search for PD-1, PD-L1, CTLA-4, and checkpoint inhibitors) returned results on 444 clinical trials in total.

〈Table 2-1〉 Clinical Trials on Oncology, CIs, and Cancer Vaccines (as of May 28, 2019)

Phase	Oncology	CIs	Cancer vaccines
0	426 (3%)	9 (2%)	5 (4%)
1	3,526 (23%)	127 (28%)	51 (45%)
1 and 2	2,222 (14%)	108 (24%)	25 (22%)
2	6,523 (42%)	172 (39%)	26 (23%)
2 and 3	397 (2%)	3 (1%)	2 (2%)
3	2,518 (16%)	25 (6%)	5 (4%)
Total (N)	15,612	444	114

Source: ClinicalTrials.gov (retrieved from https://clinicaltrials.gov/ on May 28, 2019).

High cost is the biggest problem facing these immune-oncology therapeutics. Treating a patient using either Opdivo® (nivolumab) or Keytruda® (pembrolizumab) alone would raise the cost by five to 10 times the cost of conventional drugs. Immuno-oncology therapeutics, however, hold great potential because they have been effective even for terminal-stage or recurrent-cancer patients. Clinical trials are being conducted to prove the efficacy of these new drugs for more diverse kinds of cancer. Nonetheless, there remain critical issues that must be addressed, including their high costs, insurance coverage, and selection by specialists and hospitals.

2-2. Gene Therapy

Gene therapy involves targeting, modifying, and regulating

gene expressions that cause certain types of diseases. In other words, it treats given diseases by altering the biological functions of cells.

ClinicalTrials.gov was searched for data on ongoing clinical trials on gene therapy. The keywords used were "gene therapy" and "CAR-T," and trials with a status of terminated, completed, withdrawn, or unknown were excluded from the analysis. Clinical trial phases from zero to four were added as a search condition. A search for "gene therapy" returned results on 374 clinical trials; and "CAR-T," 543 trials. Early-phase trials (Phases 1, 1 and 2, and 2) accounted for 70 percent or so of the results (as of August 13, 2019).

Our analysis of all pertinent clinical trials on gene therapy worldwide, effective as of 2017, reveals that trials were being conducted in 38 countries, with 63 percent concentrated in the United States. Cancer was the subject of 65 percent of the trials, and monogenic diseases accounted for 11 percent (Ginn, Amaya, Alexander, Edelstein, and Abedi, 2018).

Gene therapy is a cutting-edge area of new drug research that offers hope for the development of innovative approaches to treatment. Regulatory regimes and guidelines must be updated and revisited regularly to promote effective R&D and effectively manage clinical trials, authorization, safety, and quality.

Gene therapy is also garnering attention because it is capable

of completely curing particular diseases with a single or short-term treatment. However, new drugs based on gene therapy are expected to raise medical costs significantly because they target patients with specific diseases, and their production and quality control require extensive manpower. These drugs must also be handled and administered, along with patients' responses, by highly skilled specialists.

2-3. Stem Cell Therapy

Stem cell therapy is an area of regenerative medicine that seeks to restore damaged or degenerated cells/tissues using living cells. It holds much potential for various applications, such as treatments for eye diseases, blood diseases, skin diseases, central nervous system (CNS) diseases, heart diseases, cancer, immune problems, and diabetes (de Luca et al., 2019).

ClinicalTrials.gov was searched for data on current stem cell clinical trials. The keyword used was "stem cell therapy," and clinical trials in phases zero to four were subjected to analysis, except those with a status of terminated, completed, withdrawn, or unknown. A total of 92 pertinent clinical trials were found, nearly 80 percent of which were in their early stages (Phases 1, 1 and 2, and 2). The number of new clinical trials grew steadily over the last five years from 2014 to 2019, with 12 new trials registered as of June 20, 2019.

Stem cell therapy is an extremely complex technology that is likely to require quite some time before marketing is possible. The regulatory standards for the safety and efficacy of stem cell therapy for medical use are quite rigorous. Moreover, the evaluation regime currently in place is not sufficiently reflective of the particular characteristics and conditions of the products. Stem cell therapy has also been the subject of intense controversy in some societies over its ethical implications, thus limiting the prospects for the development and enforcement of a global regulatory regime. By its nature, stem cell therapy requires a personalized approach to treatment. Further innovation is needed to ensure the mass production of stem cell therapy drugs (MOHW et al., 2018, p. 211).

2-4. Digital Therapeutics

Digital therapeutics, or DTx, involves applying digital technology to the prevention, management, and treatment of illnesses. It involves quality software programs with medical efficacy that has been proven by rigorous clinical trials.

ClinicalTrials.gov was searched for the current clinical trials on DTx. Trials with uncertain recruitment information were excluded from the search results, which were confined to the "interventional" types of research. A total of 12 keywords were used, including "digital therapeutic," "digital therapeutics,"

"digital therapy," "digital therapies," "digital treatment," "digital treatments," "digital medicine," "digital medicines," "digital pill," "digital pills," "software treatment," and "ingestible sensor." The search returned 44 qualifying results from January 1, 2008, to July 15, 2019. Of these, 42 clinical trials that fit this study's definition of DTx were chosen for analysis.

In order for DTx to produce better results than conventional medicine, it is crucial that the technology underlying it is accepted. To make DTx part of the mainstream health system, medical practitioners, insurance companies, and other involved actors should accept them in actual treatment. Persuading insurers to agree to pay for these new therapeutics, in turn, will require demonstration and certification of their safety and efficacy.

There are a number of factors that are expected to accelerate the growth of DTx, such as the new technology's ability to reduce the cost of healthcare, the increasing prevalence of lifestyle diseases, and the rise of partnership and collaboration in the market, as well as the growing pressure on medical service providers. The growing risk of cyberthreats and concerns over data security, however, will likely hold DTx back from growing as expected (The Insight Partners, 2018).

3. Future Pharmaceuticals and Health Policy Issues

3-1. Insufficiency of Evidence for Decision-Making

One of the defining issues of the global new drug market over the last decade or so is the uncertainty or insufficiency of evidence for decision-making. This uncertainty problem is likely to persist for some time to come because of the very nature of future pharmaceuticals as well as the increase in accelerated approval.

Although the demand for innovations such as gene therapy, stem cell therapy, and tissue engineering is on the rise, the products of these technologies either target relatively small numbers of patients or are meant for treatments that are personalized to individual patients. Accordingly, the scale of clinical trials for these innovations remains limited, while it is also difficult to find similar treatments to which they can be compared (Degtiar, 2017).

In the meantime, governments worldwide have been increasing the accelerated approval of new drugs over the last two decades. Insofar as this policy practice persists, without rigorously verifying the final clinical efficacy of new technologies, the evidence for clinical efficacy will remain insufficient and uncertain.

3-2. Rising Costs and Issues with Fiscal Sustainability

The prices of new drugs, especially anticancer treatments, have been rising steeply over the years. Thus, the increasing demand for and use of these drugs will likely burden the healthcare system considerably.

Since 2012, the amount of spending on anticancer treatments has been growing more rapidly than the number of cancer patients and the amount of spending on health (WHO, 2018a, p. 3). New drugs for treating hepatitis-C, first introduced in 2014, were so efficacious that they raised the question of how the fiscal burden of such effective drugs should be borne by health systems worldwide. Cell therapy, gene therapy, and other cutting-edge approaches to treatment currently being employed in the global market are incredibly expensive.

3-3. Allocation of Resources to Minority Patients and Fundamental Cures

The state-of-the-art pharmaceutical innovations on the market today target small numbers of patients and strive to provide fundamental cures with one-time or short-term administration. These characteristics of new drugs carry implications for how and when limited fiscal resources for healthcare should be allocated.

Fundamental cures, needless to say, will eradicate the need for long-term management of illnesses and significantly improve quality of life for the patients in the long term. Insofar as a health system can identify patients in need of such cures early enough, the value of these cures will accrue disproportionately to these small numbers of patients. At some point, however, the society has to decide which types of treatments—fundamental cures for a few or conventional treatments for the majority—should be prioritized (Jönsson et al., 2019).

As the amount of fiscal resources that can be spent on making pharmaceuticals available and affordable cannot be increased indefinitely, policymakers worldwide will face growing debates over whether expensive fundamental cures should be paid for with public resources, and if so, how they should be paid for, and how the allocation of fiscal resources for healthcare should be adjusted accordingly.

3-4. Roles and Responsibilities of Suppliers in Ensuring Appropriate Pharmaceutical Supply

Therapeutic approaches based on patients' own cells or genetic makeup are highly personalized and advanced forms of treatment. The process of producing and supplying regenerative medicines, made by extracting and modifying patients' cells, can be extremely complex, spanning multiple

phases and settings and facing institutional hurdles in different societies. Public health systems that have been designed on the basis of conventional treatments can find such process disorientingly strange. A new therapeutic approach, in which the doctor samples the patient's cells and passes the sample onto the manufacturer, which then develops a personalized treatment based on the sample and sends it back to the doctor so that the doctor can administer it properly to the patient, can be quite baffling and requires transparent and uninterrupted communication between the doctor and manufacturer. The kind of collaboration and partnership this new approach requires goes beyond anything that has been expected by the conventional process, in which the doctor finds a suitable option among already existing treatments and administers it to the patient (Elverum and Whitman, 2019).

Although researchers worldwide have been striving to find gene- or stem cell-based cures over the last three decades, success in clinical trials is still a relatively novel phenomenon. Very few of these products have been authorized, with the vast majority having very brief and limited clinical records (Ali, Slocomb, and Werner, 2016). There still remains much uncertainty, even concerning drugs that have been proven efficacious by recent clinical trials, that these drugs may generate unexpected side effects or complications in the short and long terms. It is therefore all the more important for highly skilled

specialists or specialized institutions, capable of keeping track of such complications, to handle administration (Cancerworld, 2019).

Ⅲ

Analysis of New Drugs approved in Korea

1. Current Status and Characteristics
2. New Drugs in Korea: Use and Spending under the NHI

Ⅲ Analysis of New Drugs approved in Korea

1. Current Status and Characteristics

1-1. Method of Analysis

The new drugs subjected to our analysis are the pharmaceuticals that were authorized for marketing in Korea as new drugs or orphan drugs (ODs) from 2007 to 2018. Korea's Pharmaceutical Affairs Act (PAA) defines a "new drug" as "a drug of new materials, the chemical structure or the construction of substance of which is wholly new, or a drug of composite medication containing new materials as effective ingredients" (Article 2.8). However, the pharmaceutical authorization scheme in Korea provides for a separate category of pharmaceuticals, including orpahn drugs (ODs). An analysis that spans a comprehensive scope of new drugs should therefore include pharmaceuticals that have been categorized as new drugs as well as ODs.

The MFDS' database of authorized pharmaceuticals was accessed to identify and sort the list of drugs subject to the analysis (as of January 23, 2019).[1] From the start of 2007 to the end of 2018, a total of 25,742 drugs were authorized by the MFDS in

1) https://nedrug.mfds.go.kr/searchDrug 2019. 1. 23.

Korea, 630 of which were designated as new drugs or ODs. Of these, 60 whose authorization had expired or been revoked or terminated were excluded. This gives a final sample of 570 new drugs and ODs with "normal" authorization status. The standard codes for these drugs were then matched with the Anatomical Therapeutic Chemical (ATC) classification codes found in the Health Insurance Review and Assessment Service (HIRA)'s database.[2] The National Health Insurance Service's pharmaceutical price files[3] were then accessed to gather data on whether any of the 570 drugs were covered by the National Health Insurance (NHI), and if so, since when and what codes their main ingredients had.

Second, to determine whether the authorization for any of the new drugs or ODs was conditional, the U.S. FDA's information on accelerated approval as well as the EMA's conditional marketing authorisations (CMAs) were searched and reviewed.

Third, to determine how innovative the effects of the new drugs and ODs have been, the authors referred to the FDA's priority review (PR) information and France's Improvement in Actual Benefit evaluation data from the National Authority for Health (HAS). The FDA reviews the clinical results on all new

2) https://www.hira.or.kr/bbsDummy.do?pgmid=HIRAA020002000100&brdScnBltNo=4&brdBltNo=7135#none 2019. 4. 24.
3) https://www.hira.or.kr/rd/insuadtcrtr/InsuAdtCrtrList.do?pgmid=HIRAA030069000400 2019. 1. 23.

drug applications and prioritizes those that offer potential for significant improvement in the safety and effectiveness of treatment, diagnostics, or prevention of major illnesses (Sulman and Kaitin, 1996).

The HAS divides new drug applications into five grades according to the scale of clinical benefits. Those in Grades I to III are prioritized as innovative drugs (CEPS, 2011, p. 63).

Table 3-1 provides a summary of the sources of data used for our analysis and how we matched product information.

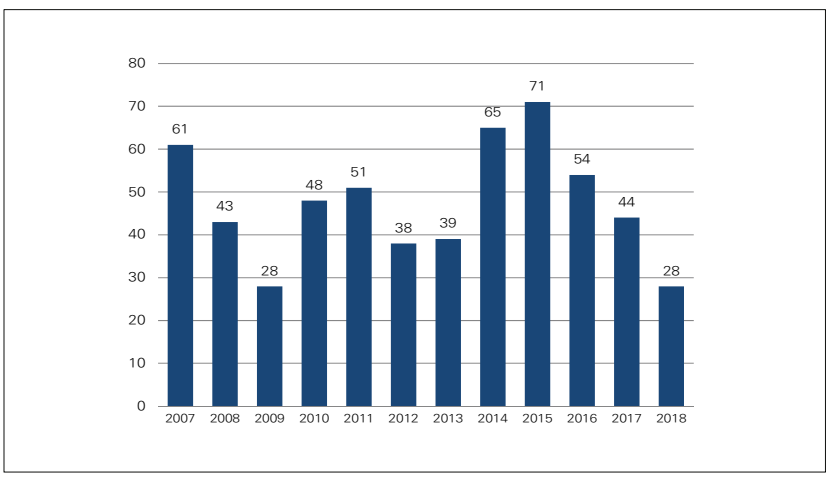
〈Table 3-1〉 Development of the New Drug/OD Dataset: Sources of Data

Data type	Data collected	Source	Matched with
Approvals and NHI benefits in Korea	Pharmaceutical authorization information	MFDS	Reference files
	ATC codes and names	HIRA	Standard codes
	NHI benefit status and main ingredient codes	HIRA	Product codes and names
Overseas approvals	Authorization of each drug in the U.S.	FDA	Names of products and ingredients
	Authorization of each drug in the EU	EMA	ATC codes and product names
Evaluation of innovation	FDA PR in the U.S.	FDA	Names of products and ingredients
	HAS Improvement in Actual Benefit	HAS	ATC codes and product names

1-2. Results

Since 2007, 47.5 of new drugs/ODs have been approved in Korea per year on average. The numbers of approved drugs were the highest, at 65 and 71, in 2014 and 2015, respectively.

[Figure 3-1] Number of New Drugs/ODs Approved in Korea by Year



Of the 570 drugs analyzed, 190 (33.3 percent) were ATC-L drugs (antineoplastic and immunomodulating agents); 83 (14.6 percent), A drugs (alimentary tract and metabolism); and 56 (9.8 percent), J drugs (antiinfectives for systemic use). The share of L-drugs (antineoplastic and immunomodulating agents) has also been increasing in recent years.

Of the 570 drugs, there were 251 ODs, making up 44 percent of the total. Anticancer agents accounted for 24.7 percent of all

new drugs and ODs analyzed (141 out of 570).

In addition, 88 of the analyzed drugs (15.4 percent) had obtained conditional approval in either the United States or the EU or both. The percentage of these conditionally approved drugs grew slowly from 2007 to 2018. Of the 251 ODs, 54 (21.5 percent) also had conditional approval in either the United States or the EU or both. Of the 141 anticancer drugs, 66 (46.8 percent) had similar conditional approval.

Of the 570 drugs, 311 had PR information from the FDA, and 139 of these (44.7 percent) were indeed given PR. The percentage of new drugs/ODs given the FDA's PR grew rapidly from 2013 and onward, making up 80 percent of the drugs that were approved in Korea in 2018.

There were 276 drugs with HAS information from France, and 76 of these (27.5 percent) had been categorized as having made significant improvements in benefit (Grades I to III). The percentage of HAS-recognized innovative drugs, however, has been declining steadily since 2013, contrasting with the pattern of the FDA's PR. This suggests a widening gap between the two authorities in terms of the criteria and evaluation timing they employ.

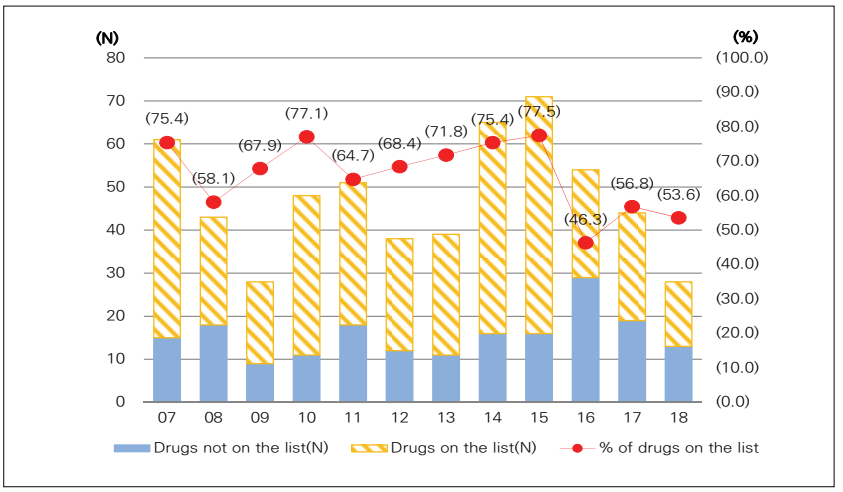
Of the ODs, 117 had FDA PR information, and 71 of those (60.7 percent) had been given approval based on PR. There were also 120 HAS-evaluated ODs, 44 of which (36.7 percent) were recognized for having made a significant improvement in

benefit.

Among anticancer drugs, 89 had FDA PR information, and 59 of those (64.8 percent) had been approved subject to PR. On the other hand, 70 anticancer drugs had been evaluated by the HAS, with 30 (42.9 percent) recognized for a significant improvement in benefit. In other words, ODs have been more innovative than new drugs in general, and anticancer drugs have been far the most innovative by far.

The NHI system in Korea has been providing benefits for drugs on its "positive list" since 2007. Of the 570 drugs analyzed, 383 (67.2 percent) had been added to the list as of April 2019. Specifically, over 70 percent of the drugs approved from 2013 through 2015 found their way onto the positive list, while the percentage of approved drugs added to the list has been on the decline since 2016, showing time spent for new drugs to be listed after being approved. The percentage of new drugs approved in these years and later added to the positive list will likely grow in the future.

[Figure 3-2] Approved New Drugs/ODs Added to the Positive List by Year



As of April 2019, 52 of the analyzed drugs were brought under risk-sharing agreements (RSAs) between the National Health Insurance Service and pharmaceutical companies. The majority of these agreements, including 42.3 percent that limited the total expenses and 36.5 percent that made payback, were financial-based agreements. The number of RSAs multiplied as the Korean government increased the NHI coverage. Accordingly, 36 of the 52 RSA-subject drugs made their way onto the positive list in 2017 and 2018. Of the new drugs added to the positive list in 2017 and 2018, benefits were paid under the respective RSAs for 40.6 percent (26 out of 64) and 32.3 percent (10 out of 31), respectively.

〈Table 3-2〉 RSAs Applied to New Drugs/ODs on the Positive List by Year

Year added to list	Number of drugs by RSA type						N/A	Total
	Conditional evidence develop-ment	Total ex-pense limit	Payback	Dose limit per patient	Other	Subtotal		
2007	·	·	·	·	·	0	13	13
2008	·	·	·	·	·	0	18	18
2009	·	·	1(100)	·	·	1(100)	20	21
2010	·	·	·	·	·	0	28	28
2011	1(100)	·	·	·	·	1(100)	21	22
2012	·	·	1(100)	·	·	1(100)	28	29
2013	·	·	·	·	·	0	26	26
2014	·	·	1(100)	·	·	1(100)	29	30
2015	·	·	2(100)	·	·	2(100)	53	55
2016	·	5(83.3)	1(16.7)	·	·	6(100)	27	33
2017	·	11(42.3)	10(38.5)	2(7.7)	3(11.5)	26(100)	38	64
2018	·	6(60)	3(30)	·	1(10)	10(100)	21	31
2019					4(100)	4(100)	9	13
Total	1(1.9)	22(42.3)	19(36.5)	2(3.9)	8(15.4)	52(100)	331	383

As for the 251 ODs approved from 2007 through 2018, 139 (55.4 percent) had been added to the positive list as of April 2019. Of the 141 anticancer drugs, 99 (70.2 percent) were added to the list. Note that the percentage of anticancer drugs added to the positive list is greater than that of all new drugs (67.4 percent) or ODs (%5.4 percent). In particular, nearly 90 percent of anticancer drugs approved from 2013 to 2015 were added to the positive list.

2. New Drugs in Korea: Use and Spending under the NHI

From 2012 to 2017, the billed costs of new drugs and ODs grew at an average rate of 22.7 percent year-on-year. Among the various types of medical institutions where these drugs were administered, long-term care hospitals reported the highest rate of increase in annual billed amounts, followed by tertiary general hospitals (TGHs), general hospitals, hospitals, and clinics, in descending order. In terms of the absolute amounts billed, TGHs dominated, accounting for 44.8 percent of the total amount billed, followed by general hospitals (26.1 percent) and clinics (23.5 percent).

〈Table 3-3〉 Annual Billing for New Drugs/ODs by Type of Medical Institution

(Unit: million KRW)

Type	2012	2013	2014	2015	2016	2017	Total	Annual rate of increase
TGHs	148,227	251,043	315,466	414,573	452,575	501,776	2,083,660	27.6%
General hospitals	101,090	145,922	177,098	204,965	268,527	316,892	1,214,494	25.7%
Hospitals	20,797	28,281	33,618	41,571	43,485	42,787	210,539	15.5%
Long-term care hospitals	882	1,423	1,758	2,175	2,376	3,055	11,669	28.2%
Clinics	117,685	168,339	182,062	199,522	209,764	218,702	1,096,074	13.2%
Other	3,825	5,477	5,823	6,279	6,439	6,585	34,428	11.5%
Total	392,506	600,485	715,825	869,085	983,166	1,089,797	4,650,864	22.7%

The pattern observed in the distribution of drugs under development by targeted medical effect emerged again in the distribution of bills, with A drugs (alimentary tract and metabolism), L drugs (antineoplastic and immunomodulating agents), and J drugs (antiinfectives for systemic use) claiming the greatest shares of NHI spending on new drugs/ODs. Specifically, from 2012 to 2017, spending on J and L drugs grew quite rapidly, reflecting the trend of the recent R&D and marketization of new drugs/ODs.

The share of new anticancer drugs in NHI spending on new drugs/ODs multiplied from 5.1 percent in 2012 to 19.2 percent in 2017. TGHs accounted for 83 percent of the billed amount of the cost for new anticancer drugs, and general hospitals, for another 17 percent.

〈Table 3-4〉 Annual Billing for New Anticancer Drugs (Including ODs)

(Units: million KRW, percentage)

Year	NHI spending on new drugs/ODs	NHI spending on anticancer drugs	Percentage
2012	392,506	20,165	5.14
2013	600,485	50,272	8.37
2014	715,825	80,984	11.31
2015	869,085	134,677	15.50
2016	983,166	147,034	14.96
2017	1,089,797	209,615	19.23
Total	4,650,864	642,747	13.82

We also analyzed whether the increasing spending on new drugs/ODs added to the NHI's positive list has accelerated the market demand for these drugs. Specifically, we analyzed the percentage of new drugs, which had been on the positive list for six years or less as of 2013 through 2017, of the total NHI spending on drugs. In 2013, new drugs that had been on the positive list for six years or less accounted for 3.66 percent of the total NHI spending on drugs and 4.48 percent in 2017. This shows that the percentage of new drugs of total NHI spending has been rising slowly but steadily year after year.

In the meantime, the share of new anticancer drugs (L01X) that had been on the positive list for six years or less among all anticancer drugs rose from 0.35 percent in 2013 to 0.91 percent in 2017. The growth in the share of these new anticancer drugs was especially prominent after 2014, when the NHI coverage of anticancer drugs was expanded drastically through RSAs.

Ⅳ

Governance on New Drugs

1. Research Plan
2. Governance on New Drug Approval
3. Governance on New Drug Coverage

Ⅳ Governance on New Drugs

1. Research Plan

In this section, we identify the latest trends and issues in policy governance concerning the introduction of new drugs and stakeholder participation. How approvals and NHI coverage are decided is the main question concerning policy trends. To facilitate the assessment of the current status of policy governance and draw implications for improvement, we identify the processes and objectives of approval and coverage inclusion. As for policy objectives, our focus is the criteria that guide whether a new drug should be approved, and, if approved, included in NHI coverage. Regarding policy processes, we interview stakeholders using a questionnaire that probes stakeholder participation, decision-making structure, information transparency, supervision and regulation, and sustainability and safety.

〈Table 4-1〉 Policy Objectives and Criteria

Type	Objective/criterion
Drug characteristics	Safety
	Efficacy in clinical trials
	Effectiveness in clinical practice
	Benefit-to-harm ratio
	Consistent evidence
Disease characteristics	Severity of disease
	Health-related quality of life (QoL)
	Availability of alternative treatments
	Burden of disease
	Patient population
Treatment characteristics	Price/cost of treatment
	Cost-effectiveness
	Fiscal impact
International comparison	Approval in other countries
	Coverage in other countries
	Covered prices in other countries

With the goal of capturing diverse opinions, we included three groups of respondents in our survey: (a) representatives of domestic pharmaceutical companies that have marketed new drugs and related organizations ; (b) representatives of foreign pharmaceutical companies that have marketed new drugs and related organizations and (c) members of consumer and patient groups. Both focus group interviews (with five or fewer respondents each) and one-on-one interviews were held. Interviews were held using two questionnaires, one structuralized and the other semi-structuralized, both developed by the authors. The study was subjected to review by Ewha Womans University's IRB(institutional review board) (ewha-201904-0010-01).

Below is a summary of the interview dates and interviewee groups.

〈Table 4-2〉 Overview of Interviews

	Approval decisions (n = 17)	Coverage decisions (n = 20)
Domestic pharmaceutical companies/related organizations	4 interviewees on May 28 1 interviewee on May 29	6 interviewees on May 14
Foreign pharmaceutical companies/related organizations	4 interviewees on June 20 1 interviewee on June 25 2 interviewees on June 27	5 interviewees on June 4 4 interviewees on June 11
Consumer/patient groups	Consumer groups: 3 interviewees on July 5	
	Patient groups: 1 interviewee on July 2, 1 interviewee on July 17	

The structuralized questionnaire asked interviewees to rate their agreement or disagreement with each given statement using a five-point scale, ranging from -2 (strongly disagree) to -1 (disagree), 0 (neutral), 1 (agree), and 2 (strongly disagree), to support intuitive understanding. The research assistant participating in each interview then recorded the interviewees' oral answers to the questions/statements on the semi-structuralized questionnaire, and made transcriptions of those recordings for analysis.

2. Governance on New Drug Approval

The interviewees were presented with a set of diverse criteria governing policy decisions on the approval of new drugs, and asked to rate each in terms of their appropriateness and priority. The five representatives of domestic pharmaceutical companies interviewed selected safety, efficacy in clinical trials, and benefit-to-harm ratios as the three most fitting objectives/criteria according to which approval decisions should be made. The seven representatives of foreign pharmaceutical companies interviewed similarly chose safety, benefit-to-harm ratios, and efficacy in clinical trials. On the other hand, these industry representatives, whether domestic or foreign, picked the price/cost of treatments, cost-effectiveness, fiscal impact, coverage in other countries, and covered prices in other countries as less-fitting criteria.

Some differences did emerge between the two groups of pharmaceutical representatives. The foreign representatives chose the severity of the given disease as a fitting criterion (1.57) because they thought it was justifiable for authorities to accelerate and decide approval in light of the severity of the diseases drugs are targeted to treat. The domestic representatives, by contrast, did not think of the severity of disease as so fitting (0.40). Furthermore, the foreign representatives thought of the patient population as a fitting criterion, a view not

shared by their domestic counterparts. foreign pharmaceutical companies have relatively greater experience with marketing anticancer drugs and ODs, a fact that appears to explain these differences.

〈Table 4-3〉 Criteria/Policy Objectives for Approval Decisions

Criteria		Domestic pharmaceutical companies (n = 5)	Foreign pharmaceutical companies (n = 7)
Drug characteristics	Safety	1.80	1.86
	Efficacy in clinical trials	1.80	1.71
	Effectiveness in clinical practice	0.25	0.86
	Benefit-to-harm ratio	1.80	1.86
	Consistent evidence	1.00	1.29
Disease characteristics	Severity of disease	0.40	1.57
	Health-related quality of life (QoL)	0.00	0.57
	Availability of alternative treatments	-0.40	0.29
	Burden of disease	-0.20	0.43
	Patient population	0.20	1.00
Treatment characteristics	Price/cost of treatment	-1.60	-1.00
	Cost-effectiveness	-1.40	-1.00
	Fiscal impact	-1.40	-1.14
International comparison	Approval in other countries	0.80	1.14
	Coverage in other countries	-1.40	-1.00
	Covered prices in other countries	-1.40	-1.14

The representatives were also asked to assess how the given criteria should be prioritized in approval decisions. Those of domestic pharmaceutical companies ranked efficacy in clinical trials, safety, and benefit-to-harm ratios as important, in that

order. foreign representatives, on the other hand, chose benefit-to-harm ratios, safety, and efficacy in clinical trials, in that order.

Most interviewees viewed the decision of whether to approval a new drug as within the exclusive purview of the MFDS, unlike the coverage decisions of the HIRA. The majority of interviewees also believed that new drugs should be approved on the basis of scientific evidence rather than social value. The four main issues of approval decisions emerging from these results are: (1) stakeholder participation, (2) consistency of the MFDS' decisions and explanations, (3) expertise of the MFDS and its committees, and (4) accountability for decisions made.

As for improving stakeholder participation, the representatives of both domestic and foreign pharmaceutical companies called for greater participation by clinical doctors. The domestic representatives also called for increased participation by pharmaceutical companies and related organizations, while the foreign representatives demanded participation by patient groups. These stakeholders also viewed the explanations given by the MFDS as lacking in consistency/predictability and as generating great uncertainty regarding how long it would take for applicants to receive decisions. The interviewees understood the expertise of the MFDS as a multifaceted concept encompassing quantity, quality, and maintenance and as affecting their communications with, and perceptions of, the ministry.

The interviewees largely viewed the MFDS' decision-making as rigid because the approval process involves much specialized expertise and emphasizes the authority and accountability of the authorities.

3. Governance on New Drug Coverage

The interviewees were also asked to rate, in terms of appropriateness and priority, the diverse criteria governing policy decisions on whether to include new drugs in NHI coverage. Representatives of domestic pharmaceutical companies (n = 6) picked the severity of diseases, availability of alternative treatments, cost-effectiveness, health-related QoL, and fiscal impact as the most appropriate criteria for guiding coverage decisions. Those of foreign pharmaceutical companies (n = 9), on the other hand, chose efficacy in clinical trials, severity of disease, health-related QoL, cost-effectiveness, and safety.

The severity of diseases, health-related QoL, cost-effectiveness, and availability of alternative treatments emerged as the overlapping choices between the two groups. However, whereas foreign representatives viewed efficacy in clinical trials as a more appropriate criterion, they did not think of effectiveness in clinical practice as so appropriate. Their domestic counterparts, on the other hand, viewed both criteria similarly. Moreover, domestic representatives counted fiscal impact as appropriate, while their foreign counterparts did not.

〈Table 4-4〉 Criteria/Policy Objectives for Coverage Decisions

Criteria		Domestic pharmaceutical companies (n=6)	Foreign pharmaceutical companies (n=9)
Drug characteristics	Safety	0.17	1.22
	Efficacy in clinical trials	1.00	2.00
	Effectiveness in clinical practice	1.17	0.78
	Benefit-to-harm ratio	0.67	0.67
	Consistent evidence	1.17	0.89
Disease characteristics	Severity of disease	1.50	1.89
	Health-related quality of life (QoL)	1.33	1.67
	Availability of alternative treatments	1.50	1.11
	Burden of disease	1.00	1.11
	Patient population	0.17	0.56
Treatment characteristics	Price/cost of treatment	1.17	0.56
	Cost-effectiveness	1.33	1.44
	Fiscal impact	1.33	0.67
International comparison	Approval in other countries	0.17	0.56
	Coverage in other countries	0.67	0.44
	Covered prices in other countries	0.50	0.67

Interviewees were also asked to prioritize the criteria. Representatives of domestic pharmaceutical companies prioritized effectiveness in clinical practice, efficacy in clinical trials, and the severity of diseases, in that order. Their foreign counterparts, on the other hand, prioritized the severity of diseases, efficacy in clinical trials, and health-related QoL. The severity of diseases and efficacy in clinical trials once again emerged as commonalities between the two groups, but the interviewees differed on the priority of effectiveness in clinical practice.

The four main issues emerging from these results had to do with the: (1) transparency and predictability of decision-making, (2) functions and roles of committees, (3) operation of committees, and (4) accountability for decision-making. Representatives of pharmaceutical companies, both in domestic and foreign, assessed that the decision-making on NHI coverage lacked transparency and accountability.

These interviewees likened the process of decision-making on coverage to a black box. They suggested greater disclosure of information and stakeholder participation as the keys to overcoming the lack of transparency and unpredictability. Decision-making on NHI coverage involves multiple committees and subcommittees, the respective roles of which must be clarified, with no redundancies, and the results produced by each should be published. Accountable decision-making requires specifying the issues up for discussion beforehand, as well as the commitment of committee members to accountability. These interviewees also expressed concerns that coverage decisions prioritized fiscal impact over the accessibility of new drugs. The significance of improving access to the given drugs should be discussed in depth in the review process for coverage. In assessing the prices and cost-effectiveness of new drugs, decision-makers should take into account a comprehensive range of factors, including the nature of pharmaceutical R&D and the characteristics of the given

drugs. They should also consider both the mid- and long-term fiscal impacts of including the given drugs in coverage and the more complex and long-term effects of providing benefits for those drugs.

V

Health Policy and Governance for Enhancing the Capability of the Health System to Manage Future Pharmaceutical Innovations

V Health Policy and Governance for Enhancing the Capability of the Health System to Manage Future Pharmaceutical Innovations

1. Challenges

In the global pharmaceutical market, new drug R&D never stops. Technological innovations have made it possible to design treatments for what have been regarded as severe and intractable diseases, and groundbreaking drugs with the capability to provide fundamental cures continue to enter the market. These inventions not only expand the scope of available treatments, but also demand fundamental changes in regulations, medical cost calculations, and health systems, at an increasingly accelerated pace.

As much of new drug R&D and distribution have become globalized, the majority of the new drugs marketed in Korea in recent years have been imported from overseas. New drugs first launched in other markets around the world inevitably arrive in Korea after a slight time lag, repeating the issues of innovation, cost, and access in the Korean market as well.

Now that the Korean market cannot avoid the impact of international pharmaceutical innovations, it is time for Korean policymakers to ask whether the current Korean health system —its coverage, payment, and service structures—would be ca-

pable of ensuring access to these innovative drugs for treating severe and rare diseases, while also maintaining fiscal sustainability, when the prices of new drugs continue to go up. An exceptional program for reimbursement, RSA has been in effect for anticancer drugs and ODs since 2014, but expanding its application in the future could undermine the overall payment structure and render the Korean health system unviable in the long run.

While most countries around the world adopt similar new drugs and face the same run of challenges, policy responses to these challenges have varied significantly from country to country, mainly due to differences in health systems, cultures, and infrastructure.

A government may rationally decide the price of a new drug based on the evidence of its effectiveness, but the multiplication of similar drugs covered by the public health insurance system and growing demand for such drugs can present significant threats to public finance. Furthermore, a necessary new drug may be approved and included in coverage, but failure to ensure its appropriate handling and administration in clinical practice can result in unnecessary financial burdens on patients while also denying them of the expected medical benefits. New drugs that lack sufficient evidence of their efficacy may be brought under coverage due to pressing medical needs, but failure to follow up with the use of these drugs

through reliable evaluations can also result in additional waste of resources. Decision-makers may succeed in identifying criteria for assessing the clinical effectiveness of new drugs under coverage and evaluating their value, but their inability to base their decisions on such assessment would weaken the health system.

To ensure appropriate spending on and use of new drugs, efficiency of fiscal spending, and satisfaction of stakeholders in the future, it is critical to change not only the drug policy but also the underlying health policy and governance. The health system and its service, payment, and operating structures must support the making and implementation of the new policy on new drugs with new scientific mechanisms, significant fiscal impacts, and potential for revolutionizing treatment.

2. Health Policy and Governance for a More Capable and Responsive Health System

Keeping the foregoing discussion in mind, we suggest, to ensure Koreans' continued access to new drugs and the mid- to long-term stability of the Korean health insurance system, the following health policy changes.

First, a macroscopic spending plan for pharmaceutical benefits should be established to ensure the sustainability of NHI drug coverage in the future. Such an overarching plan would

help decision-makers decide how much of fiscal resources are to be spent on a given drug in light of its estimated value, and thereby better manage spending. Second, horizon scanning—of prospective inventions and technologies—should be made an institutional practice. By predicting the clinical and fiscal effects of a new drug before its adoption, decision-makers can speed up the coverage decision-making process, while enabling the health system to reallocate its resources to ensure the appropriate use of the drug and allowing patients to access the innovative treatment without delay. Third, the system for post-marketing evidence development should be strengthened. Accelerated approval is on the rise, as is interest in performance-based contracts as part of coverage. Therefore, in order for the system to maintain the public's trust and acceptance, an institutional structure should be established to ensure the post-marketing development of evidence on the effectiveness of new drugs and appropriate policy adjustments accordingly. Fourth, the system of medical practitioners' self-regulation and payment should be reformed to ensure the appropriate use of new drugs. Medical practitioners should be free from financial and non-financial factors that encourage the inappropriate use of new drugs, and their independence should be reinforced and protected by the system. Fifth, it should be possible for decision-makers to cancel coverage for drugs for which taxpayers' money should no longer pay. Policy effectiveness should be

maintained by communicating the limits of health resources and applying a transition strategy for the phase-by-phase exit of obsolete drugs from the market.

The current structure of governance in Korea on the approval and NHI coverage of drugs is generally seen as capable of hearing the voices of diverse stakeholders and channeling them toward building a societal consensus. Social value trumps scientific evidence particularly in coverage decisions. Accordingly, the Korean government is hard at work at finding and building societal consensus through diverse institutional channels. Nevertheless, the current governance should be improved in the following regards.

First, accountability should be reinforced. Accountability is about deciding who can demand explanations, and who are responsible for justifying their decisions. The survey and interview results suggest that the Korean authorities need to do a better job at explaining themselves, such as by disclosing the minutes kept of decision-making meetings or allowing the public to observe those meetings if necessary.

Second, the demand for participation by diverse stakeholders should be heeded. The current governance structure allows stakeholders to participate in advisory capacity where necessary. However, what is really needed is the ongoing participation of pharmaceutical companies and related organizations as observers. These groups have been demanding per-

mission to participate as observers because the Korean authorities' explanations of their decisions often fall short of being satisfactory. Therefore, before increasing these stakeholders' participation, the HIRA should make active efforts to explain and disclose how decisions on coverage are made.

Third, public participation in decision-making should be increased. Participation by consumers and citizens in the health system is emerging as a solution to the increasingly complex structure of accountability today. Public participation is presumably more suited to issues of value judgment, such as controversial and ethical issues, than to technical questions. As future new drugs will require ever-greater technical expertise, decision-makers should begin discussing to what extent, and at what stage of decision-making, the public should participate.

These issues of accountability and participation are pertinent to the making and implementation of a new health policy as well. Detailed and persuasive explanations are needed, with respect to the overall scale of fiscal resources and their management, for payers, the medical community, and the industry before deciding on the NHI coverage of drugs. Accountable decision-making, however, requires expertise and freedom from conflicts of interest. A system is needed for developing evidence to support informed decision-making, and the organizations making decisions should be free from conflicts of interest.

The fiscal sustainability of health systems is a pressing issue faced by each and every nation today, and accountability is required of all stakeholders to ensure it. New drugs carry great uncertainty in terms of clinical effectiveness, fiscal impact, and cost-effectiveness. RSAs on these drugs attest to the importance of sharing fiscal risks. As risks are determined and shared in relation to the aggregate health expenditure, payers and the industry alike, as well as the medical community and the public, should participate and share risks. Participation by the medical community and the public, however, has been overlooked in Korea so far. It is thus high time for us to start serious discussions on how to ensure that all participants are held accountable for their behavior and decision-making, particularly by enforcing the self-regulation of medical practitioners, reforming the NHI payment system, and making coverage and its continuation dependent on technology evaluation.

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