New Drug Accessibility and Value-Based Pricing in Japan

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Abstract

A common concern about universal health insurance coverage is how to control health expenditure. The escalation of health care costs raises public awareness of the optimization of drug price. On the other hand, for the pharmaceutical industry, which invests a great amount of resources including development cost and time, predictively as well as attractiveness of the market is important. Against this background, with the purpose of improving Japanese health insurance system and drug price calculation method, the present research was conducted.

Firstly, we compared health insurance coverage proportion of newly approved drugs and promptness of reimbursement decision in Japan and major European countries, France, Germany and the United Kingdom (UK). Japan had higher health insurance coverage proportion compared to the major European countries. In Japan, all the drugs that were approved in 2015 had been already listed in the latest formulary of February 2016.

Second, we reviewed the transparency and predictability of Japanese National Health Insurance (NHI) drug price calculation method. The drugs with a new mechanism of action had more chance to gain premium for usefulness than the other drugs. The drugs with clinical trial results which demonstrated its superiority to an active control had more chance to gain premiums for usefulness than those showed inferiority to an active control drug and those demonstrated superiority to a placebo control. However, proportion of the amount of upward adjustment of operating profit to

pre-adjustment price was smaller than that of innovativeness or usefulness premium. Furthermore, proportion of the amount of upward adjustment based on foreign price was greater than that of innovativeness or usefulness premium.

Third, we investigated the factors that affect the discrepancy between the NHI reimbursement price and actual market price of new drugs. The price discrepancy of drugs with four or more competitors was greater than that of products with three or fewer competitors.

Japanese NHI scheme has ensured good access to new drugs for patients. Additionally, it was confirmed that new drug's clinical value was reflected to its price in Japanese NHI drug price calculation method, and the opportunity to re-evaluate the market value of the drugs was ensured by periodic NHI drug price revision system. However, our findings suggest that it is necessary to revise the balance between the impact of premium for new drugs with existing similar drugs, that for new drugs without existing similar products, and adjustment based on the foreign price.

While extensive coverage of health insurance and prompt reimbursement decisions lower the hurdles to access new drugs, they could lead to increased medical expenditure. We should continue to discuss sustainable health insurance systems and drug price calculation schemes that properly reflect the drug's clinical value while ensuring the availability of new drugs to patients.

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Abbreviations

ADEC	Australian Drug Evaluation Committee
ATC classification	Anatomical therapeutic chemical classification
BNF	British National Formulary
Chuikyo	Central Social Insurance Medical Council
DPO	Drug Pricing Organization
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GDP	Gross Domestic Product
ICER	Incremental cost-effectiveness ratio
MHLW	Ministry of Health, Labour and Welfare
NASs	New Active Substances
NHI	National Health Insurance
OECD	Organization for Economic Co-operation and Development
PBS	Pharmaceutical Benefits Scheme
PMDA	Pharmaceuticals and Medical Devices Agency
UHC	Universal Health Coverage
UK	the United Kingdom
US	the United States of America
WHO	World Health Organization

Chapter 1

Introduction

Every year, a number of new prescription medicines obtain marketing authorization in countries and regions worldwide. For example, 22, 28, and 48 new products containing new active substances (NASs) were approved in 2016 in the European Union (EU), the United States of America (US), and Japan, respectively [1]. However, it is only after the new drug is used appropriately in medical practice that it elicits its effect, and health care system including health insurance serves as a basis for this purpose. The World Health Organization (WHO) has emphasized the importance of universal health coverage (UHC), defined as ensuring that all people are able to use the promotive, preventive, curative, rehabilitative, and palliative health service they need, of sufficient quality to be effective, without exposing them to financial hardship [2]. Currently, it has been ensured that almost all citizens use health services they need based on the public health insurance system in a lot of developed countries including Japan.

It is a common concern about universal health insurance coverage to control health expenditure [3]. Because the increasing cost of new medical technology including new drugs is one of the significant contributors to greater health care spending, rational use of newly approved drugs has been enhanced to maintain comprehensive equal health

services under the limited financial resources [4]. In some countries, the evidence of cost-effectiveness is required to make a decision on reimbursement and to set the health insurance price of a new drug. Currently, Japanese National Health Insurance (NHI) listing scheme does not require the evidence of cost-effectiveness to list and set the price of a new drug. However, the Japanese Ministry of Health, Labour and Welfare (MHLW) has adopted a policy, on a trial basis, of introducing a cost-effectiveness perspective in re-pricing the listed drug products with high projected peak sales since April 2016 [5].

Furthermore, development of new drugs has become increasingly challenging. For the pharmaceutical industry, which invests a great amount of resources including development cost and time, predictively as well as attractiveness of the market is important [6]. From this aspect, the medical insurance system affects the strategy of new drug development in a country, and transparency and predictability of reimbursement decision and pricing is required.

Against this background, with the purpose of improving Japanese health insurance system and drug price calculation method, we conducted the present research focusing on the following 3 points.

1) To identify difference of health insurance coverage proportion of newly approved drugs, promptness of reimbursement decision and reimbursement price between

Japan and major European countries, in which the means for maintaining comprehensive equal health services under the limited financial resources are different (Chapter 2)

2) To review the transparency and predictability of Japanese NHI drug price setting (Chapter 3)

3) To investigate factors affecting the degree of price gap between the NHI reimbursement price and the actual market price of new drugs (Chapter 4)

Based on the results, we discussed the issues for better health insurance system and NHI drug price calculation method from the viewpoint of better patient access to new drugs as well as health expenditure control.

Chapter 2

New drug accessibility and price in Japan and the major European countries

2.1. Introduction

In Japan, it has been ensured that all Japanese citizens use health services they need based on the NHI Act for more than 50 years. Actually, patient direct burden was 11.9% of the total health care costs in 2012 [7]. On the other hand, sustainability of the social security program including health insurance is an issue of great concern. In Japan, nearly 40% of the population will be over 65 years of age by 2050, and it is expected that the increase of medical expenditure will be much larger than the growth of Gross Domestic Product (GDP) in the near future [8]. The most daunting challenge for Japanese NHI scheme is the national fiscal situation and the way health care is financed [9].

It is a common concern about universal health insurance coverage to control health expenditure [10]. Because the increasing cost of new medical technology including new drugs is one of the significant contributors to greater health care spending, cost-effectiveness assessment procedure has been introduced into health insurance listing scheme in some countries. Currently, Japanese NHI listing scheme does not require the evidence of cost-effectiveness to list and set price of a new drug. However, the Japanese MHLW has adopted a policy, on a trial basis, of introducing a cost-effectiveness

perspective in re-pricing the listed drug products with high projected peak sales since April 2016 [11].

While the new scheme in Japan is supposed to favor the health insurance finances, there are concerns about its negative impact on patient access to new treatments. In some developed countries that introduced the cost-effectiveness assessment scheme, “market access delay” defined as the time between marketing authorization and completion of reimbursement procedure for a new medicine has been recognized as a common problem [12-14].

In Chapter 2, we focused on health insurance coverage proportion of newly approved drugs and promptness of reimbursement decision in Japan and major European countries to explore the differences in patient access to new drugs, in which the situation of introduction of cost-effectiveness assessment for new drugs is different. Then, we surveyed drug price in Japan and the European countries to explore the differences between them. Based on the results, we discussed the issue of drug price setting and health insurance system from the viewpoint of better patient access to new drugs as well as health expenditure control.

2.2 Method

2.2.1 Health insurance coverage proportion and promptness of reimbursement decision in Japan and major European countries

All the NASs which were approved between January 2009 and December 2015 in Japan were picked out from the lists of approved new drugs disclosed by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) [15]. All the NASs which were approved through the centralized procedure in the EU during the same period were picked out from the lists of drugs which have a European Public Assessment Report (EPAR) disclosed by the European Medicines Agency (EMA) [16]. We reconfirmed the products by referring reports by the Centre for Innovation in Regulatory Science [17-20].

We selected France, Germany and the United Kingdom (UK) as major European countries for our study and checked the presence or absence of the approved products in the printed formularies of Japan as well as of the 3 European countries. The following printed books were referred: Hokenyakujiten plus August 2015 for Japan, ViDAL 2016 for France, ROTE LISTE 2016 for Germany, and British National Formulary (BNF) September 2015 and MIMS September 2015 for the UK. Then, the proportion of the number of listed drugs to that of approved drugs in each country was calculated based on the drugs which were approved before the data cutoff date of the latest printed formularies

of February 2016. Furthermore, cumulative health insurance coverage proportion in each country was calculated by going back the approval year from 2015 to 2009 and adding the number of drugs on annual basis. Additionally, information of health spending as share of GDP (2013) in each of the countries was collected based on a public document disclosed by Organization for Economic Co-operation and Development (OECD) [21].

2.2.2. Coverage situations in major European countries of the drugs listed in Japanese NHI price list

All the NASs which were listed in the Japanese NHI price list between October 2004 and December 2015 were picked out and classified by therapeutic group based on the first level of WHO's Anatomical Therapeutic Chemical (ATC) Classification. For each of these drugs, we identified its approval date in France, Germany and the UK based on the Interview Form, which is a supporting document to a package insert of each product in Japan made by a marketing authorization holder. For products of which approval status in the European countries were not clear in the document, we made inquiries to the marketing authorization holder in Japan. Then, for products that were approved in the European countries ahead of Japan, we checked its presence or absence in each of the European countries' latest printed formulary at its Japanese reimbursement date.

2.2.3. Drug price comparison between Japan and the European countries

From NASs that were listed in the Japanese NHI price list between October 2004 and December 2015, drugs that were also reimbursed in France, Germany and the UK with the same dosage form and strength were picked out for comparison of the price among the countries. For each selected drug, information of drug price in France, Germany and the UK at its Japanese reimbursement date was collected. Then, price data for the 3 European countries was converted into Japanese YEN as of the average yearly exchange rate of each drug's reimbursement date in Japan, as of the average yearly exchange rate of each drug's reimbursement date in Japan, as indicated by the Central Social Insurance Medical Council (Chuikyo), which is an advisory panel to Japanese MHLW on health insurance system and medical fees. Finally, we compared the price of each drug between Japan and the European countries.

2.2.4 Details of Japanese patient access to new drugs

All the NASs which were approved between October 2004 and December 2017 in Japan were picked out from the lists of approved new drugs disclosed by the Japanese PMDA [15]. For each of the NASs that were approved between October 2004 and September 2017, we checked its presence in the NHI drug price list as of December 2017, to calculate

the percentage of newly approved drugs covered by NHI and identify the drugs which has not been covered by NHI. We also calculated the time period between the date of marketing approval in Japan and the date of Japanese NHI drug price listing for each NAS listed over the same period.

2.3 Result

2.3.1 Health insurance coverage proportion and promptness of reimbursement decision in Japan and major European countries

Between January 2009 and December 2015, 229 NASs were approved in Japan (Table1). Two hundred and seven drugs were approved before the data cutoff date of the Japanese latest printed formulary of February 2016. Of these 207 drugs, 204 drugs (98.6%) were listed in the Japanese formulary. In the EU, 186 NASs were approved through the centralized procedure in the study period. The health insurance coverage proportion in the European countries was as follows: 52.2% in France, 74.7% in Germany, and 77.1% in the UK. Japan had the highest health insurance coverage proportion in the 4 countries. In France, only half of the approved drugs were listed in the printed formulary. In 2013, health spending as a share of GDP in the 4 countries was as follows: 10.2% in Japan, 10.9% in France, 11.0% in Germany, and 8.5% in the UK.

Table 1 Health insurance coverage proportion of approved drugs in Japan and major European countries

Region	Japan	EU central		
Number of approved drugs between January 2009 and December 2015	229	186		
Country	Japan	France	Germany	UK
Health spending as a share of the GDP (2013), %	10.2%	10.9%	11.0%	8.5%
Printed Formulary	Hokenyaku jiten Plus August 2015	VIDAL 2016	ROTE LISTE 2016	BNF September 2015 MIMS September 2015
Data cutoff date	15-Jun	15-Nov	15-Dec	15-Jul
Number of approved drugs	207	184	186	166
Approval date	Jan 2009 - Jun 2015	Jan 2009 - Nov 2015	Jan 2009 - Dec 2015	Jan 2009 - Jul 2015
Number of listed drugs	204	96	139	128
Health insurance coverage proportion, %	98.6%	52.2%	74.7%	77.1%

Figure 1 shows the transition of cumulative health insurance coverage proportion in the surveyed countries. In Japan, all the drugs that were approved in 2015 had been already listed in the latest printed formulary of February 2016. Although the cumulative health insurance coverage proportion in Germany was also broadly flat, only 26 drugs of 41 approved in 2015 had been listed in the latest printed formulary of February 2016. The cumulative health insurance coverage proportion in France and the UK was on the upward trend in the drugs which were approved up to 5 years before February 2016.

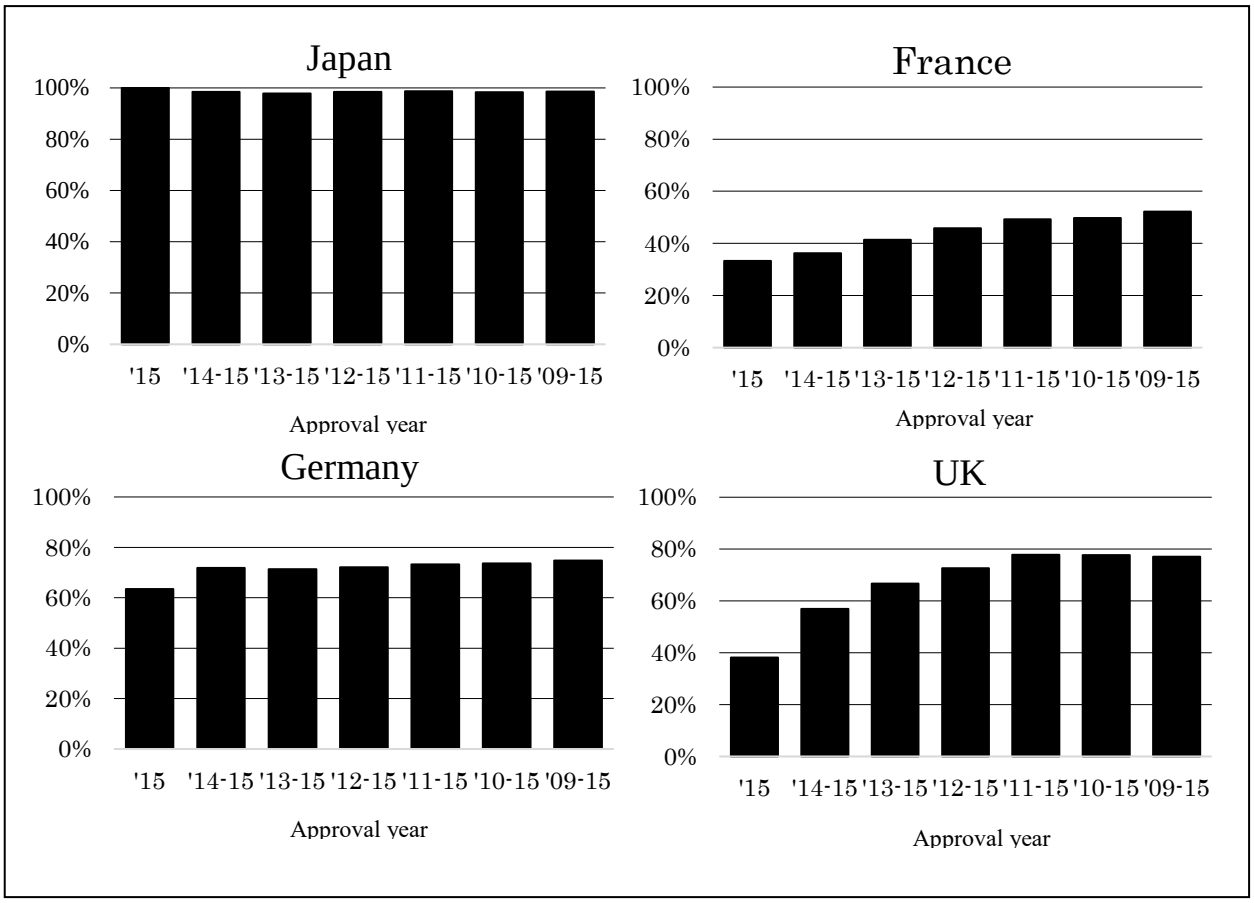

Figure 1 Cumulative health insurance coverage proportion in Japan and major European countries

2.3.2. Coverage situations in major European countries of drugs listed in Japanese NHI price list

Between October 2004 and December 2015, 350 NASs were listed in the Japanese NHI price list. Of these 350 drugs, 348 were selected for analysis; 2 were excluded because they had been marketed as medical devices in Europe. Of the selected 348 drugs, 286(82.2%) were also approved in the 3 European countries. Most of them were approved in Europe prior to Japan (Table 2). The number of listed drugs in France was smaller than

that in Germany and the UK.

Table 2 Coverage situations in major European countries of drugs listed in Japanese NHI price list

Country	France	Germany	UK
The situation of marketing approval in Europe as of January 2016			
The number of drugs which were approved in Europe prior to Japanese approval	246 drugs	253 drugs	246 drugs
The number of drugs which were approved in Europe posterior to Japanese approval	31 drugs	32 drugs	30 drugs
The number of unapproved drugs	71 drugs (20.3%)	63 drugs (18.0%)	72 drugs (20.6%)
The situation of reimbursement as of reimbursement date in Japan			
The number of listed drugs	106 drugs	185 drugs	206 drugs
Health insurance coverage proportion	43.10% (106/246)	73.10% (185/253)	83.70% (206/246)

Figure 2 shows the situations of approval and reimbursement in the 3 European countries of drugs that were listed in Japanese NHI price list by therapeutic area. Proportion of the number of listed drugs to that of approved drugs was different by therapeutic area, and it was small in therapeutic area J (anti-infectives for systemic use) and L (antineoplastic and immunomodulating agents).

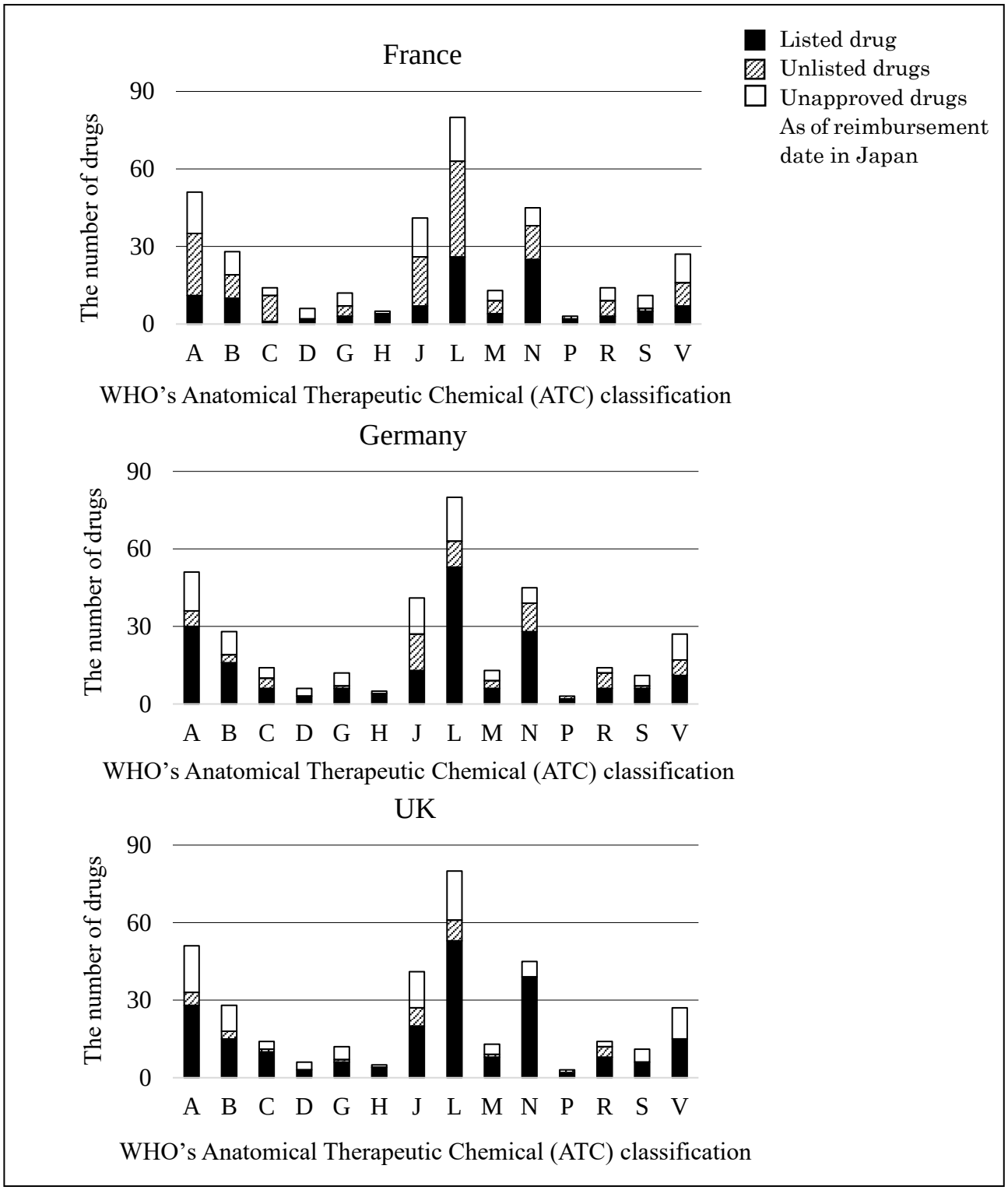

Figure 2 Coverage situations in major European countries of drugs listed in Japanese NHI price list by therapeutic area (ATC classification)

2.3.3. Drug price comparison between Japan and the European countries

Of the selected 348 NASs, 90 drugs were also listed in France, Germany and the UK with the same dosage form and strength. Major therapeutic areas covered by these drugs were L (24.4%), nervous system (N: 23.3%), alimentary tract and metabolism (A:12.2%), and blood and blood forming organs (B: 11.1%) (Table 3).

Table 3 ATC classification of the drugs for price comparison

Therapeutic area (WHO's Anatomical Therapeutic Chemical (ATC) classification)	Number of drugs (%)	
A: Alimentary tract and metabolism	11	(12.2%)
B: Blood and blood forming organs	10	(11.1%)
C: Cardiovascular system	1	(1.1%)
D: Dermatological drugs	2	(2.2%)
G: Genitourinary system and reproductive hormones	2	(2.2%)
H: Systemic hormonal preparations	3	(3.3%)
J: Anti-infective for systemic use	6	(6.7%)
L: Antineoplastic and immunomodulating agents	22	(24.4%)
M: Musculoskeletal system	2	(2.2%)
N: Nervous system	21	(23.3%)
P: Antiparasitic products, insecticides and repellents	1	(1.1%)
R: Respiratory system	3	(3.3%)
S: Sensory organs	4	(4.4%)
V: Various ATC structures	2	(2.2%)
Total	90	

Figure 3 provides the ratio of the European price to Japanese price of the surveyed drugs. Prices in Germany ranked highest, and those in the UK were the lowest. However, the gap was small, and there wasn't much difference between the price in Japan and the European countries in many cases. For 16 products, the price in the European countries was less than half of the Japanese price: 13 drugs in France, 1 drug in Germany, and 8 drugs in the UK. For 10 products among these 16, European approval was ahead of Japan for over 10 years. Additionally, for 15 products, the price in the European countries was double or more than double of the Japanese price: 4 drugs in France, 14 drugs in Germany, and 3 drugs in the UK. These drugs belong to the therapeutic area B (4 drugs), J (2 drugs), L (4 drugs), M (1drug), and N (4 drugs). The price in Germany was more than double of the Japanese price in 4 drugs of 10, which were classified in the therapeutic area B.

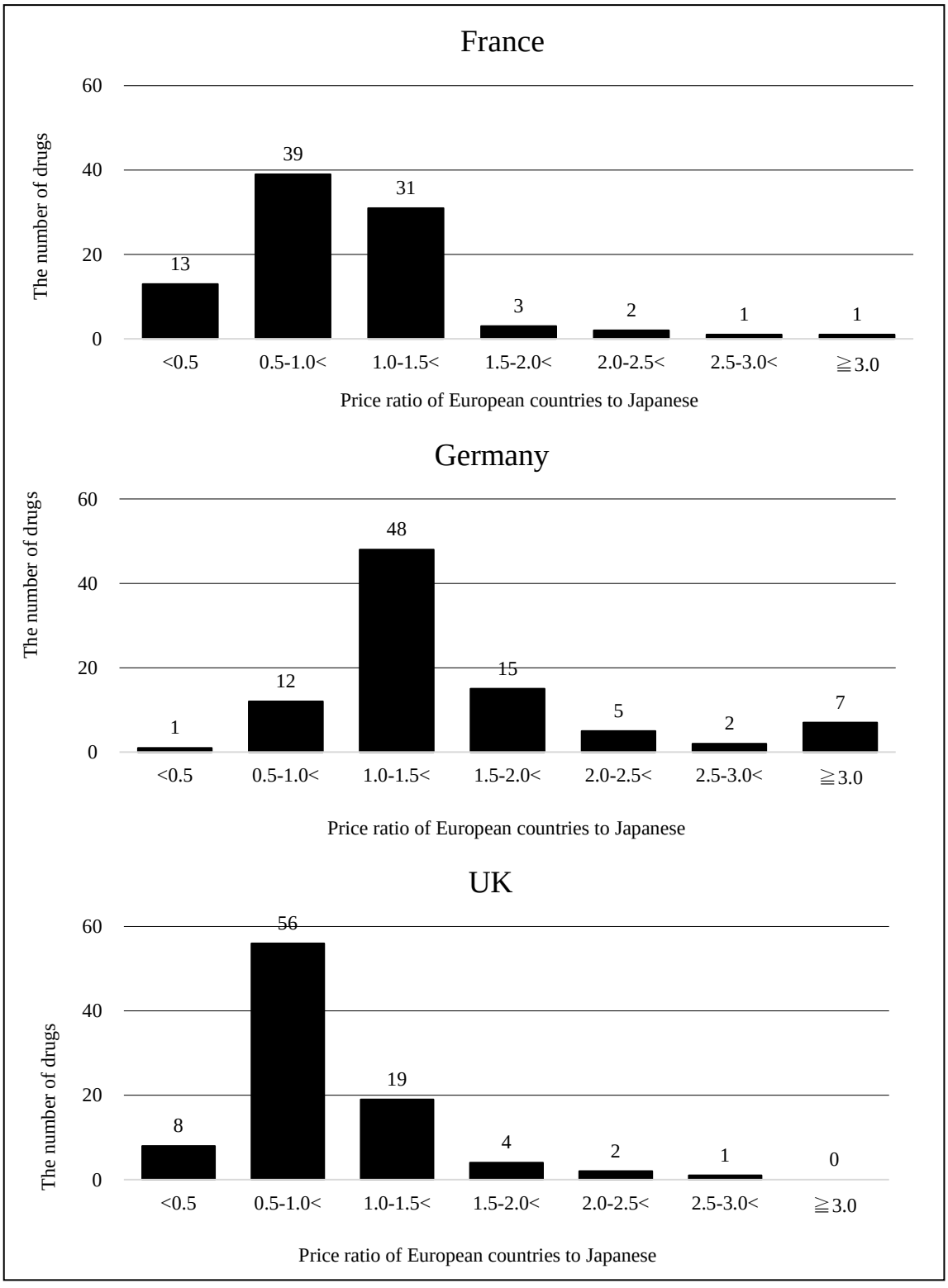

Figure 3 Comparison of drug price between Japan and major European countries

When the products for price analysis were restricted to 16 drugs in the therapeutic area L which were approved in Japan within 5 years of the approval in Europe, the ratio of European to Japanese prices ranged between 0.61 and 2.07, and the median of each European country was as follows: 1.08 in France, 1.40 in Germany, and 1.09 in the UK (Figure 4). The difference between the drug price of Japan and the European countries in the selected drugs was smaller than that in the overall surveyed drugs.

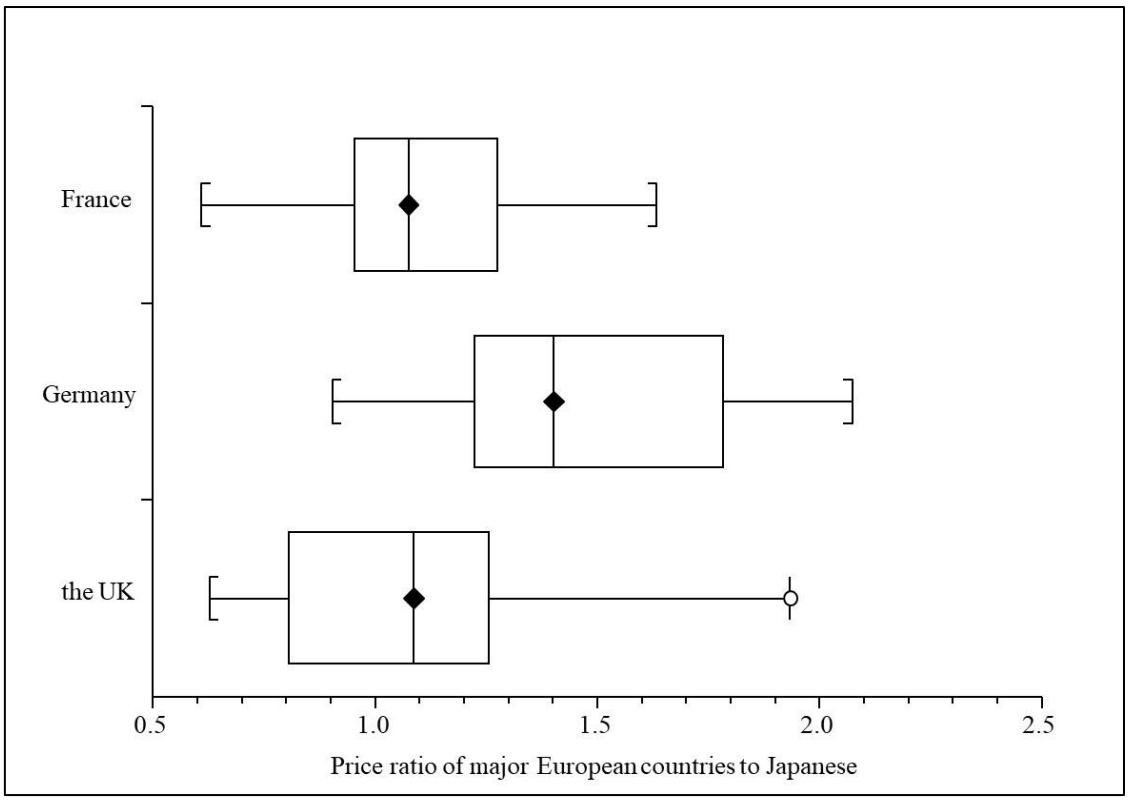

Figure 4 Price ratio of European to Japanese for drug in ATC classification L and approved in Japan within 5 years of their approval in Europe

2.3.4 Details of Japanese patient access to new drugs

Between October 2004 and September 2017, a total of 458 NASs were approved in Japan. Of these 458 drugs, 455 were selected for this calculation; 2 were excluded because they were reimbursed as a medical device or a diagnostic agent, and 1 product was recognized as a product which can be used under NHI without setting of the NHI reimbursement price.

Of the selected 455 approved NASs, 415 were listed in the NHI price list, whereas 40 were not. NHI price listing rate was therefore calculated to be 91.2%. Among the unlisted 40 drugs, 26 were preventive vaccines. Although preventive vaccines are usually not covered by NHI, other governmental supports are provided for those who are vaccinated based on the Preventive Vaccination Act. In view of fact, when we excluded these 26 vaccines from the calculation, we find that 96.7% of NASs that obtained marketing approval are covered by the NHI (Figure 5).

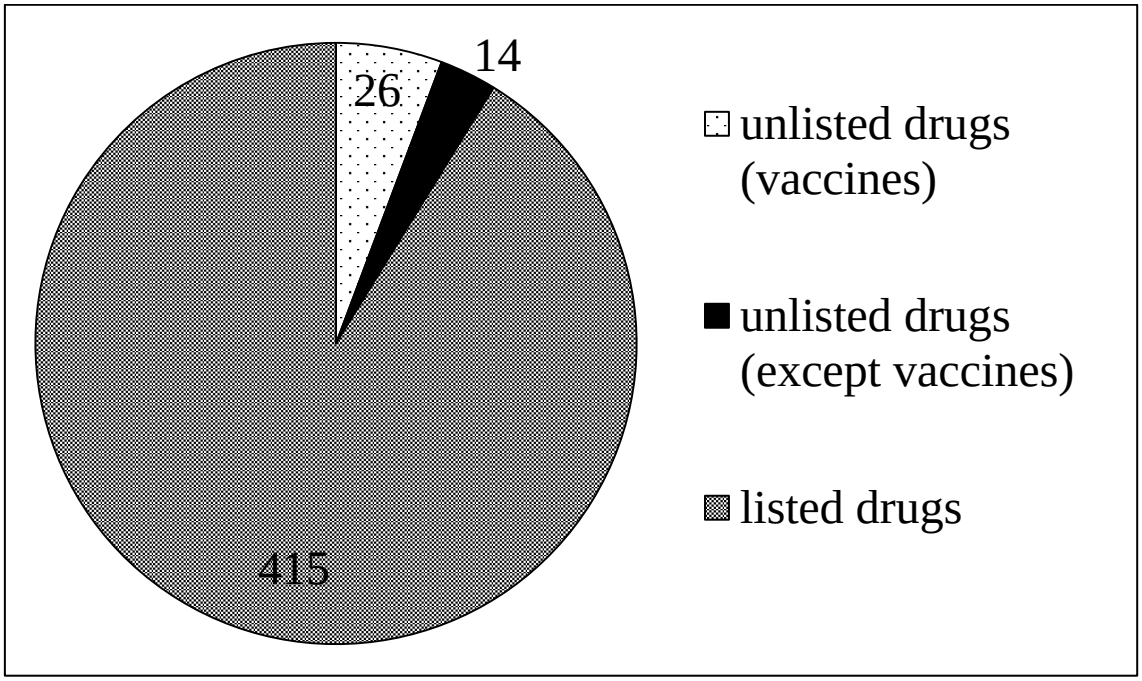

Figure 5 NHI price listing rate in Japan

Among the 14 unlisted drugs, 3 were not listed because they were supposed to be used only in emergencies like disaster or accident with special compensation, 5 were not listed because they were regarded as drugs used for promoting better life rather than for injuries or diseases. They represented hair loss, erectile dysfunction, obesity, and fertility treatment. Of the other 6, 2 were diagnostic products for diagnosis which were not covered by NHI, and 4 were during preparation or negotiation for reimbursement (table 4).

Table 4 Unlisted drugs in Japan

active ingredient	indication
Finasteride	male pattern for hair loss
Cetrorelix Acetate	the inhibition of oremature LH surges
Tadalafil	erectile dysfunction (ED)
Ganirelix Acetate	the inhibition of oremature LH surges
Potassium ferrocyanide trihyrate	cesium elimination
Pentetate Calcium Trisodium	uran elimination
Cetilistat	obesity
Favipiravir	novel or re-emerging pandemic influenza virus infection
Oxcarbazepine	epilepsy
florbetapir (18F)	PET scanning radiopharmaceutical compound for Alzheimer's disease
Crisantaspase	acute lymphoblastic leukaemia (ALL)
Pemafibrate	Hyperlipidemia
Romidepsin	peripheral T-cell lymphoma and cutaneous T-cell lymphoma
flutemetamol (18F)	PET scanning radiopharmaceutical compound for Alzheimer's disease

Of the listed 421 NASs, 347 (82.4%) appeared in the NHI price list within 60 days after marketing approval. The average time between the marketing authorization and the initiation of reimbursement was 66 days, and the median was 58 days. Furthermore, 93.1% of the approved NASs were listed within 90 days. Some drugs such as anti-HIV drugs, anti-influenza drugs, drugs for mucopolysaccharidosis, drugs for multiple myeloma, and drugs for malignant pleural mesothelioma were regarded as priority drugs and listed within 30 days after marketing approval (Figure 6).

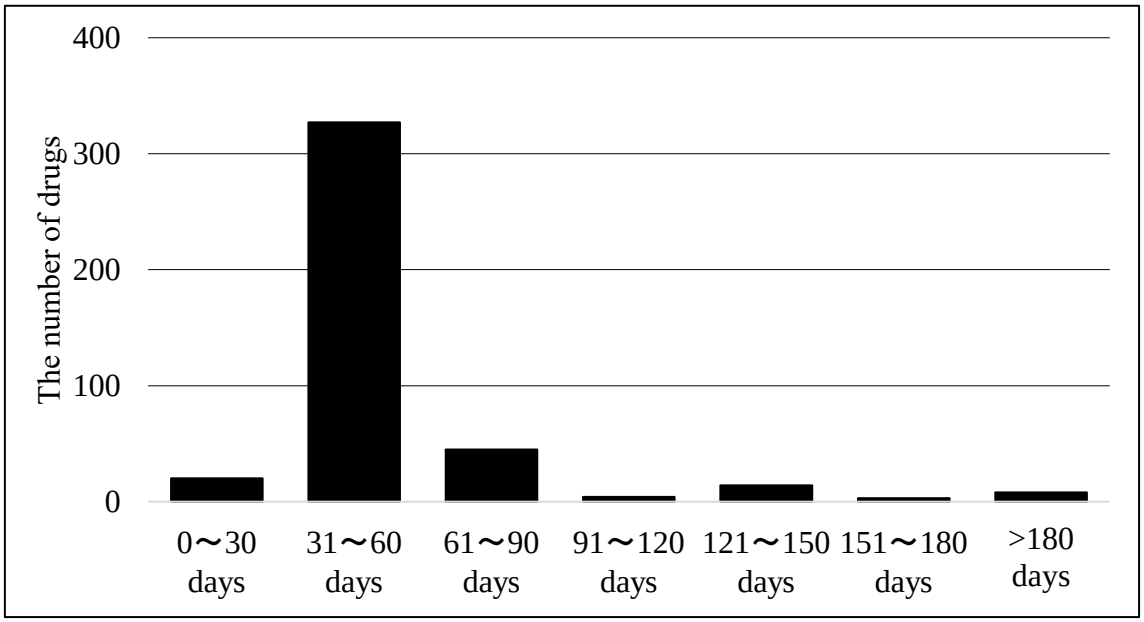

Figure 6 Speed of reimbursement decision in Japan

2.4 Discussion

In our analysis, it was shown that almost all the approved drugs were listed in the formulary in Japan, and Japan had the highest health insurance coverage proportion in the 4 countries. Furthermore, although almost all the approved drugs in 2015 were already listed in the latest formulary of February 2016 in Japan, the cumulative health insurance coverage proportion in France and the UK was on the upward trend. Additionally, while almost all the approved drugs in any therapeutic area were listed in the formulary in Japan, proportion of the number of listed drugs to that of approved drugs in the European countries was different depending on the therapeutic area; it was small in therapeutic areas in which expensive anticancer drugs and antiviral drugs were classified. Health spending as a share of GDP in the 4 countries was ranged from 8.5 to 11.0 %. The share in Germany ranked highest, and that in the UK was the lowest, and Japanese health expenditure was not extraordinary expensive. From the viewpoint of health insurance coverage proportion and the speed of reimbursement decision, it is suggested that the hurdle to access new drugs in Japan is lower than that in the European countries.

In Japan, MHLW declares that NHI price listing process is usually completed within 60 days after the marketing authorization, or within 90 days at the longest. Actually, it was confirmed that the Japanese average time between the marketing authorization and the

initiation of reimbursement was 66 days. In Europe, the EU transparency Directive (89/105/EEC) obliges the member states to reach pricing and reimbursement decision within 120 days after the marketing authorization or within 180 days at the longest in 2012 [22]. Nevertheless, it was only Germany and the UK that the average time from regulatory approval to first sales of the products which were launched in 2014 was within 4 months; these countries have initial free pricing policies while preparing for price and access negotiations. Additionally, the range of average time from marketing authorization to full reimbursement access among the EU 5 countries was between 14.9 and 18.1 months [23]. In view of the circumstances, the speed of reimbursement decision after a new drug's marketing approval has been emphasized as an important factor to improve patient access to new drugs in Europe [12].

Market access delay is also concerned in other developed countries as well as in European countries. In Canada, the average time taken for the public reimbursement decision of new drugs approved in 2010 was 359 days. On average, only 23% of the new drugs approved between 2004 and 2010 were declared eligible for reimbursement under provincial public drug programs as of January 1, 2012 [14]. In Australia, the time between Australian Drug Evaluation Committee (ADEC) recommendation and Pharmaceutical Benefits Scheme (PBS) listing has increased from 13.6 months in 2000 to 34.2 months in

2009 [24].

Comparison of health insurance coverage proportion and the speed of reimbursement decision among countries is sometimes misleading because of the difference in reimbursement procedure and drug price setting methods among them. Budget for health spending and the priority are also different in countries. Furthermore, it is one of the unavoidable limitations of our analysis that the reimbursement situation of each surveyed drug was confirmed by published formularies. It was because there wasn't any alternative public data source. Newly approved drugs might have been reimbursed in lead time to prepare and print formularies. Moreover, in European countries, drugs for hospital use are usually a cost to the hospital medical service fee, and they are not listed in the community reimbursement lists. Therefore, actual health insurance coverage proportion and speed of reimbursement decision in each country might be better. However, these results in our study were similar to the finding in other report [25]. Coverage of health insurance and promptness of reimbursement decision are important factors that can affect patient access to new drugs, and we believe it is worthwhile to grasp a big picture of the situation of new drug reimbursement.

In the past, Japanese government took several corrective measures to resolve delay in marketing approval of new drugs, known as the "drug lag", for better patient access to

innovative treatments. Although Japan historically had the longest regulatory approval time among the 3 regions (the US, the EU, and Japan), PMDA is the agency with the shortest median approval time in 2016. However, for 71% (34/48) of NAS which were approved by PMDA in 2016, the applications for Japanese marketing authorization were submitted after the approval in the US or the EU [1]. In most cases, new drugs are still approved in other countries prior to Japanese marketing authorization. To improve such a situation, Sakigake strategy was initiated as a pilot program in 2015 by the Japanese government to lead the world in the practical application of innovative products [26]. In addition to such a regulatory scheme, the maintenance and enhancement of the attractiveness of Japanese market is also important. Medical health insurance system in each country has the potential to impact the attractiveness of its market. The maintenance of the Japanese NHI program which has extensive coverage of new drugs and prompt reimbursement decision might attract global pharmaceutical companies to Japanese market.

As for the difference of drug price between Japan and the European countries, there wasn’t much difference between Japan and the European countries in many cases. The trend was same even if therapeutic area of drugs for analysis were restricted to antineoplastic and immunomodulating agents (L in ATC classification) in which many

expensive drugs were included. Additionally, prices in Germany ranked highest, and those in the UK were the lowest. These results were similar to the findings which were reported in other price studies [27-30]. Furthermore, we found that the price in the European countries tended to be less than half of the Japanese price for the drugs which were approved in Japan after more than 10 years in the Europe. It was also confirmed that price in Germany tended to be more than twice as expensive as in Japan for drugs which were classified in the therapeutic area B (blood and blood forming organs). From these aspects, it was suggested that the difference in drug price among countries should be analyzed in consideration of the presence or absence of its generic drugs and its therapeutic area.

In our analysis, price data of each drug was collected based on the published formularies in the surveyed countries. However, in practice, pharmaceutical companies grant different kinds of discounts and rebates on drugs to public pay [31]. In Japan, the price of a new drug is revised biennially based on its market price, and drug price in published formularies has been maintained to approximate actual market price. However, such a re-pricing scheme is unique to Japan, and there is a gap between listed price and actual market price in Europe; drugs are actually traded in Europe at lower price than the price listed in the formulary. Accordingly, price comparison analysis among countries should

be conducted based on the discounted price. However, access to the information about discounts and rebates on drugs in European countries is difficult for researchers who belong to outside academic institutions. The lack of transparency in the discounting system leads to the inability to assess the impact of financial agreements on price and budget, and it can affect the accuracy of the priority of a drug in clinical guidelines which are set based on the incremental cost-effectiveness ratio (ICER) [32]. This issue of price confidentiality as well as differentiated pricing policies that reflect variations in the ability to pay at national level is being discussed especially in Europe [32, 33].

A common concern about universal health insurance coverage is how to control health expenditure while maintaining the service quality [10]. Because the increasing cost of new medical technology including new drugs is one of the significant contributors to greater health care spending, rational use of newly approved drugs has been enhanced to maintain comprehensive equal health services under the limited financial resources [34]. In some countries, the evidence of cost-effectiveness is required to make a decision on reimbursement and set the health insurance price of a new drug. Currently, Japanese NHI listing scheme does not require the evidence of cost-effectiveness to list and set price of a new drug. However, the Japanese MHLW has adopted a policy on a trial basis of introducing a cost-effectiveness perspective in re-pricing the listed drug products with

high projected peak sales since April 2016 [11].

The escalation of health care cost raises public awareness of the optimization of drug price and increase demand for cost-effectiveness assessment. However, it is also a fact that the introduction of cost-effectiveness assessment scheme has a potential for delaying patient access to innovative drugs. From these aspects, it is required to improve the implementation of cost-effectiveness assessment. Additionally, in our analysis, there wasn't much difference in drug price between Japan and the European countries, in which the situation of introduction of cost-effectiveness assessment for new drugs is different. Narrowing the range of drugs subjected to the cost-effectiveness assessment might be one of the useful remedies. Moreover, it is suggested that ensuring competition in the pharmaceutical market and improving the transparency in discounting for drug prices are important to evaluate the real value of a new drug in clinical practice and to set its price appropriately. Extensive coverage of health insurance and prompt reimbursement decision lower the hurdles to access new drugs and expand treatment options. On the other hand, they could be contributors to swelling medical expenditure. In order to provide many treatment options to patients under the limited financial resources, the importance of considering drug pricing that properly reflects the drug's clinical value increases. Furthermore, readjustment and rationalization of the contents of prescription is

also required. We should continue to discuss sustainable health insurance systems and drug price calculation schemes that properly reflect the drug's clinical value while keeping the availability of new drugs to patients.

Chapter 3

Predictability of Clinical Value Assessment in Japanese NHI reimbursement price calculation

3.1 Introduction

3.1.1 Listing procedure

In Japan, NHI has ensured, for more than 50 years, that all Japanese citizens can access health services they need based on the NHI Act. Under the scheme, the reimbursement price of a drug is set by the government as an official price, applied universally in Japan. Obtaining regulatory approval for marketing is the first and essential step for a drug to be listed in NHI. In order that an approved new drug is used under health insurance, the NHI price listing procedure is needed.

First, a manufacturer submits an application for NHI price listing to MHLW. It is accompanied by documents which describe the basis and rationale for the price calculation, regulatory review report by PMDA, package insert, copies of foreign public price list, and so on. The evidence of cost-effectiveness is not required for the application.

MHLW prepares a draft calculation result according to the official rule for drug price calculation [35] and submits it to the Drug Pricing Organization (DPO), which is a subordinate organization of Chuikyo, an advisory panel to MHLW on health insurance system and medical fees. DPO then gives its draft calculation result to the manufacturer after the assessment. If the manufacturer disagrees with the suggested price, it can file an appeal against the price and DPO recalculates the price taking the manufacturer's comments into consideration. Finally, the resulting price is reported to Chuikyo, and the name and its price approved by Chuikyo is listed in NHI price list. (Figure 7) MHLW declares that this process is usually completed within 60 days after the marketing authorization, or within 90 days at the longest.

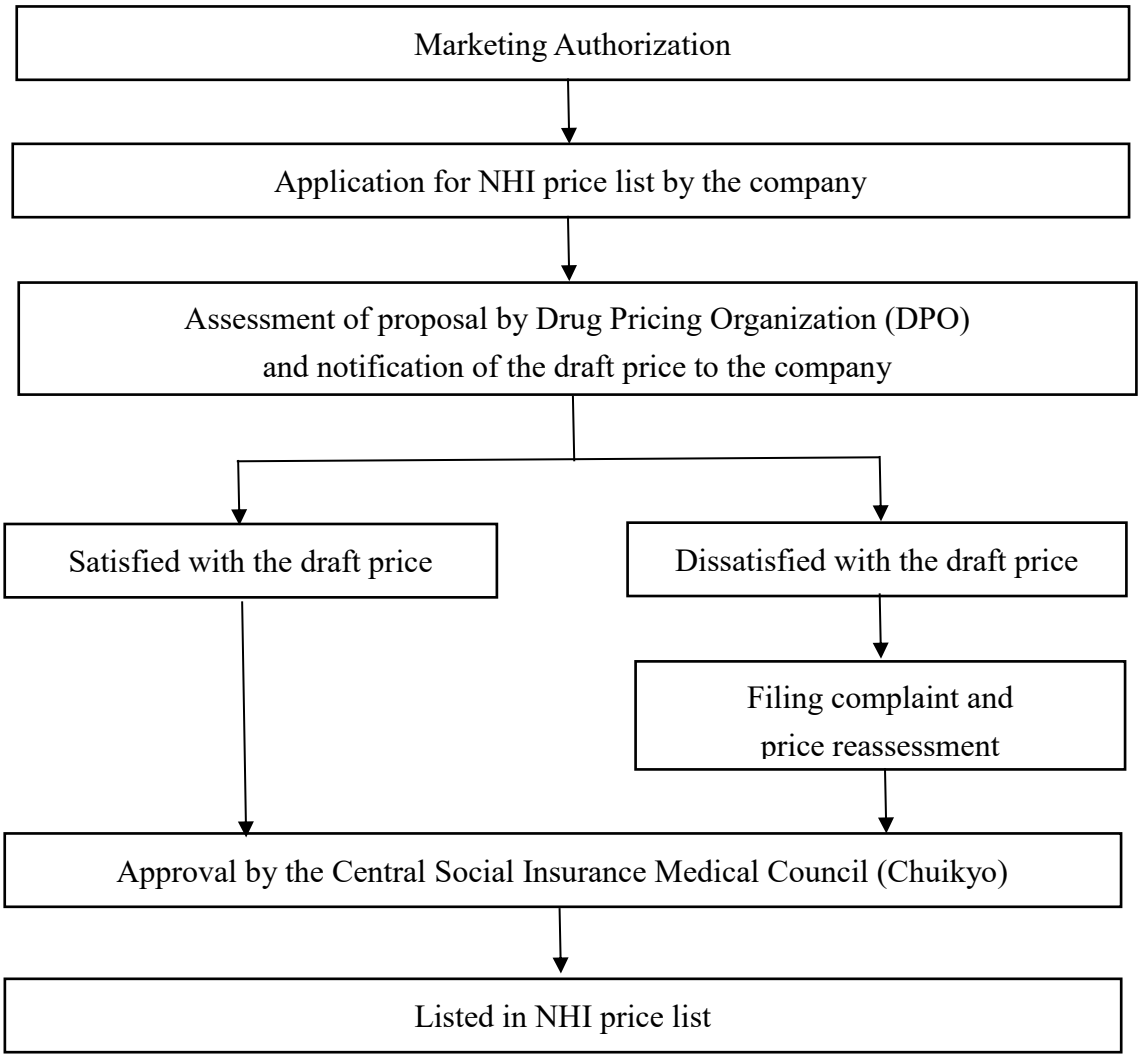

Figure 7 Listing procedure in Japan

3.1.2 NHI price calculation method

In principle, the price of a new drug is calculated by reference to the price of a similar drug on the market (a comparable drug). This calculation method is called “similar efficacy comparison method”. A comparable drug is selected from the existing, reimbursed drugs from the viewpoint of similarity in indication, mechanism of action, molecular formula, route of administration and dosage form. Secondly, the daily price of the new drug is set as the same daily cost of the comparable drug to ensure competition in the market. Additionally, when the new drug meets certain criteria, one or more premiums are added to the calculated price. This premium is considered from the following 4 points of view: innovativeness or usefulness, support for small market size, support for pediatric indication, and early development in Japan ahead of other countries (Table 5).

Table 5 Types of premiums and requirement in similar efficacy comparison method

Premiums	Premium rate	Requirements for premium
Innovativeness	70～120%	All of the following should apply to the new drug: (i) A novel, clinically useful mechanism of action (ii) Evidence of higher efficacy or safety compared to the existing similar drugs (iii) Evidence of improvement in the treatment method of the target disease
Usefulness I	35～60%	Two of the following should apply to the new drug: (i) A novel, clinically useful mechanism of action (ii) Evidence of higher efficacy or safety compared to the existing similar drugs (iii) Evidence of improvement in the treatment method of the target disease
Usefulness II	5～30%	One of the following should apply to the new drug: (i) A novel, clinically useful mechanism of action (ii) Evidence of higher efficacy or safety compared to the existing similar drugs (iii) Evidence of improvement in the treatment method of the target disease (iv) Evidence of higher clinical usefulness due to formulation improvements compared to the existing similar drugs
Small market size	5～20%	The new drug is or has considerably small market size
Pediatric medicine	5～20%	The new drug that has pediatric indications
Sakigake	10～20%	The new drug is designated as a Sakigake product

If no comparable drug is available, the price of the new drug is calculated based on costs, including manufacturing cost, sales and general administrative cost, operating profit, and distribution and marketing cost. This method is known as “cost accounting method.” In this method, the standard operating profit percentage is adjusted up and down depending on the novelty, efficacy, and safety of the drug compared with existing therapies.

Finally, in either method, the price is compared with the average foreign price (public

price in US, UK, Germany and France), if available, and is adjusted accordingly if the price difference is substantial. This adjustment is called “foreign price adjustment.” (Figure 8)

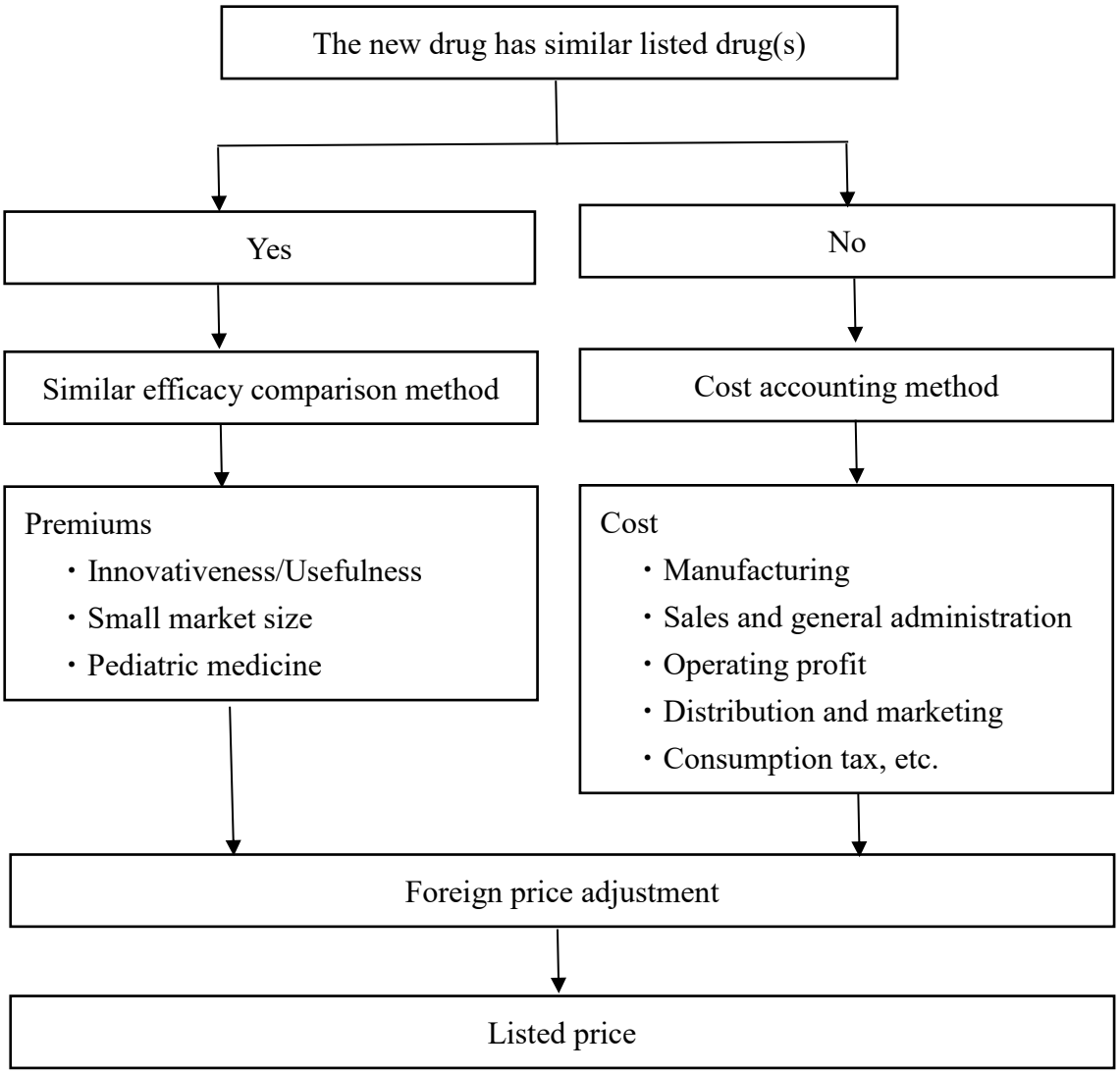

Figure 8 NHI price calculation method

3.1.3 Transparency and predictability of Japanese NHI drug price setting

In similar efficacy comparison method, one or more premiums are added to the calculated price when the new drug meets certain criteria. While the requirements for the premium for small market size, pediatric medicine, and Sakigake products are defined clearly, those for innovativeness or usefulness have some uncertain factors. Additionally, the premium rate for innovativeness or usefulness is on a wide sliding scale from 5% to 120%. However, there are no transparent criteria to decide the position on the scale.

For the pharmaceutical industry, which invests a great amount of resource including cost and time in new drug development, predictability as well as attractiveness of the market is important. Enhancing the predictability of a future drug reimbursement price is a critical issue. Furthermore, as the control of health expenditure becomes strict, the importance of considering drug pricing policy that properly reflects the drug's clinical value increases.

Against this background, an academic study to develop a method to quantify the size of premium for innovativeness or usefulness was performed in 2013-2014 by a team led by Prof. Narukawa at Kitasato Univeristy, School of Pharmacy in Tokyo. They prepared a

report to propose a point-based system for premium calculation. Consequently, since the summer 2014, this point-based system has been applied to the premium rate calculation as a reference [36].

In Chapter 3, we focused on the characteristics of the drugs which obtained innovativeness or usefulness premium. Furthermore, we reviewed the drugs that gained premiums for innovativeness or usefulness after the introduction of the point-based system. We also compared the proportion of the amount of premium or adjustment to pre-adjustment drug price in 3 group (drugs which obtained innovativeness or usefulness premium, drugs of which operating profit was adjusted upward, and drugs of which price was adjusted upward based on the foreign price).

3.2 Method

3.2.1 Characteristics of the drugs that obtained premium for Innovativeness or Usefulness

3.2.1.1 Investigated products and items

All the new drugs that were listed in the NHI price list between October 2004 and December 2014 were investigated. For those drugs, the following information was collected from the documents distributed at the Chuikyo meeting and its meeting minutes disclosed by the MHLW, as well as the review reports published by PMDA.

- NHI drug price calculation method
- Presence or absence of a new mechanism of action
- Presence or absence of premiums and the premium rate
- Result of confirmatory clinical trials, which was submitted to PMDA for application for marketing authorization

3.2.1.2 Analysis about presence or absence of premium for innovativeness or usefulness

All the new listed drugs which were assessed by similar efficacy comparison method (I) were classified into 2 groups based on the presence or absence of a new mechanism of

action. The proportion of the number of drugs that gained a premium for innovativeness or usefulness to that of listed drugs were compared between the 2 groups by chi-square test.

All the new listed drugs which were assessed by similar efficacy comparison method (I) were classified into 4 groups (superiority study to positive control drug, non-inferiority study to positive control drug, placebo-controlled study, and single-arm study) based on the result of confirmatory clinical trial. The drugs which were approved based on the articles for publication were excluded from the analysis. The proportion of the number of drugs that gained a premium for innovativeness or usefulness to that of listed drugs were compared in the above 4 groups by chi-square test.

3.2.2 Predictability and transparency of the premium rate for innovativeness or usefulness

From all the new drugs which were listed in the NHI price list between June 2014 and December 2017, drugs which gained premium for innovativeness or usefulness were picked out. For them, the applied premium rate and the fulfilled factors were identified through the documents for the Chuikyo meeting. Then, we reviewed the consistency between the rate actually applied and that was calculated based on the point-based system.

3.2.3 Impact of premium for innovativeness or usefulness, operating profit adjustment, and foreign price adjustment

Among the new drugs that were listed in the NHI price list between October 2004 and December 2017, drugs that obtained a premium for innovativeness or usefulness, drugs of which operating profit was adjusted upward, and drugs of which price was adjusted upward based on the foreign price were picked out. Then, for drugs of which operating profit was adjusted upward or those of which price was adjusted upward based on the foreign price, the proportion of adjustment amount with respect to the pre-adjustment price was calculated. Finally, those proportions were compared in the 3 classifications: premium for innovativeness or usefulness, adjusted amount of operating profit, adjusted amount based on the foreign price.

The proportions in the above 3 groups were compared by Kruskal-Wallis test. When a significant difference was observed in the comparison among the 3 groups, the Dwass-Steel-Critchlow-Flinger method was applied.

For the analysis, StatsDirect (ver.2.7.9; StatsDiret Ltd. UK) was used, and the level of statistical significance was set at 5%.

3.3 Result

3.3.1 Characteristics of the drugs that obtained premium for innovativeness or usefulness

3.3.1.1 Investigated products and items

Between October 2004 and December 2014, a total 464 new drugs were listed in the NHI price list. The NHI drug price was calculated by similar efficacy comparison method (I) for 256 drugs (55.2%), and by similar efficacy comparison method (II) for 29 drugs (6.2%). The price was calculated by cost accounting method for 135 drugs (29.1%), and the price of 45 drugs (9.5%) was calculated by other exceptional methods.

Of the 256 drugs which were assessed by similar efficacy comparison method (I), 89 drugs obtained premium for usefulness. No drugs received a premium for innovativeness.

3.3.1.2 Analysis of presence or absence of premium for innovativeness or usefulness

Of the 256 drugs which were assessed by similar efficacy comparison method (I), 47 drugs had a new mechanism of action. The proportion of the number of drugs which obtained a premium for usefulness to that of listed drugs in the group with a new mechanism of action was greater than that in the group without a new mechanism ($p<0.0001$) (Figure 9-1). However, no trend was observed with respect to the rate of the

obtained premiums.

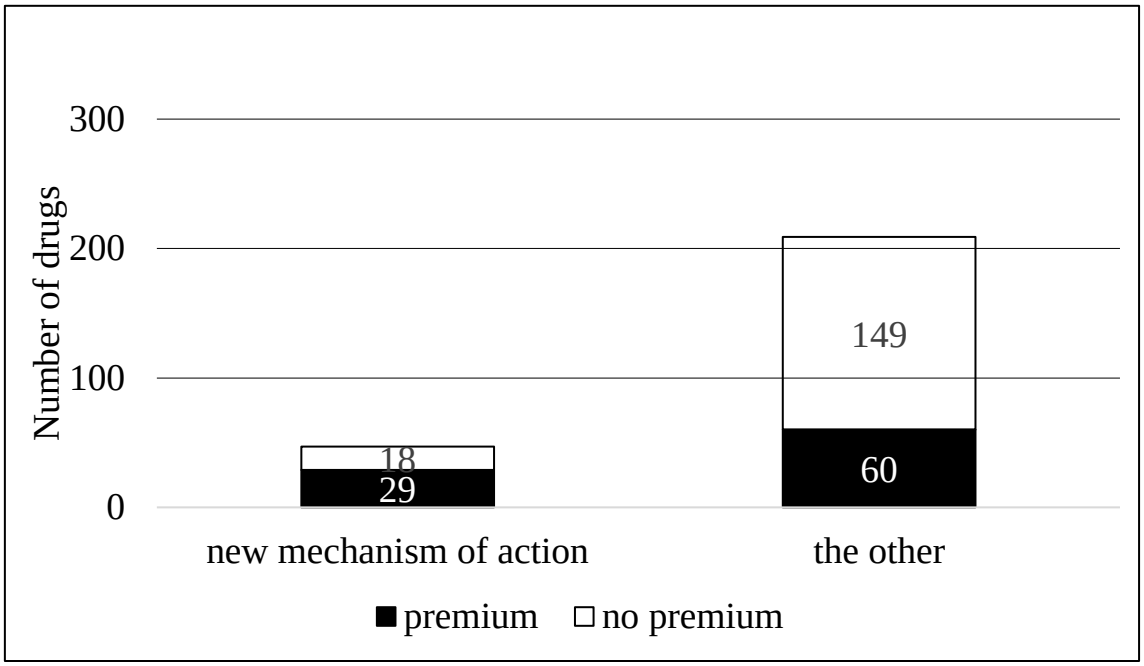

Figure 9-1 Characteristics of the drugs which gained premium for innovativeness or usefulness (new mechanism of action)

Of these 256 drugs, 239 products were classified into 4 groups based on the result of the confirmatory clinical trial. With 28 products, a significant advantage in the new product was evident compared with positive-controlled drugs. For 72 products, the efficacy of the new drug was demonstrated by non-inferiority to positive-controlled drugs. Placebo-controlled studies were conducted for 99 products; single-arm studies were performed for 40 products.

The proportion of the number of drugs which obtained a premium for usefulness to that of the listed drugs in the group showing superior results to positive control drugs was

greater than in the group with non-inferior results to positive control drugs (p=0.0013), and in the group with placebo-controlled studies(p=0.0046) (Figure 9-2). However, no trend was observed with respect to the rate of the obtained premiums.

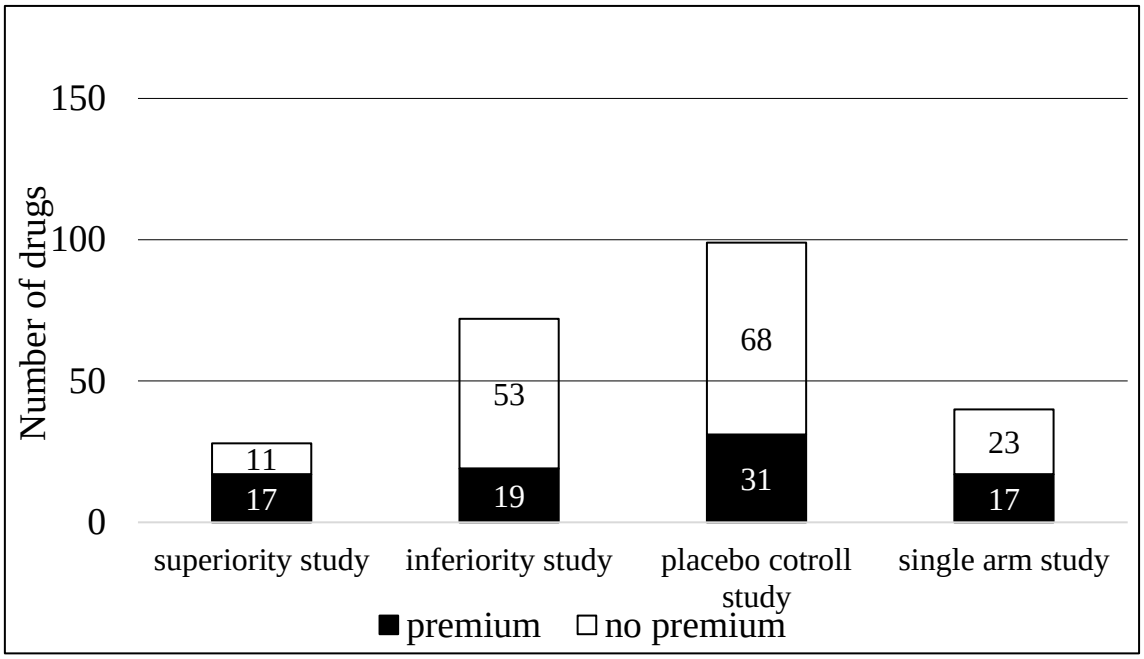

Figure 9-2 Characteristics of the drugs which gained premium for innovativeness or usefulness (confirmatory study)

3.3.2 Predictability and transparency of premium rate for innovativeness or usefulness

Between June 2014 and December 2017, the NHI price was calculated by similar efficacy comparison method for 192 drugs. Among them, 1 drug gained a premium for innovativeness, and 18 drugs gained a premium for usefulness. Their premium rates were judged with reference to the point-based system.

In 18 drugs out of 19, the applied rates of premium were consistent with the calculated rate based on the point-based system (Table 6).

Table 6 Listing of drugs gained premiums for innovativeness/usefulness after June 2014

Applied premium		Type of drugs	Drug name (Brand name)	Fulfilled criteria		Rate calculated by the point-based system	
Innovativeness	100%	NASs	Sofosbuvir (SOVALDI)	(i), (ii), (iii) (i) - b (i) - d (ii) - 1 - a (ii) - 1 - b (ii) - 1 - c (ii) - 2 - b (iii) - a (iii) - b (iii) - c (iii) - e	11p 1p 1p 1p 1p 1p 1p 1p 1p 1p 1p	20p	100%
Usefulness I	45%	NASs	Dabrafenib Mesilate (TAFINLAR)	(ii), (iii) (ii) - 1 - a (ii) -2 -a (iii) - b (iii) - f	5p 1p 2p 1p 1p	9p	45%
	45%	NASs	Trametinib Dimethyl Sulfoxide (MEKINIST)	(ii), (iii) (ii) - 1 - a (ii) - 2 - a (iii) -b (iii) - f	5p 1p 2p 1p 1p	9p	45%
	40%	NASs	Daclatasvir Hydrochloride (DAKLINZA)	(i), (iii) (i) - a (iii) - a	5p 2p 1p	8p	40%
	35%	NASs	Ibrutinib (IMBRUVICA)	(i), (iii) (i) - b (iii) - a	5p 1p 1p	7p	35%
Usefulness II	20%	NASs	Lenvatinib Mesilate (LEMVIMA)	(iii) - a (iii) - e (iii) - f	1p 1p 1p	3p	15%
	10%	NASs	Naldemedine Tosilate (SYMPROIC)	(i) - a	2p	2p	10%
	10%	NASs	Alectinib Hydrochloride (ALECENSA)	(iii) - a (iii) - e	1p 1p	2p	10%
	5%	NASs	Glecaprevir, Pibrentasvir (MAVYRET)	(iii)-a	1p	1p	5%
	5%	New dosages New indications New formulations	Drospirenone and Ethinylestradiol Betadex (YAZ FLEX)	(ii) - 1 - a (ii) - 2 - a	1p 1p	1p	5%
	5%	NASs	Pasireotide Pamoate (SIGNIFOR LAR)	(iii) - a	1p	1p	5%
	5%	NASs	Osimertinib Mesilate (TAGRISSO)	(iii) - a	1p	1p	5%

	5%	NASs	Eftrenonacog Alfa（Genetical Recombination）(ALPROLIX)	(iii) - c	1p	1p	5%
	5%	NASs	Suvorexant (BELSOMRA)	(i) - b	1p	1p	5%
	5%	NASs	Pegfilgrastim（Genetical Recombination）(NEWLASTA)	(iii) - c	1p	1p	5%
	5%	NASs	Pomalidomide (POMALYST/IMNOVID)	(iii) - a	1p	1p	5%
	5%	NASs	Nintedanib Ethanesulfonate (OFEV)	(iii) - c	1p	1p	5%
	5%	New dosage form	Colistin Sodium Methanesulfonate (ALDREV)	(iii) - a	1p	1p	5%
	5%	New dosage form	Anhydrous Caffeine (RESPIA)	(iii) - c	1p	1p	5%

3.3.3 Impact of premium for innovativeness or usefulness, operating profit adjustment, and foreign price adjustment

One hundred and two drugs gained premium for innovativeness or usefulness between October 2004 and December 2017. Of those, the premium rate for 88 drugs were identified based on the documents distributed at the Chuikyo meeting. Operating profit was adjusted upward in 47 drugs, and price of 76 drugs were adjusted upward based on the foreign price (Table7).

Table 7 NHI drug price calculation method

NHI drug price calculation method	Number of drugs (%)	Premiums	Number of drugs (%)
Similar efficacy comparison method	387 (62.5%)	Innovativeness	1 (0.26%)
・Similar efficacy comparison method (I)	338	Usefulness	101 (26.1%)
・Similar efficacy comparison method (II)	49	Unknown	14
		5%	42
		10%	18
		15%	7
		20%	6
		25%	3
		30%	2
		35%	3
		40%	4
		45%	2
		Small market size	27 (7.0%)
		Pediatric medicine	23 (5.9%)
		Foreign price adjustment	87 (11.5%)
		Upward	67
		Downward	20
Cost accounting method	172 (27.7%)	Adjustment of the operating profit percentage	57 (33.1%)
		Upward	47
		110%	19
		120%	17
		125%	2
		130%	5
		135%	1
		140%	2
		160%	1
		Downward	10
		95%	7
		90%	3
		Foreign price adjustment	20 (11.6%)
		Upward	9 (4.9%)
		Downward	11
The other method	61 (9.8%)	Foreign price adjustment	3
		Upward	0
		Downward	3

Proportion of the amount of upward adjustment for operating profit to pre-adjustment price was smaller than that of premium for innovativeness or usefulness ($p<0.0001$). Furthermore, proportion of the amount of upward adjustment based on the foreign price to pre-adjustment price was greater than that of premium for innovativeness or usefulness, and also that of upward adjustment of operating profit ($p<0.0001$) (Figure 10).

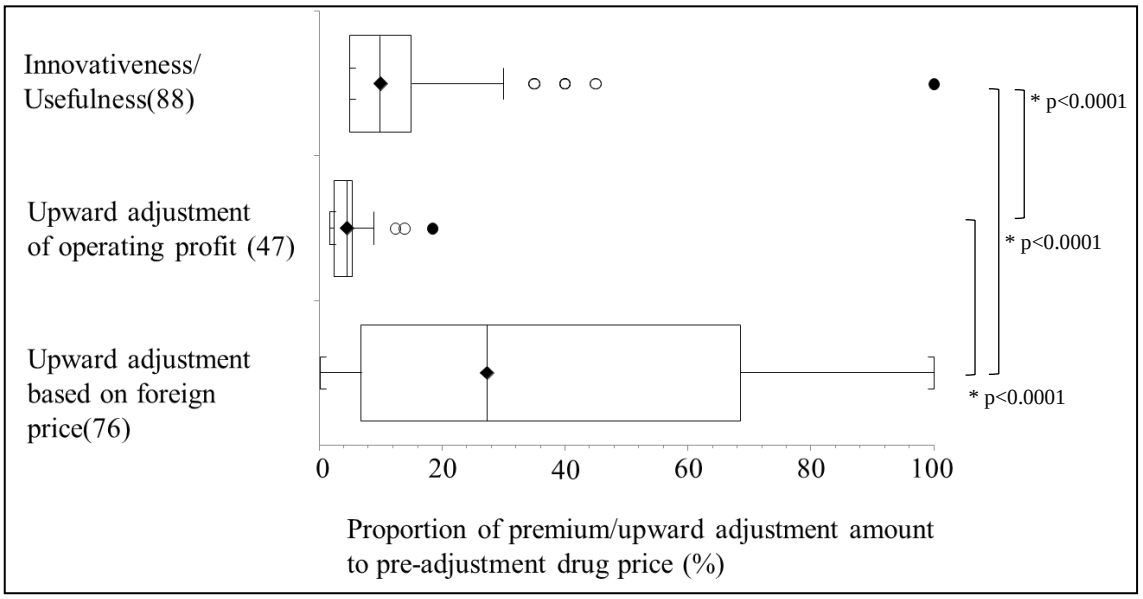

Figure 10 Proportion of premium/upward adjustment amount to pre-adjustment drug price

3.4 Discussion

For drugs that were listed in the NHI price list between October 2004 and December 2017, 102 gained premium for innovativeness or usefulness. The premium was applied not only to NASs but also to other types of new drugs. The actual premium rate applied to each of the drugs varied from 5% to 100%. In 18 drugs (94.7%) out of 19 that gained the premium between June 2014 and December 2017, the applied rate of the premium was consistent with those calculated based on the point-based system; fairly good consistency has been observed. However, the system was developed based on a retrospective analysis, and continuous review of the criteria and its performance will be required with the advancement of medical technology and the accumulated information for future improvement of evaluation. It is also important to examine the drugs that were not given premium in light of the proposed criteria in the future.

With regard to the impact of the premium or price adjustment, the proportion of the amount of upward adjustment of operating profit to pre-adjustment price was smaller than the proportion of premium for innovativeness or usefulness to pre-adjustment price. Furthermore, the proportion of the amount of upward adjustment based on average foreign price was greater than that of premium for innovativeness or usefulness or upward operating profit adjustment.

Innovative drugs that are dissimilar to existing products are generally assessed using cost accounting method. By contrast, new drugs that are similar to existing products are normally evaluated using similar efficacy comparison method. Our findings suggest that the NHI needs to employ a more effective price calculation method that incorporates innovativeness or usefulness of new drugs into their price. It is also necessary to revise the balance between the impact of premium based on the clinical value and the price adjustment based on the foreign price. NHI drug price calculation method was revised, and the new method has been enforced since FY 2018; some of the above concerns were addressed [37], but not enough.

The environment of new drug development has moved into the era of intense global competition. Furthermore, development of new drugs has become increasingly challenging by the changes in medical need from for lifestyle-related diseases to for those currently lacking in established medical treatment. For the pharmaceutical industry, which invests a great amount of resource including development cost and time for future new drugs, predictability as well as attractiveness of the market is important [6]. From this aspect, enhancing the predictability of the future drug reimbursement price is an important issue. Furthermore, the importance of properly reflecting the drug's clinical value to the drug price while maintaining good patient access to new drugs has been

increasing.

The current Japanese price setting system based on the market price can be considered as a reasonable approach to evaluate the value of new drugs in clinical practice. Furthermore, it is expected to enhance the predictability of future drug price. We should continue to discuss price calculation schemes that properly reflect the drug's clinical value while keeping the availability of new drugs under a sustainable budget.

Chapter 4

Factors affecting the degree of price discrepancy between the NHI reimbursement price and the actual market price of new drugs

4.1 Introduction

In Japan, NHI has ensured that all Japanese citizens can access the health services they need based on the NHI Act. Under the scheme, the reimbursement price of a drug is set by the government as an official price, applied universally in Japan. The name and reimbursement price of each drug which can be used under NHI is listed in the NHI price list.

The reimbursement price of all listed drugs is revised based on the results of biennial survey of drug price. In the survey, for all the listed drugs, the actual market prices that pharmaceutical wholesalers use when selling to NHI medical institutions or pharmacies are investigated by inquiries to those wholesalers. The NHI price of each listed drug is then revised based on the actual market price so as to decrease the difference between the two [38, 39]. Currently, the revised NHI price is determined as the actual market price plus 2% of the existing NHI price (Figure 11). The adjustment rate of 2% was set to stabilize the distribution of pharmaceuticals [40].

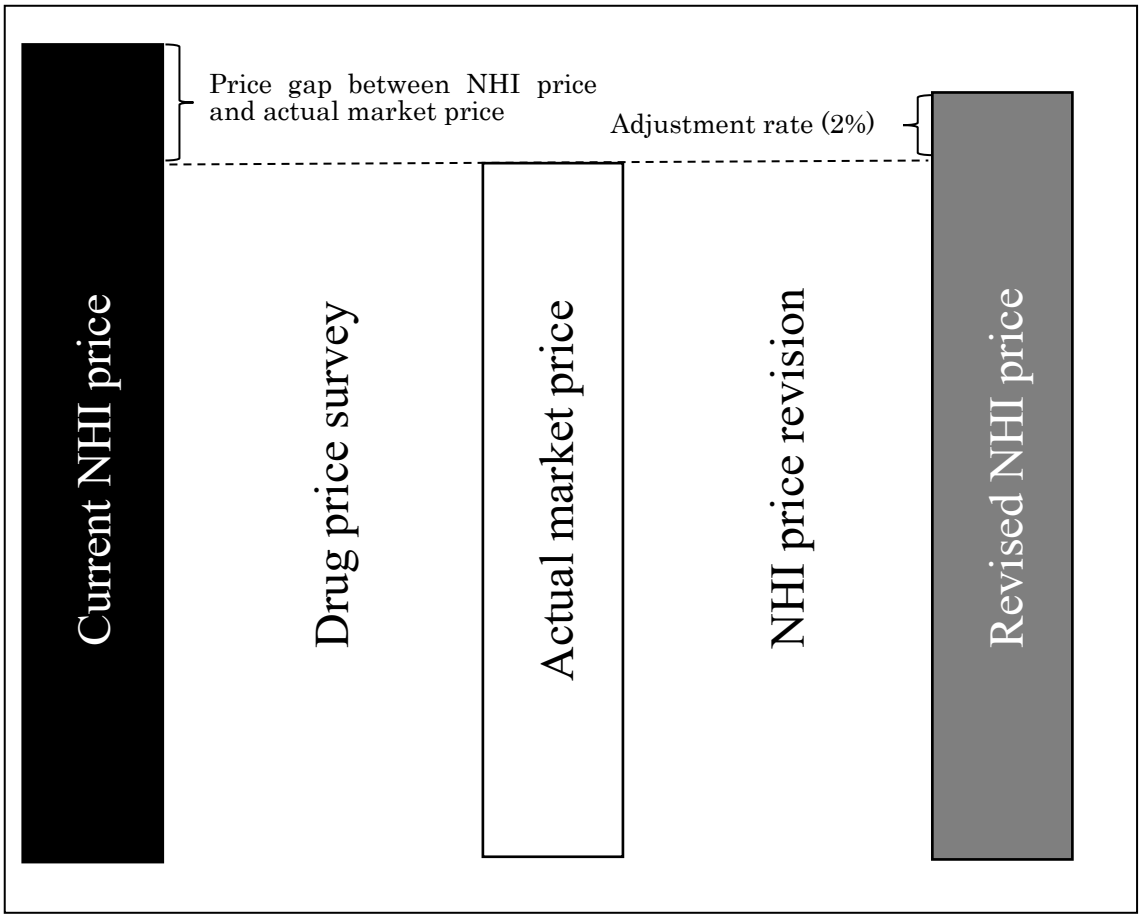

Figure 11 NHI price revision process

NHI price revisions are based on actual market prices, but there are some exceptions. For the long-listed drugs of which generic drugs have been already launched, when share of the generics is below the set reference level, the revised NHI price is set at a value lower than that calculated from the actual market price. For the drugs of which indications are expanded to orphan or pediatric diseases, the revised NHI price is set at a value higher than that calculated from the actual market price. In the cases of drugs where the market size turns out to be very different from that anticipated at the product launch, the revised

NHI price is adjusted based on re-pricing principles. Furthermore, price maintenance premium has been introduced on a trial basis since 2010 to facilitate the development of future innovative drugs. When the premium is applied, NHI price contains the value of that premium, which is added to the calculation based on the actual market price.

Under the market conditions, listed drugs are delivered by pharmaceutical wholesalers to NHI medical institutions or pharmacies. For pharmaceutical wholesalers, their revenue is based on the difference between the consumer purchase price (i.e. the actual market price) and the wholesale purchase price from pharmaceutical companies. [41, 42]. The consumer purchase price of each listed drug is determined by negotiation among pharmaceutical wholesalers and NHI medical institutions or pharmacies; actual market price constantly fluctuates based on market trends [41].

In the above manner, the value of listed drugs is assessed in clinical practice, and that evaluation is reflected in the revised NHI price. In Chapter 4, we examined the factors that affect the discrepancy between the NHI reimbursement price and actual market price of new drugs at the time of their first NHI drug price revision after having been listed in the NHI price list.

4.2 Method

4.2.1 Calculation of discrepancy between the NHI reimbursement price and the actual market price

For the NASs which were listed between October 2004 and December 2014, the discrepancy between the NHI reimbursement price and the actual market price was calculated; we estimated it based on the first revised NHI reimbursement price (Table 8). The drugs which gained the price maintenance premium or were subject to re-pricing were excluded from the analysis. In cases where we encountered multiple strengths or multiple brand drugs listed in the NHI price list, a product with the greatest price discrepancy was selected for this study.

Table 8 Calculation method of price discrepancy

$$\text{Price discrepancy (\%)} = \frac{\text{【first NHI price (tax excluded)} \times 1.02\text{】} - \text{【revised NHI price (tax excluded)】}}{\text{【first NHI price (tax excluded)】}} \times 100$$

Among the drugs for which we calculated the discrepancy between the NHI reimbursement price and actual market price, the following information was collected from the documents distributed at the Chuikyo meeting and its meeting minutes disclosed by the MHLW.

- NHI drug price calculation method
- Route of administration
- Estimated market size when the drug first appeared in the NHI price list
- Presence or absence of a premium for innovativeness or usefulness or operating profit adjustment

In addition, for each examined drug, the number of competitive products, which was defined as drugs that had similar indications and the same route of administration, was investigated based on the “Konnichi-no-Chiryoyaku:kaisetsu-to-binran [43-47]”, which was published in January of the NHI price revision year for each product.

4.2.2 Analysis about factors affecting the degree of discrepancy between the NHI reimbursement price and the actual market price

4.2.2.1 Comparison between group

(a) NHI drug price calculation method

The drugs of which discrepancy between the NHI reimbursement price and actual market price was calculated were classified into 2 groups (similar efficacy comparison method, cost accounting method) based on the price calculation method that was applied when the first NHI drug price was set. Then, the price discrepancy was compared between the 2 groups.

(b) Route of administration

The drugs of which discrepancy between the NHI reimbursement price and actual market price was calculated were classified into 3 groups (oral, injection, external) based on the route of administration. Then, the price discrepancy was compared among the 3 groups.

(c) Presence or absence of premium

The drugs of which discrepancy between the NHI reimbursement price and actual market price was calculated were classified into 2 groups (presence premium, absence premium) based on the presence or absence of a premium for innovativeness or usefulness or upward adjustment of operating profit. Then, the price discrepancy was compared

between the 2 groups.

(d) Market size

The drugs of which discrepancy between the NHI reimbursement price and actual market price was calculated were classified into 2 groups (large or small market) based on the estimated market size when the first NHI drug price was set, using the median value as the threshold for classification. Then, the price discrepancy was compared between the 2 groups.

(e) The number of competitors

The drugs of which discrepancy between the NHI reimbursement price and actual market price was calculated were classified into 2 groups (many or few competitors) based on the number of competitors when NHI drug price was revised firstly, using the median value as the threshold for classification. Then, the price discrepancy was compared between the 2 groups.

(f) Market size and the number of competitors

The drugs of which discrepancy between the NHI reimbursement price and actual market price was calculated were classified into 4 groups (large-market and many-competitors, large-market and few-competitors, small-market and many-competitors, or small-market and few-competitors). Then, the price discrepancy was compared among the 4 groups.

To compare the median in 3 groups, Kruskal-Wallis test was employed. When a significant difference was observed among the 3 groups, Dwass-Steel-Critchlow-Finger method was applied. For comparison between 2 groups, Mann-Whitney U test was used.

4.2.2.2 Factors affecting the price discrepancy

Multiple regression analysis was conducted to investigate potential factors affecting the price discrepancy. The pre-specified factors such as NHI drug price calculation method, route of administration, presence or absence of premium, market size and the number of competitors were used as explanatory variable, and price discrepancy was used as dependent variable in the analysis. For each factor, similar efficacy comparison method, oral, small-market size, few-competitors, absence of premium was set as a reference, and the variable was handled as quantitative.

For the analysis, StatsDirect (ver.2.7.9; StatsDiret Ltd. UK) was used, and the level of statistical significance was set at 5%.

4.3 Result

Between October 2004 and December 2014, a total of 303 NASs were listed in the NHI price list. Of those 303 drugs, 104 were selected to investigate the price discrepancy; 3 were excluded because they experienced re-pricing, 196 were excluded because they were applied price maintenance premium.

4.3.1 Comparison between group

(a) NHI drug price calculation method

Seventy-four (71.2%) drugs were assessed by similar efficacy comparison method, and 30 (28.8%) drugs were assessed by cost accounting method. For drugs where the reimbursement price was calculated based on similar efficacy comparison method, the price discrepancy was greater compared to those calculated based on cost accounting method (p=0.0001) [Figure 12-1].

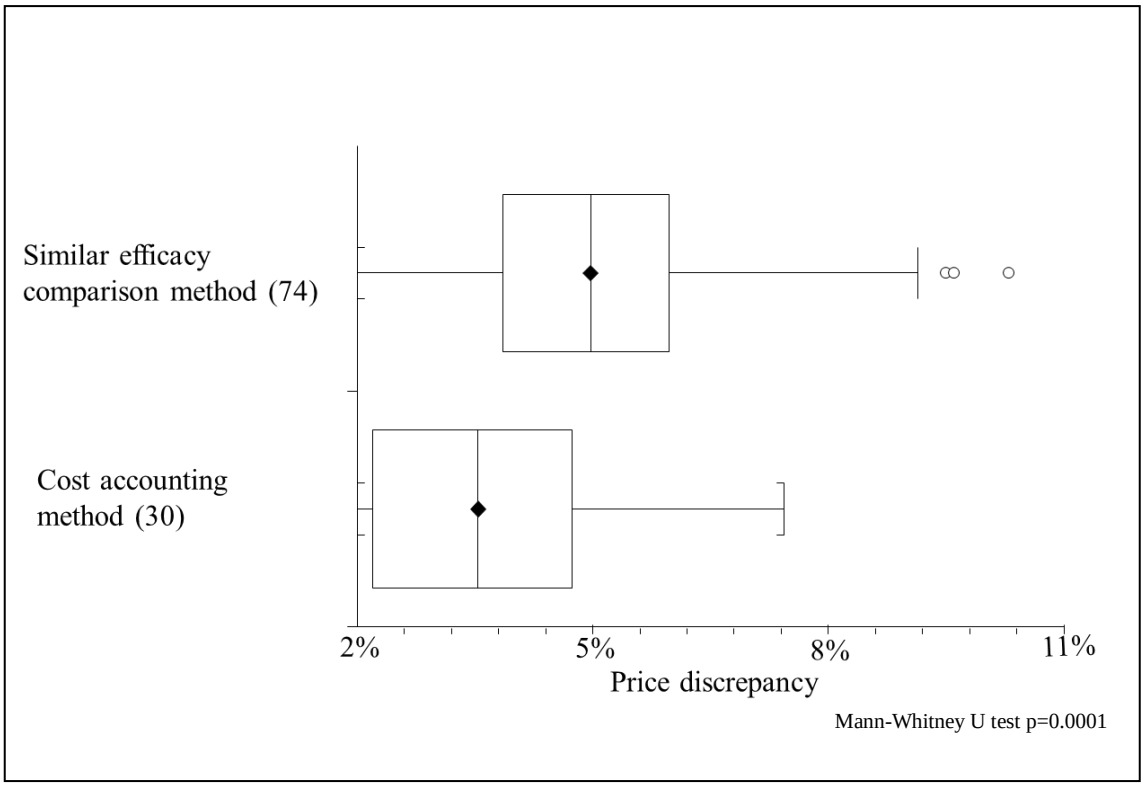

Figure 12-1 Factors affecting the degree of price discrepancy between the NHI price and the actual market price of new drugs (NHI drug price calculation method)

(b) Route of administration

Of the 104 NASs, the route of administration of 49 (47.1%) was oral, 47 (45.2%) was injection, and 8 (7.7%) was external. The price discrepancy for oral drugs was greater than that for injection drugs (p=0.0011) [Figure 12-2].

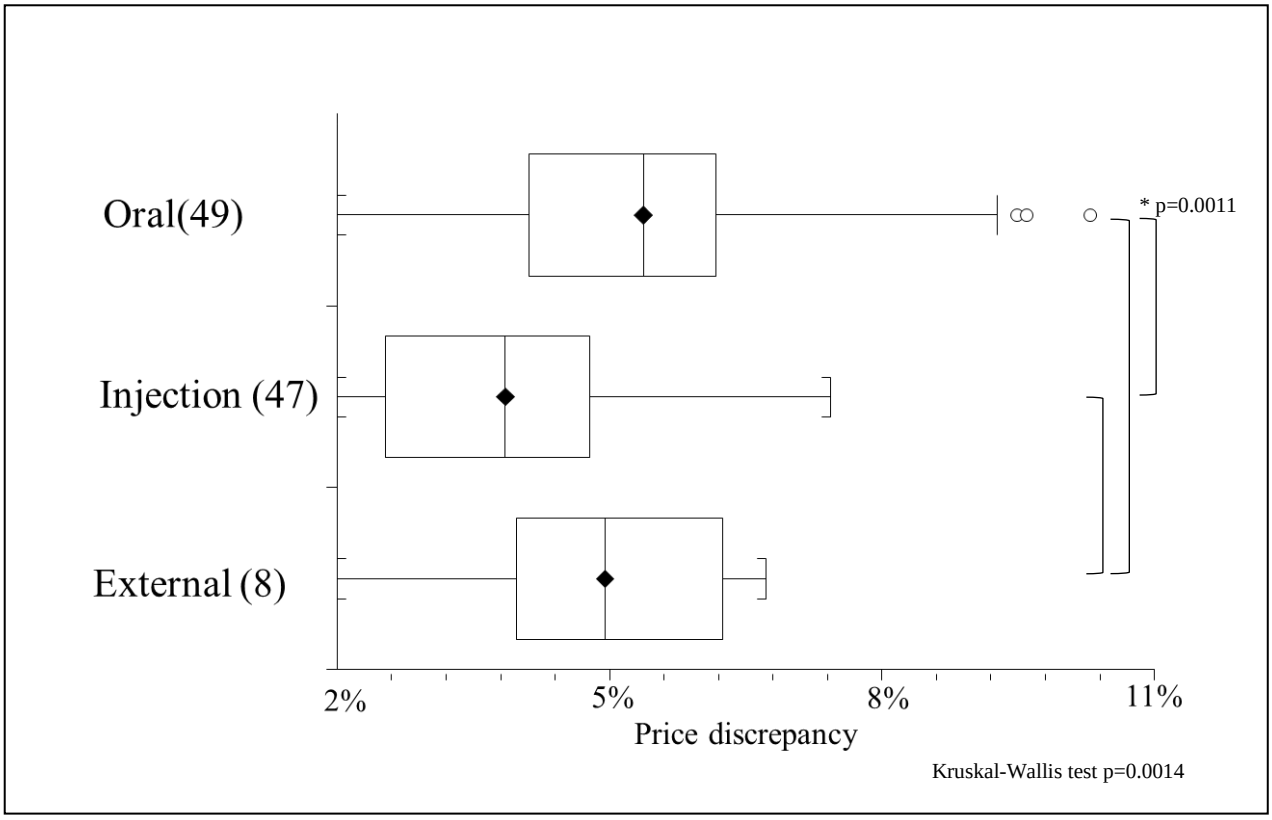

Figure 12-2 Factors affecting the degree of price discrepancy between the NHI price and the actual market price of new drugs (route of administration)

(c) Presence or absence of premium

Of the 104 drugs of which price discrepancy was calculated, 38 drugs (36.5%) had obtained a premium for usefulness or upward adjustment of operating profit. No difference in the price discrepancy was observed between the groups (p=0.4296) [Figure 12-3].

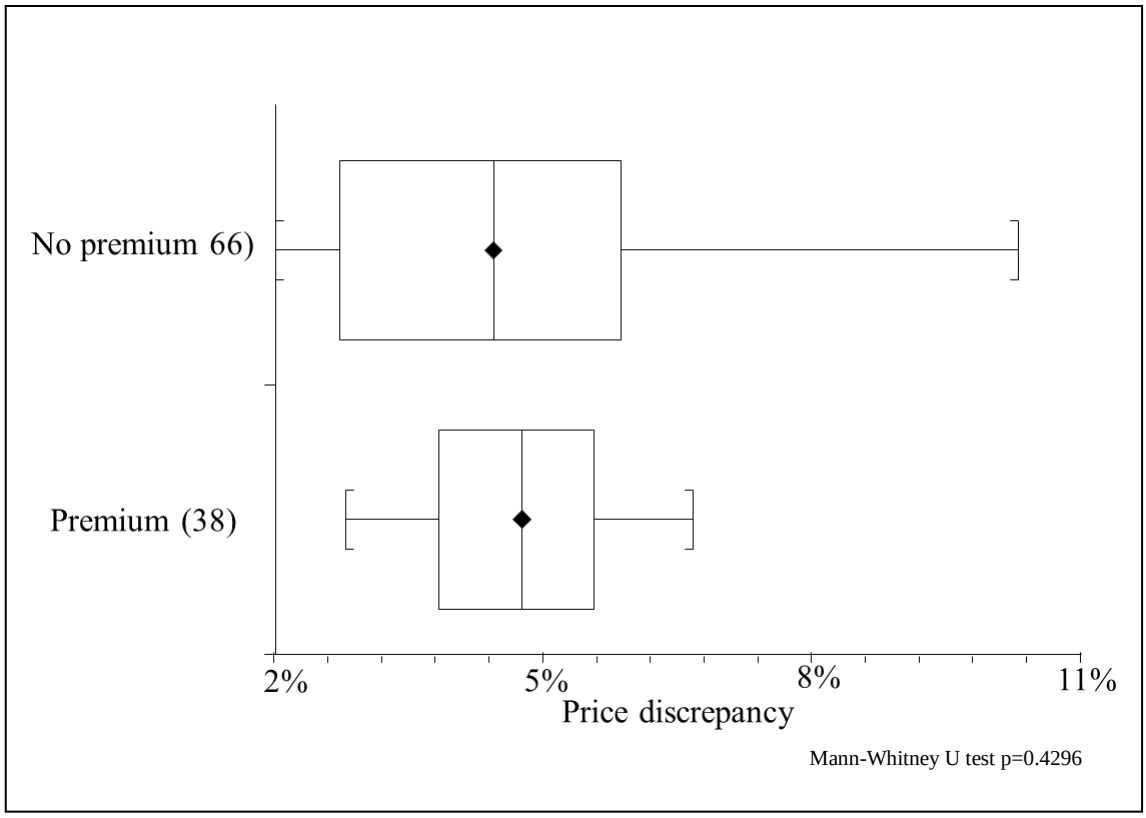

Figure 12-3 Factors affecting the degree of price discrepancy between the NHI price and the actual market price of new drugs (presence or absence of premium)

(d) Market size

The median market size for the 104 drugs was 5.24 billion Japanese Yen. The threshold for group classification was set at 5.0 billion Japanese Yen. Fifty-one drugs (49.0%) were classified in small-market group, and 53 drugs (49.0%) were classified in large-market group. The price discrepancy of drugs in the large-market group was greater than that of products in the small-market group (p=0.0003) [Figure 12-4].

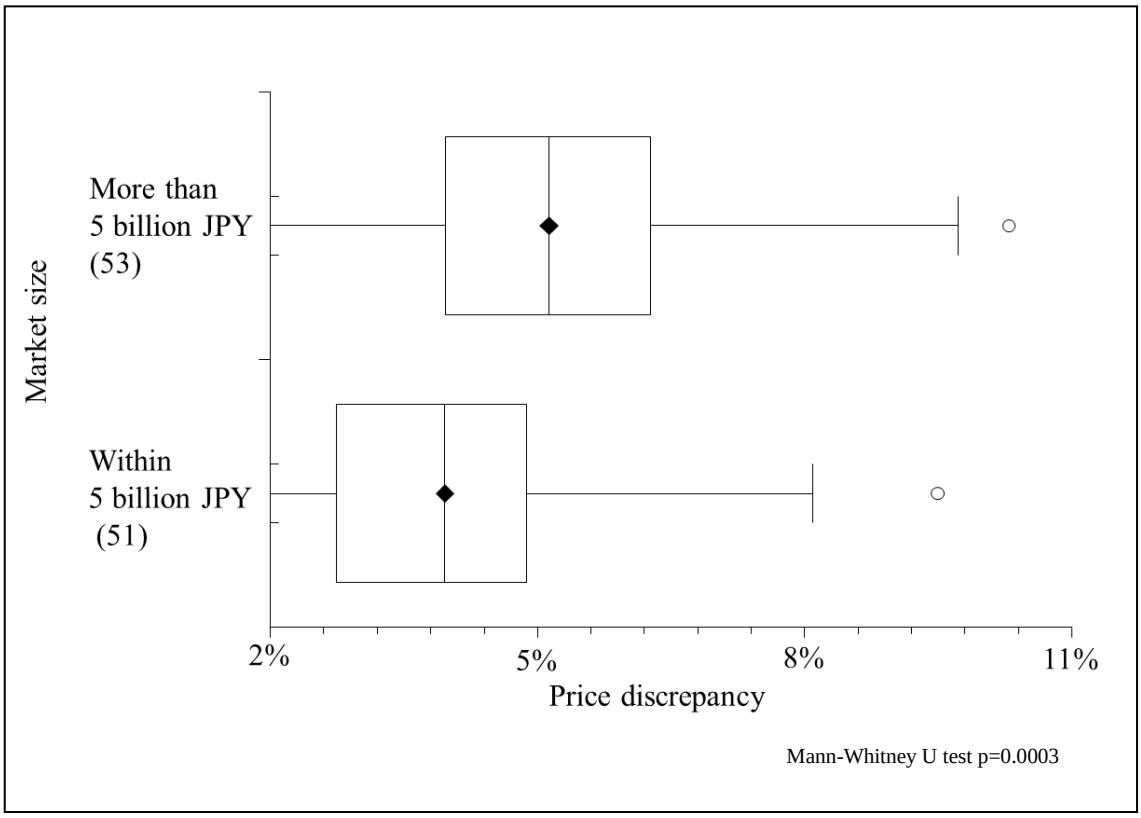

Figure 12-4 Factors affecting the degree of price discrepancy between the NHI price and the actual market price of new drugs (Market size)

(e) The number of competitors

The median of the number of competitors was 3, and threshold for group classification was set at 3 competitors. Fifty-five drugs (52.9%) were classified in few-competitors group, and 49 drugs (4.1%) were classified in the many-competitors group. The price discrepancy for products with 4 or more competitors was greater than that of drugs with 3 competitors or fewer ($p<0.0001$) [Figure12-5].

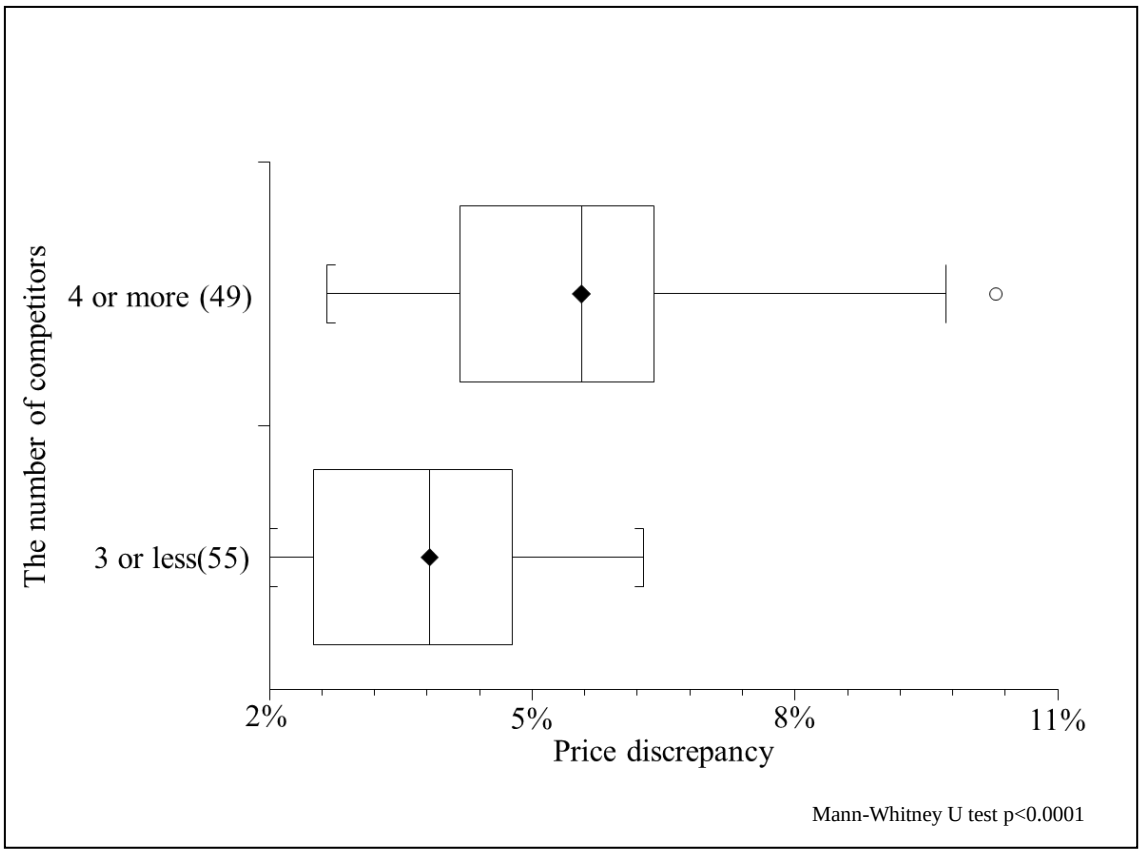

Figure 12-5 Factors affecting the degree of price discrepancy between the NHI price and the actual market price of new drugs (the number of competitors)

(f) Market size and the number of competitors

The 104 drugs examined in this investigation were classified as follows: 39 (37.5%) in the group with large-market size and many-competitors, 13 (12.5%) in the group with large-market size and few-competitors, 16 (15.4%) in the group with small-market size and many-competitors, and 36 (34.6%) in the group with small-market size and few-competitors. The price discrepancy of drugs with large-market size and many-competitors was greater than that of the following: products with large-market size and few-competitors, and products with small-market size and few-competitors

($p=0.0004$, $p<0.0001$, respectively) [Figure 12-6].

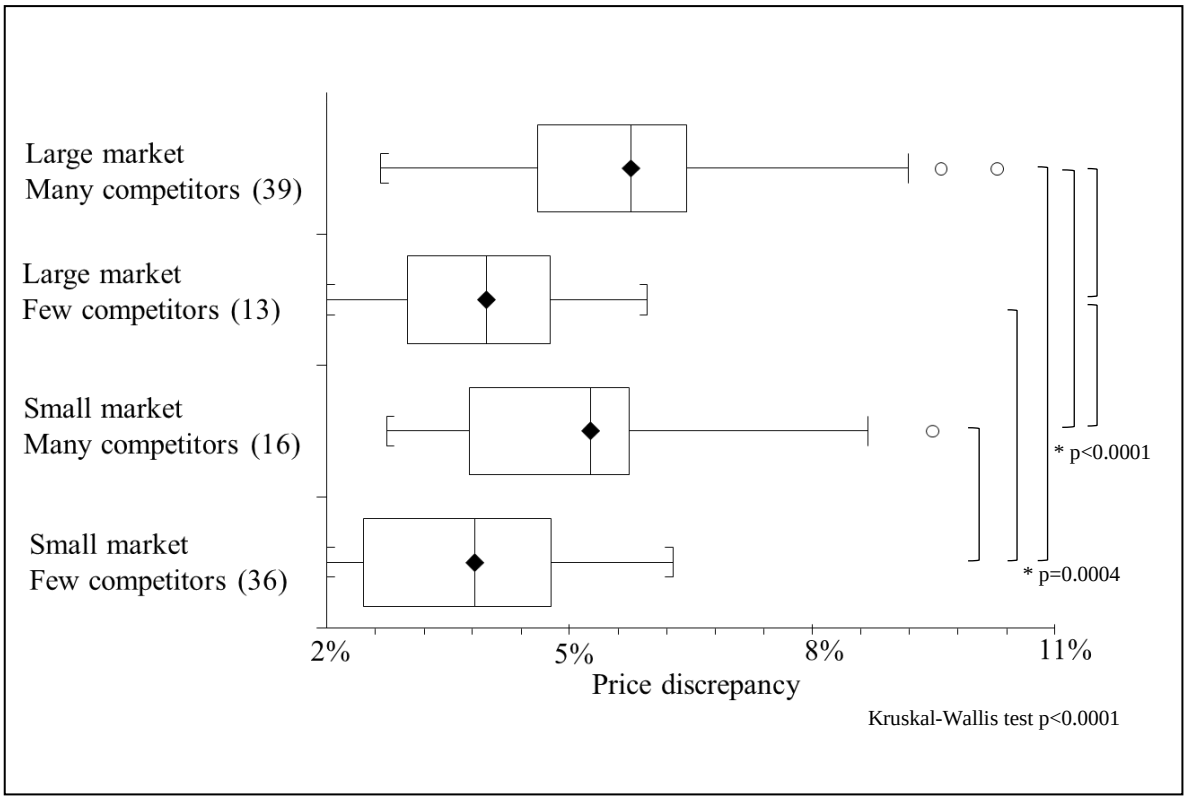

Figure 12-6 Factors affecting the degree of price discrepancy between the NHI price and the actual market price of new drugs (market size and the number of competitors

4.3.2 Factors affecting the price discrepancy

The price discrepancy of drugs with 4 or more competitors was greater than that of products with 3 or fewer competitors (p=0.0001) [Table 9].

Table 9 Factors affecting the price discrepancy

Explanatory variable		regression coefficient	p
NHI drug price calculation method	Similar efficacy comparison method		
	Cost accounting method	-0.3357	0.4157
Rote of administration	Oral		
	Injection	-0.6629	0.0512
	External	-0.6423	0.2660
Market size	Small market (within 5billion JPY)		
	Large market (50 billion or more JPY)	0.3452	0.3023
The number of competitors	Few competitors (3 or less)		
	Many competitors (4 or more)	1.3696	0.0001
Premium	Absence		
	Presence	-0.0785	0.8080

4.4 Discussion

The results of the multiple regression analysis indicated that the price discrepancy of drugs with 4 or more competitors was greater than that of products with 3 or fewer competitors. However, no significant difference was observed in a comparison by market size. These trends were also confirmed in the pair-wise comparison. This finding suggests that the number of competitors had a greater effect on the market price than the size of the market. Many competitors in a market lead to stiff competition, and so the clinical value of a new drug tends to be compared with that of competitive products. As a result, when there are many competitors, the market price tends to decrease. Conversely, if a new drug appearing for the first time provides effective treatment to a disease, medical need for that product is very high; the price of such a drug would be maintained nearly equal to the NHI price.

Regarding the price calculation method, in the pair-wise comparison, the discrepancy with drugs whose price was calculated using similar efficacy comparison method was greater than that of products with cost accounting method. The NHI drug price is calculated using cost accounting method only when there are no similar products on the NHI list. This result would be related to the fact that cost accounting method tends to be applied in the case of drugs with few-competitors. However, no difference was observed in the multiple regression analysis for the price calculation method presumably due to the

fact that it related to the other factor “the number of competitors.”

Similar trend was confirmed for the route of administration. In usual practice, oral drugs are prescribed for both outpatients and inpatients in many medical institutions from small clinics to university hospitals. However, the use of injection drugs tends to be less, and the possibilities for price negotiation are somewhat limited. Accordingly, injection drugs tend to be traded at approximately the same price as that of the NHI. Although significant difference was confirmed in the pair-wise comparison, no significant difference was observed in the multiple regression analysis. This finding indicates that with respect to price discrepancy, the impact of the route of administration was smaller than that of other factors.

With regard to premium for innovation or usefulness, no significant difference was observed in either the pair-wise comparison or multiple regression analysis. This result suggests that the degree of price reduction in drugs with such a premium was the same as that of products without a premium.

To make a reimbursement for drugs that are traded on the market, the NHI is required to set a price that is based under fair market competition [39]. The clinical value of new drugs varies according to market factors, and it has to be routinely confirmed in clinical practice. The market price may be regarded as one evaluation result of a new drug’s

clinical value through clinical practice. We believe that the periodic revision of NHI drug prices is a useful system for re-evaluating the market value of drugs, by which changes in the market price are reflected to the NHI reimbursement price.

However, the pharmaceutical market has been facing some problems [48]. In the council for improvement of pharmaceutical distribution, many issues have been discussed to ensure fair market competition [49]. Attempts were made to deal with those problems in September 2007, and some improvement was confirmed. However, further efforts for improvement are required; a guideline was issued in this regard in FY 2018 [41, 50]. To bring about a better pharmaceutical market, in which manufacturers can make a profit that is commensurate with the value of their products, it is necessary to have a fair, competitive market; the market price of each drug should be an index of its clinical value. In this study, the drugs which obtained price maintenance premium (196 drugs) were excluded, because price discrepancy for the products was not able to be calculated based on the disclosed documents. Quite a number of products have received the premium; thus, to assess the validity of the premium, it is necessary to undertake a similar analysis about such drugs. In addition, this study investigated only the discrepancy upon the first NHI price revision. It is also important to investigate the long-term trends for such discrepancies.

The environment of new drug development has moved into the era of intense global competition. Furthermore, development of new drugs has become increasingly challenging by the changes in medical need from for lifestyle-related diseases to for those currently lacking in established medical treatment. For the pharmaceutical industry, which invests a great amount of resource including development cost and time, obtaining adequate profit commensurate with the value of their products is important. We should continue to discuss price calculation and revision schemes that properly reflect the drug's clinical value while improving the trade practice of pharmaceuticals.

5. Overall Discussion and Conclusion

From the viewpoint of the health insurance coverage proportion and the speed of reimbursement decision, the hurdle to access new drugs in Japan is lower than in major European countries. In Europe, the EU transparency Directive (89/105/EEC) obliges the member states to reach pricing and reimbursement decision within 180 days from marketing authorization. However, slippage well beyond this period occurs regularly in most EU member states. Therefore, the European Commission urged strong enforcement measures in case where member states do not comply, and it also proposed that in future, such decisions should be taken within 120 days for innovative drugs in 2012 [22]. Nevertheless, it was only Germany and the UK that the average time from regulatory approval to the first sale of new drugs launched in 2014 was within 4 months; these countries have initial free pricing policies while preparing for price and access negotiations. It is important to continually follow up the trend in Europe. It is also a fact that the introduction of cost-effectiveness assessment scheme has often resulted in delays in patient access to innovative drugs in many countries. When such a new scheme is incorporated into Japanese reimbursement framework, it should not be implemented in a manner negatively affecting the rapid reimbursement decision in Japan.

The current Japanese price setting system based on the market price of similar drugs can

be considered as a reasonable approach to evaluate the value of new drugs in clinical practice while ensuring competition in the market. Additionally, it was confirmed that predictability of the applied premium rate was enhanced after the introduction of a point-based system. However, the proportion of the amount of upward adjustment of operating profit to pre-adjustment price was smaller than the proportion of the innovativeness or usefulness premium to pre-adjustment price. Furthermore, the proportion of amount of upward adjustment based on foreign price was greater than that of premium for innovativeness or usefulness or upward adjustment of operating profit. Further discussion to improve the scheme to reflect innovativeness or usefulness of new drugs to their price is expected. Additionally, it is also necessary to revise the balance between the impact of premium based on the clinical value and price adjustment based on the foreign price.

Japanese NHI scheme has ensured good access to new drugs for patients. Additionally, it was confirmed that new drug' clinical value was reflected to its price in Japanese NHI price calculation method to a certain extent, and the opportunity to re-evaluate the market value of the drugs were ensured by periodic NHI price revision system. While extensive coverage of health insurance and prompt reimbursement decisions lower the hurdles to access new drugs and expand treatment options, they could lead to increased medical expenditure. We should continue to discuss sustainable health insurance systems and drug

price calculation schemes that properly reflect the drug's clinical value while ensuring the availability of new drugs to patients.

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