Characteristics of the Japanese Pharmaceutical Market: Implications for the Direction of Pharmaceutical Companies' Research and Development Strategy

A thesis submitted in fulfillment of the requirements for the degree of

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Preface

This thesis is composed of papers I wrote with my co-authors, noted in the Acknowledgements, over the past three years, first, as an MBA candidate (2018–2020) and then, as a DBA candidate (2020–2021) at the University of Tsukuba. These papers address issues regarding the promotion of the Japanese pharmaceutical industry, presenting strategies that Japanese pharmaceutical companies can adopt from both the management and policy perspectives. Regarding the motivation for this specific study, as someone who works for a pharmaceutical company and is involved in the research and development (R&D) of new drugs, I believe it is necessary to present and discuss the findings— specifically those addressing how to deliver innovative new drugs to Japanese people—not only from a scientific perspective but also from a business perspective, so as to promote the development of the Japanese pharmaceutical industry.

The probability of success in the R&D of a new drug is extremely low. Nevertheless, pharmaceutical companies invest significant resources in the R&D of new drugs, undertaking R&D projects for multiple candidate compounds simultaneously. Moreover, pharmaceutical companies often work on candidate compounds in more than one therapeutic area. Therefore, companies must consider the lifecycle of the drugs they own and the profitability of their product portfolios over the long term. Furthermore, there is a widespread call for Japan to reform its drug pricing system drastically. To the best of my knowledge, very few studies have sought to clarify the basis of these policy discussions, even though it is important to understand the magnitude and impact of the issues involved and the factors driving them. Considering the complexity of the pharmaceutical industry, this thesis discusses growth strategies for the Japanese pharmaceutical market and pharmaceutical companies from both the market structure and regulatory perspectives. Although the research was challenging, the extensive investigation has allowed me to address the aforementioned issues.

Many scientists deserve recognition for their contribution to this thesis, including my supervisors and co-authors, as well as the editors and referees of the journals in which the original articles were published, most of whom are mentioned in the Acknowledgements.

I hope you enjoy reading this work.

Shoyo Shibata, University of Tsukuba

January 2021

Abstract

Characteristics of the Japanese Pharmaceutical Market: Implications for the Direction of Pharmaceutical Companies' Research and Development Strategy

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Japan is one of the few countries that can independently develop innovative new drugs. The pharmaceutical industry is a knowledge-intensive industry, and is positioned as an important growth industry in Japan. Accordingly, this thesis undertakes the following work with an aim to help Japanese pharmaceutical companies create internationally competitive new drugs for both the domestic and global pharmaceutical markets:

1. Defines "innovativeness" in relation to new drugs, specifically in the Japanese context and from the perspective of therapeutic areas
2. Elucidates the profile of the Japanese pharmaceutical market compared to the global market and the markets of major European and American countries
3. Considers the current status and offers a prognosis on the Japanese anti-cancer drug market
4. Discusses implications for anti-cancer drug development strategies and outlines important points to be made when filing for approval
5. Evaluates the drug pricing policy under the National Health Insurance system

Taken together, these perspectives clearly establish the strategies that should be adopted by Japanese pharmaceutical companies, not only to contribute to the development of the pharmaceutical industry, but also to ensure the timely provision of innovative new drugs to Japanese cancer patients.

Acknowledgements

At the outset, I express my sincere gratitude to my advisor, Associate Professor Ozaki Koken, for his continuous support of my study and related research, and for his patience, motivation, and immense knowledge. His guidance was invaluable at all stages of researching and writing this thesis. I am also grateful to Professor Suzuki Takeshi from the Education Research Center for Pharmaceutical Sciences at Keio University, for continuing to collaborate with me after my completion of the Ph.D. program at the Graduate School of Pharmaceutical Sciences, Keio University in March 2018, as well as for encouraging me and sharing insightful suggestions. Associate Professor Ozaki Koken and Professor Suzuki Takeshi have played a major role in giving shape to my research and polishing this thesis. I will always cherish their guidance and support.

I also thank Professor Chiba Koji from the Laboratory of Clinical Pharmacology, Yokohama University of Pharmacy; Professor Tsukamoto Katsura from the Laboratory of Global Regulatory Science at Gifu Pharmaceutical University; Associate Professor Maiko Matsushita from the Division of Physiology and Therapeutics at Keio University; and Dr. Noguchi Emi from the Department of Breast and Medical Oncology and Rare Cancer Center at the National Cancer Center Central Hospital for their valuable advice and direction as collaborators.

I express my special thanks to the rest of my thesis committee: Professor Tatsumoto Hirofumi and Professor Nishio Chizuru not only for their insightful comments and encouragement, but also for posing the difficult questions that motivated me to extend my research by incorporating multiple perspectives. I am also grateful to the two anonymous referees among the committee members who reviewed the preliminary version of this thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Business Administration at the University of Tsukuba.

Last but not least, I thank my family from the bottom of my heart for continuously supporting me spiritually throughout my research and my life.

As a result of their unwavering support, I will have earned two PhDs: a PhD in Pharmacy earned in 2018 from Keio University and a PhD in Business Administration, which I will earn in 2021 at the University of Tsukuba. I am very proud to have two PhDs.

I developed my background in pharmacy in the process of obtaining the Bachelor of Pharmacy degree from Gifu Pharmaceutical University and the Doctor of Pharmacy degree from Keio University. Obtaining a Doctorate in Business Administration at the University of Tsukuba would mean I have

acquired knowledge of Business Science as well.

I was a junior high school student when my grandfather died of hepatocellular carcinoma. I strongly hoped that cancer would be eradicated from this world, so I vowed to study hard and work for patients around the world in the future. When I was a child, my grandfather would proudly report to those around him when I had done well in my exams. Perhaps I continue to work hard at my studies to this day so as to receive praise from him in heaven.

Now, I have two specialties. People with two PhDs are rare. I will definitely put my expertise to good use in the pharmaceutical industry and strive to deliver as many innovative new drugs as possible to patients, to be complimented by my beloved grandfather in heaven.

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1. Introduction

1.1 The Pharmaceutical Industry

This thesis focuses on the pharmaceutical industry. This section describes the characteristics of the pharmaceutical industry. The mission of the pharmaceutical industry is to contribute to the improvement of people's welfare and the quality of medical care through the research and development (R&D) of innovative new drugs, and to contribute to the realization of a healthy and high quality of life (QoL). In terms of economic growth, the industry also contributes to maintaining and expanding the proportion of the working and consuming populations, given companies' significant investment in R&D and the improvement in patients' QoL or healthy life expectancy made possible by the development of innovative new drugs. In recent years, there has been a shift in the industry's focus from infectious diseases and lifestyle diseases such as hypertension, to diseases with high unmet medical needs (UMN), such as cancer and central nervous system diseases, for which effective treatments are yet to be established. The future is expected to bring great advances in fields such as genome analysis and regenerative medicine as well as in the discovery of new disease mechanisms and the creation of new medical interventions, with the R&D of next-generation medicines being based on new technological innovations. Specifically, collaboration with a wide range of related fields will be increasingly encouraged to promote the development of innovative drugs that actively utilize various technologies, in response to diseases whose onset and development mechanisms are unknown.

In 2017, Japan's Ministry of Health, Labour and Welfare (MHLW) revised the "Comprehensive Strategy to Strengthen the Pharmaceutical Industry" originally developed in 2015, to reiterate that Japan is one of the few countries with the capability of developing new drugs and that the pharmaceutical industry, a knowledge-intensive industry, is an important engine for economic growth [1]. The report states that the Japanese pharmaceutical industry should be supported to promote the R&D of innovative pharmaceuticals—thereby helping the industry achieve higher drug discovery capabilities—and that the continuous development of the pharmaceutical industry is a policy priority.

The pharmaceutical industry is characterized by diverse end users, purchase decision-makers, and payers (**Figure 1.1**). For example, when a doctor sees a patient—a user of medical services—at a medical institution, it is the physician who decides what kind of medical service will be provided. Most of the patient's medical costs are reimbursed by insurance companies, although the patient pays a part of the cost as out-of-pocket expenses. Other industries are relatively free from such complex relationships. For example, in the automotive industry, the decision-maker is often the user, and the user bears all the

costs and makes the purchase. In other words, the final user, the decision-maker, and the payer are one single stakeholder. Thus, in industries other than the pharmaceutical industry, a company's focus is likely to be on a single stakeholder—the user, the decision-maker, and the consumer, who is also the payer. In other words, non-pharmaceutical companies emphasize consumer-conscious R&D and marketing strategies. By contrast, in the case of the pharmaceutical industry, the users, decision-makers, and payers are different entities, and all of them must all be taken into account when drawing up strategies.

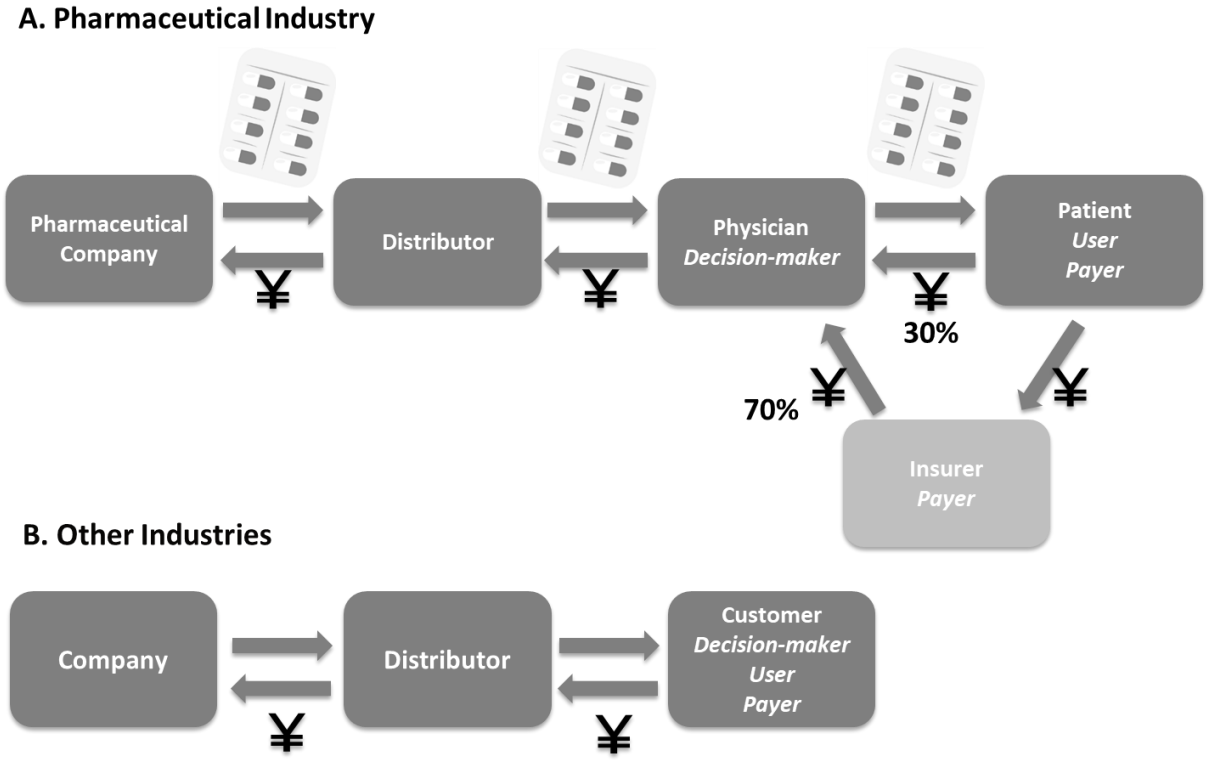


Figure 1.1. Users, purchase decision-makers, and payers in pharmaceutical and other industries

What is clear from the aforementioned discussion is that the pharmaceutical industry is a complex industry with many stakeholders. Nakamura emphasized that "six perspectives" (Market, Product and Technology, R&D, Market Approval, Pricing, and Distribution) and "six players" (Patient, Medical Staff, Payer, Government, Competitor, and Distributor) were essential to navigate this complexity (**Figure 1.2**) [2]. However, the presence and influence of numerous stakeholders make it difficult to formulate strategies and policies and to implement them. Therefore, it is important to better understand these "six

perspectives" and "six players" when considering corporate strategies and institutional design in the pharmaceutical industry. Inadequate understanding may result in the business or policy for one player being found, after implementation, to have unexpected effects on other players, resulting in confusion or backlash. For example, even if a product is good for patients, medical institutions may not adopt it if physicians find the product difficult to use. Alternatively, a reduction in medical fee points, while welcome to payers, will lead to lower revenues for health care providers and a potential backlash. The discussion in this thesis proceeds on the basis of this framework. Indeed, this thesis proposes future R&D strategies for pharmaceutical companies based on the totality of the findings ("R&D" in **Figure 1.2**). Although the recommendations are from the standpoint of a pharmaceutical company, the discussions involve careful consideration of the impact on other stakeholders as well, to avoid self-serving recommendations.

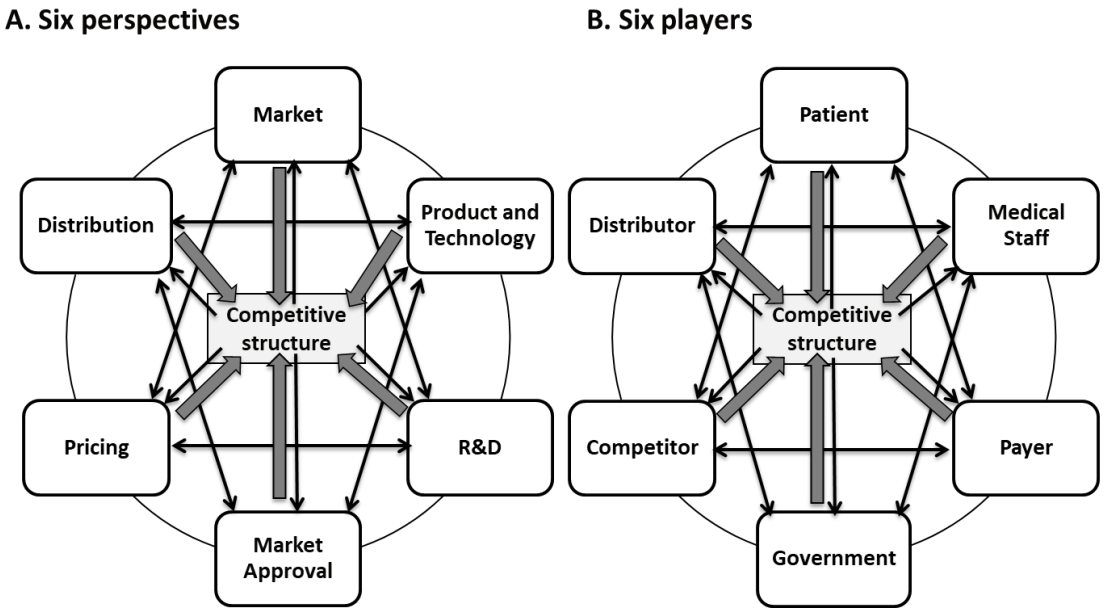


Figure 1.2. "Six perspectives" and "Six players"

In addition to the aforementioned characteristics, the pharmaceutical industry has the following features that distinguish it from other industries.

Enormous financial and time costs

The R&D of a new drug is not only costly, but also involves multiple stages that can sometimes span

over 10 years (**Figure 1.3**). Research on new drugs is typically based on a disease of interest as established through "basic research." First, researchers determine the approach to the disease and search for candidate compounds (seeds) that can trigger the desired pharmacological action. Then, they select compounds with the highest efficacy and best safety profile from among the approximate compounds through screening, and synthesize derivative compounds to investigate their efficacy and safety. Investigations are first conducted via "non-clinical research" using rats, monkeys, dogs, rabbits, and so on, with the seeds that pass the criteria going through a certain review before moving on to the next stage—"clinical research." In clinical trials, the seeds are administered to humans to evaluate their efficacy and safety. The process of clinical trials is divided into "Phase I" with a limited number of subjects, "Phase II" with a small number of patients, and "Phase III trials" with a large number of patients. A "new drug application" is submitted for those seeds that demonstrate high efficacy and a good safety profile in these studies, with the data having to undergo a round of review and approval by the Pharmaceutical and Medical Devices Agency (PMDA) before the drug can be marketed as a new drug. Even after launch, information on the drug's efficacy is continuously collected through "post-marketing surveillance," and a system is established to reflect the latest information in local medical practices in a timely manner.

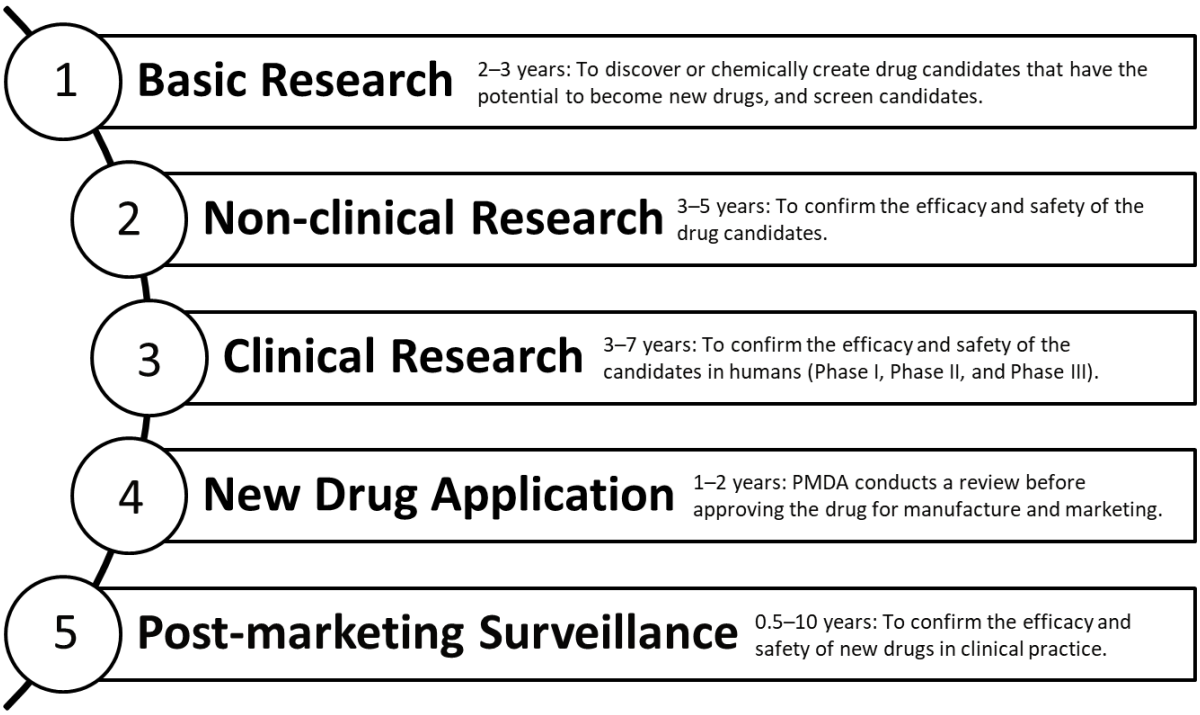


Figure 1.3. Process and timeline for the research and development of new drugs

While the probability of success in new drug development has been decreasing over the years, the costs of such development have continued to increase. In fact, the probability of successful development for clinical trials has decreased to 10% as of 2014 [3], and with the annual R&D investment of pharmaceutical companies in 2014 being USD 800 million, compared to an average annual investment of USD 500 million in the 1990s. [4]. Nevertheless, pharmaceutical companies continue to develop new therapies by undertaking R&D even as they seek to control R&D costs, such as by outsourcing R&D-related tasks to a contract research organization [5] or streamlining the development of clinical trial implementation plans [6]. Despite the low probability of success, if companies do not keep pace with scientific advancements, they will quickly lose market share to competitors developing new drugs successively, and their very survival will be threatened [7], [8].

Thus, it can be concluded that pharmaceutical R&D, although costly and time-consuming, has a very low probability of success and always poses a high risk for pharmaceutical companies.

Knowledge-intensive industry based on R&D

The R&D of new drugs is a fundamental activity for pharmaceutical companies, which is why they invest significant resources in it.

According to a report by the Statistics Bureau of Japan's Ministry of Internal Affairs and Communications, in 2018, the ratio of research expenses to the value of sales was the highest in the "pharmaceutical manufacturing industry" (at 11.10%), followed by the "professional machinery and equipment manufacturing industry" (9.26%) and the "information and communication machinery and equipment manufacturing industry" (6.39%). In terms of the expenditure per researcher, the "pharmaceutical manufacturing industry" is the highest among all manufacturing industries, at JPY 65.63 million [9]. In the pharmaceutical industry, there is a positive correlation between R&D cost and sales amount [10]. In addition, intellectual property, especially patents, plays a crucial role in enabling continued investment in the R&D of new drugs by allowing companies to recoup and profit from R&D investments. Moreover, in contrast to products in other industries, which are typically covered by a large number of patents, pharmaceutical protects have fewer patents [11]. In addition, corporate activities aimed at establishing synergies—such as entering into alliances with other companies to improve the efficiency of R&D processes and share expertise—are also pursued more aggressively in the pharmaceutical industry than in other industries [12].

Thus, the pharmaceutical industry is a knowledge-intensive industry based on R&D.

Regulated industry

The pharmaceutical industry is heavily regulated because of the characteristics of pharmaceuticals, which can significantly influence the quality of human life.

In Japan, the aforementioned research, development, production, and marketing functions of pharmaceutical companies are regulated under the Pharmaceutical and Medical Devices Act. In addition, there are several regulations and voluntary codes governing the promotion of medicines. The promotion of medicines is a marketing and informational activity that seeks to share relevant details with medical staff to help them make decisions when performing medical services. Information on products, such as the results of clinical research, is provided through published papers and conference presentations. However, this does not mean that a pharmaceutical company can undertake any kind of publicity to sell its products. There are various regulations governing the marketing of pharmaceutical products, which prohibit companies from using products for promotional activities unless they are backed by scientific evidence. Information on the efficacy and safety of individual products and their superiority or inferiority compared to other options should be statistically proven through clinical trials that comply with various regulations, just as in the case of a new drug application. In Japan, companies are prohibited from directly providing information on or advertising individual drugs to the general public, which has no expertise, because there is a high risk of inculcating a false image and misleading patients [13]. Furthermore, medicine-related costs are an important consideration in the social security and health care systems. Under the National Health Insurance (NHI) pricing system, the official prices of medicines are determined by the government.

1.2 The Present and Future of the Japanese Pharmaceutical Industry

International competition for drug discovery is becoming increasingly fierce, and it is predicted that the Japanese pharmaceutical industry will find it difficult to survive if there is no change in the industry's structure or its ability to generate innovation [1]. This section examines three external environmental factors affecting the Japanese pharmaceutical industry, which the MHLW referred to in its "Comprehensive Strategy for Strengthening the Pharmaceutical Industry" [1]. These factors are:

(1) The low growth rate of Japan's new drug market

(2) The low evaluation of innovative new drugs in terms of their price

(3) Japan's new drug development environment

The low growth rate of Japan's new drug market

This section discusses the reasons for the low growth rate of the new drug market in Japan in terms of quantity and price.

With regard to "quantity," the number of new drugs approved annually in Japan is lower than that in Europe and the United States (US) [14]. The launch of innovative new drugs will greatly contribute to the expansion of the market, especially if they enable the treatment of diseases that can currently only be treated by medical techniques other than drug therapy—such as surgical resection—with drug therapy alone. The low number of new drug approvals in Japan can be attributed to the "drug lag" problem, in which new drugs already approved for the US and European markets receive delayed approvals for use in Japan [15].

Turning to the "price" aspect, the issue largely concerns the drug pricing system. In Japan, the official price of a drug is determined by the government. As NHI prices are calculated based on the prevailing market price, which is lower than the insurance reimbursement price, the NHI prices of existing drugs are reduced each time the NHI price list is revised (**Figure 1.4**). The drug price (A) determined by the government is the price paid by the insurer and the patient for the drug. This price constitutes the selling price for medical institutions and insured pharmacies. By contrast, the medical institutions and insured pharmacies pay a purchase price (B) to wholesalers. The difference between the selling price and the purchase price (that is, A-B) is the profit earned by the medical institution or insured pharmacy. Therefore, medical institutions and insured pharmacies will try to reduce the purchase price as much as possible. However, the drug price (selling price) is periodically revised based on the prevailing market price (the purchase price). Thus, the constant pressure from medical institutions and pharmacies to reduce the purchase price also leads to a reduction in the drug price over time.

In Japan, even for innovative new drugs, the drug price will decrease cyclically during the patent period, meaning that companies take a long time to recover their investments. Compared to foreign pharmaceutical companies with a significant proportion of sales in overseas markets, Japanese pharmaceutical companies can only recover a relatively small portion of their R&D costs from the sales of new drugs. In other words, the problem with the current NHI drug pricing system is that it becomes difficult for pharmaceutical companies to recover their investments in R&D and, consequently, to direct

additional investments to the R&D of the next new drug [16], [17].

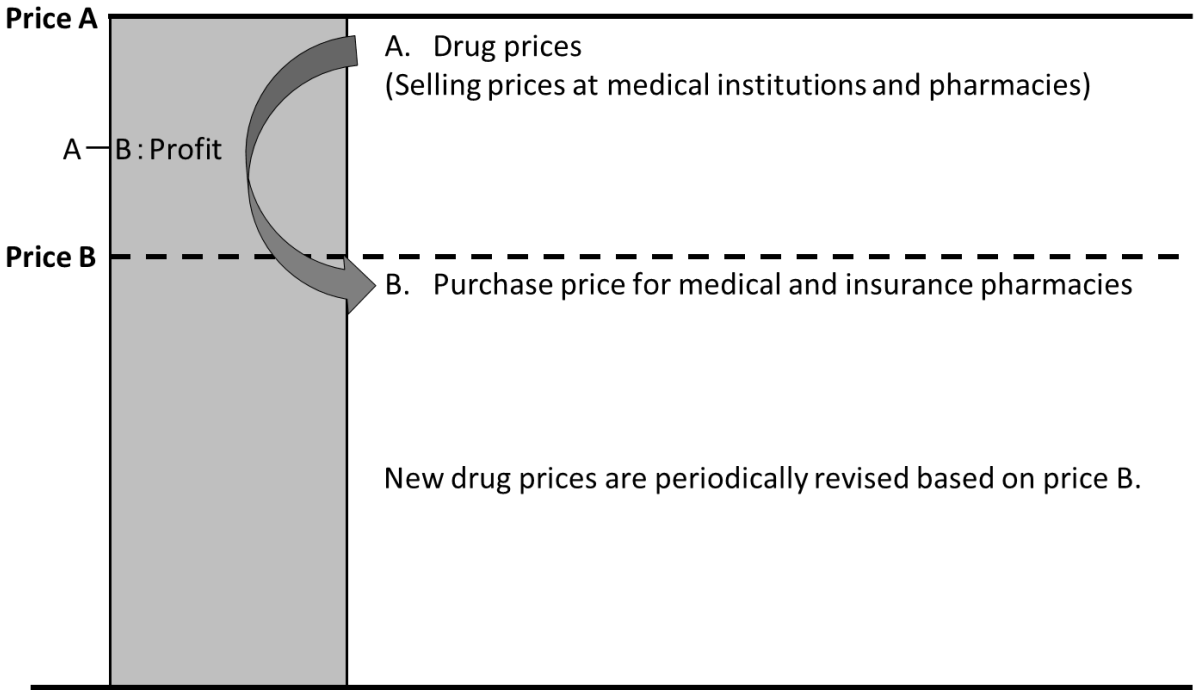


Figure 1.4. Conceptual diagram of NHI price margin

The low evaluation of innovative new drugs in terms of their price

Another consequence of Japan's NHI price system is the low evaluation of innovative new drugs. An example is the "market expansion re-pricing system." Under this system, the price of a drug is reduced when the drug is prescribed more than was initially expected. However, because of its innovation, it will continue to sell better than expected, which will depress its price. Thus, companies that create innovative medicines do not profit. In addition, because of the poor accuracy of "Re-pricing following market expansion", domestic pharmaceutical companies are at a disadvantage in terms of their international competitiveness compared to Western companies with large sales in overseas markets.

Japan's new drug development environment

Discussions involving the Japanese government on the R&D environment for new drugs have been ongoing since around 2000. For instance, the "Pharmaceutical Industry Vision" published by the MHLW in 2002 points to the slowness, low quality, and high cost of clinical trials as factors hindering the development of the industry in Japan [15]. In particular, the high cost issue remains unresolved. One

downside to this poor clinical trial environment is the overall decline in Japan's drug discovery capacity. Therefore, from the perspective of cost and efficiency, pharmaceutical companies will tend to choose Western countries, which have a better environment for clinical trials, than Japan, for drug development. When pharmaceutical companies conduct clinical trials in Europe and the US instead of in Japan, they do not accumulate the know-how to implement their findings; as a result, the environment for cultivating Japanese seeds in Japan remains immature, which may lead to a decline in the level of R&D in Japan as a whole.

Furthermore, there is a possibility that the innovation of pharmaceutical companies may not be properly evaluated as a result of Japan's unique NHI price system, and thus, pharmaceutical companies doing business in markets around the world may hesitate to select Japan as a location for the advanced development of new drugs. As a result, the structure of the Japanese and global markets may diverge, and different drugs may be used to treat the same disease in different markets.

The development of the pharmaceutical industry is highly dependent on policy. In other words, the government interferes in business activities, whether directly or indirectly. As a result, the impact of policy on management outcomes is likely to be greater in this industry than in other industries. In other words, policy considerations are essential to the analysis of this industry. To analyze policy, it is also necessary to consider the industrial structure, such as the market configuration, through the associated health care and insurance systems.

As mentioned earlier, the Japanese pharmaceutical industry is positioned as a growth industry. Japan is the second largest market in the world, accounting for approximately 10% of all pharmaceutical trade (about JPY 10 trillion) [18]. For the Japanese pharmaceutical industry to develop as a growth industry, it is necessary to develop drugs that can be sold not only in Japan but also in overseas markets. However, with the exception of the top two companies, in terms of sales, the percentage of overseas sales in domestic pharmaceutical companies' revenues does not exceed 50% (**Table 1-1**), with the companies largely relying on the domestic market [19]-[21]. However, Japanese pharmaceutical companies are gradually establishing a strong presence in overseas markets. The financial results of the 12 major Japanese pharmaceutical companies reveal that, in 2019, 10 of these companies recorded an increase in their overseas sales compared to the previous year, with the exceptions of Mitsubishi Tanabe Pharma Corp. and Shionogi Co., Ltd. Seven companies posted a double-digit growth in sales. Overseas sales accounted for 51.2% of total sales, up 3.4% from 2018. However, the overall average is only 51.2%, leaving room for further market expansion.

Table 1-1. Overseas sales ratio for major Japanese pharmaceutical companies

Company	Overseas Sales Ratio (%)				
	2015	2016	2017	2018	2019
Takeda Pharmaceutical Co., Ltd.	61.9	62.2	67.2	72.8	82.0
Astellas Pharma Inc.	63.8	63.3	67.6	69.6	73.4
Sumitomo Dainippon Pharma Co., Ltd.	53.3	55.3	60.3	63.5	63.8
Eisai Co., Ltd.	46.0	45.2	49.6	53.8	59.8
Shionogi Co., Ltd.	38.0	42.8	51.8	57.7	58.6
Otsuka Pharmaceutical Co., Ltd.	55.8	47.8	48.5	50.0	50.6
Kyowa Kirin Co., Ltd.	31.4	28.1	31.8	35.2	39.1
Daiichi Sankyo Co., Ltd.	43.7	39.1	35.6	35.9	38.1
Chugai Pharmaceutical Co., Ltd.	21.8	19.6	23.1	27.3	35.3
Santen Pharmaceutical Co., Ltd.	27.4	27.0	29.5	31.4	31.7
Ono Pharmaceutical Co., Ltd.	1.6	12.6	22.1	28.2	30.6
Mitsubishi Tanabe Pharma Corp.	27.1	24.2	26.0	27.6	17.3
Average	40.4	40.3	44.3	47.8	51.2

≥ 50 ≥ 30–49 < 30

1. 3 Cancer

As described previously, new drug development and approvals have tended to focus on UMN. In this context, the social need for medicines has also shifted to diseases with high levels of UMN, such as cancer and central nervous system diseases. This thesis presents the results of a study focusing on the anti-cancer drug market in Japan. Accordingly, this section discusses the epidemiology and UMN of cancer.

Cancer has been the leading cause of death in Japan since 1981, according to a demographic survey by the MHLW. According to the National Cancer Center, the predicted number of cancer cases in 2018 was 1,013,600 (men: 574,800; women: 438,700); furthermore, the predicted number of cases by site was as

follows: colon (152,100), stomach (128,700), lung (125,100), breast (86,500), and prostate (78,400) [22]. The predicted number of cancer deaths in 2018 was 379,900 (men: 223,000; women: 157,000), and the predicted number of deaths by site was: lung (77,500), colon (53,500), stomach (45,900), pancreas (34,900), and liver (27,000) [22].

In recent years, novel chemotherapy, molecularly targeted drugs, and immune checkpoint inhibitors have been shown to improve treatment outcomes; however, they are limited to certain types of cancer [23]. Moreover, the number of patients who can be cured via pharmacotherapy remains low [24], while the number of patients is expected to increase along with the aging of the population.

The Cancer Control Act, enacted in 2006 and partially revised in 2016, aims to promote comprehensive and systematic cancer control by establishing basic principles; clarifying the responsibilities of the national government, local governments, health insurers, citizens, physicians, and employers; and establishing basic items of cancer control. In addition, the "Expert Committee on the Future of Cancer Research" of the MHLW has consistently positioned the R&D of new drugs, a major element in cancer countermeasures, as one of the important issues facing Japanese medicine [25].

In summary, the R&D of new drugs in oncology is an area that all stakeholders—including patients, physicians, and pharmaceutical companies—are looking forward to and striving for, and its importance is immeasurable.

1.4 Problem Statement

Each country's economic situation, disease prevalence, medical environment, and pharmaceutical system differ, with medical needs becoming increasingly diverse. The largest markets for the pharmaceutical industry are the developed countries, mainly Japan, the US, and Europe. However, in these countries, rising medical costs has become a problem due to factors such as the aging of the population, and curtailing medical costs has become an important public health issue.

Particularly in Japan, the government has been promoting the penetration of generic drugs to control medical costs, and pharmaceutical companies have been struggling to develop appropriate sales strategies in response. In addition, while there is high demand for drugs for diseases with high UMN, such as cancer, the new drug market in Japan is growing at a low rate, possibly due to the low evaluation of innovative new drugs in terms of drug prices.

However, there are few reports on the Japanese pharmaceutical market in the context of promoting the industry itself, leaving substantial room for consideration. In addition, very few reports evaluate the

current NHI price system from the perspective of growing the Japanese pharmaceutical industry, creating scope for further investigation. Moreover, the term “innovative drug” seems to lack a unanimous definition—with vague criteria such as the drug meeting UMN—warranting additional studies to clarify the term as it applies to the target therapeutic area.

Therefore, findings resulting from a comprehensive consideration of the future direction of the Japanese pharmaceutical industry using the aforementioned framework (**Figure 1.2**) will not only be timely and relevant, but can also quantitatively demonstrate the characteristics of the Japanese pharmaceutical market based on the influence of the current NHI price system, and establish a clear definition of “innovative drug,” specifically for target therapeutic areas.

1.5 Research Purpose

This thesis undertakes the following work with an aim to help Japanese pharmaceutical companies create internationally competitive new drugs for both the domestic and global pharmaceutical markets. The principal focus of this thesis is the Japanese pharmaceutical market. The reasons for also studying the drug pricing system in Japan include the fact that the price is a direct factor in determining sales and these results, although preliminary, suggest that the direction of the Japanese pharmaceutical industry:

1. Defines “innovativeness” in relation to new drugs, specifically in the Japanese context and from the perspective of therapeutic areas
2. Elucidates the profile of the Japanese pharmaceutical market compared to the global market and the markets of major European and American countries
3. Considers the current status and offers a prognosis on the Japanese anti-cancer drug market
4. Discusses implications for anti-cancer drug development strategies and outlines important points to be made when filing for approval
    - Studies the sales of rare cancer drugs by pharmaceutical companies
    - Studies the contents of the package insert of each drug used in combination anti-cancer drug therapy
5. Evaluates the drug pricing policy under NHI
    - Studies NHI price calculation methods using projected sales amounts
    - Performs a trend analysis of new drugs categorized by drug price calculation method

For “Purpose 1,” the “innovativeness” of new drugs, specifically in the Japanese context and from the perspective of therapeutic areas, along with future research areas to be addressed in this thesis, are

discussed through a literature review (Chapter 2) and a comparative study between the top-selling pharmaceutical products in the Japanese pharmaceutical market and those in the Western countries (Chapter 3).

For “Purpose 2,” the profile of the Japanese pharmaceutical market is quantitatively examined by comparing it with the pharmaceutical market in major European and American countries (Chapter 3).

For “Purpose 3,” a market analysis is conducted, focusing on the anti-cancer drug market among the therapeutic areas identified through “Purpose 2,” and the current situation of the Japanese market as well as the future market structure are discussed (Chapter 4).

For “Purpose 4,” focusing on the sales of rare cancer drugs, which could potentially increase the revenues of pharmaceutical companies, and the contents of the labeling of anti-cancer drug combination therapy, new types of drug development are proposed (Chapters 5 and 6). Even though “Purpose 3” discusses the importance of the development of anti-cancer drugs in the Japanese market, it does not address the actual development strategy companies should adopt; “Purpose 4” helps fill this gap.

For “Purpose 5,” the study considers the strategies that Japanese pharmaceutical companies should adopt, from the management and policy perspectives, and evaluates whether the NHI drug pricing system can support the Japanese pharmaceutical industry, though preliminary and limited in scope (Chapters 7 and 8).

1.6 Research Hypotheses

This thesis tests the following research hypotheses, to determine the optimal R&D strategy for Japanese pharmaceutical companies, by focusing on the characteristics of the Japanese pharmaceutical market and, appraising the drug pricing system as a preliminary investigation among pharmaceutical regulations in Japan:

1. “Innovativeness” is applied to a therapeutic area as unique in the Japanese pharmaceutical market compared to the market structure of other countries around the world.
2. The structure of the Japanese market differs from that of global markets, and different drugs are often used to treat the same disease in different countries. This discrepancy is particularly pronounced in high UMN areas such as cancer and central nervous system diseases.
3. One therapeutic area that is likely to witness innovative new drugs is oncology.
4. Utilizing pharmaceutical regulations and considering the characteristics of anti-cancer drugs with the potential for high sales will enable the development of new drugs with high sales potential in

Japan.

5. The Japanese NHI price system underestimates the value of new drugs and must be restructured.

Research hypotheses and corresponding Chapters are described in **Table 1-2**.

Table 1-2. Research hypotheses and corresponding Chapters

Research Hypothesis	Corresponding Chapter
Hypothesis 1: "Innovativeness" is applied to a therapeutic area as unique in the Japanese pharmaceutical market compared to the market structure of other countries around the world.	Chapter 3
Hypothesis 2: The structure of the Japanese market differs from that of global markets, and different drugs are often used to treat the same disease in different countries. This discrepancy is particularly pronounced in high UMN areas such as cancer and central nervous system diseases.	Chapter 3
Hypothesis 3: One therapeutic area that is likely to witness innovative new drugs is oncology.	Chapter 4
Hypothesis 4: Utilizing pharmaceutical regulations and considering the characteristics of anti-cancer drugs with the potential for high sales will enable the development of new drugs with high sales potential in Japan.	Chapter 5 Chapter 6
Hypothesis 5: The Japanese NHI price system underestimates the value of new drugs and must be restructured.	Chapter 7 Chapter 8

1.7 Research Design

1.7.1 Description of the Research

This is a database research focusing on the Japanese pharmaceutical market designed to help Japanese pharmaceutical companies create internationally competitive new drugs in the domestic and global pharmaceutical markets. A preliminary evaluation of the Japanese pharmaceutical regulation scheme is also conducted, focusing on the drug pricing system. To summarize, the main theme of this research is

the Japanese pharmaceutical market. A preliminary investigation on the drug pricing system is also conducted to augment the discussion. Hence, this research employs a database research design to both allow access to the Japanese pharmaceutical market and drug pricing system and to derive additional data on the combination.

Taken together, these perspectives clearly establish the strategies that should be adopted by Japanese pharmaceutical companies, not only to contribute to the development of the pharmaceutical industry, but also to ensure the timely provision of innovative new drugs to Japanese patients.

1.7.2 Rationale for Research Design

1.7.2.1 Rationale for Assessing the Japanese Pharmaceutical Market in Primary Analyses

There are few published reports on the Japanese pharmaceutical market from the perspective of promoting the industry itself, and there is much room for investigation. In addition, there does not appear to be a consistent definition of the term “innovativeness”, and additional investigations are needed to define the term to better represent the target therapeutic area. Therefore, on the basis of the data above, the Japanese pharmaceutical market is selected as of main interest for this research.

1.7.2.2 Rationale for Assessing the Drug Pricing System in Exploratory Analyses

In the evaluation of the pharmaceutical regulatory scheme, a consideration of the relevant pharmaceutical regulations, such as the health care system and reimbursement system, as well as the drug pricing system, are required. However, since R&D strategies discussed in this thesis depend highly on the drug pricing system and it suggests that the Japanese drug pricing system may be underestimating the value of new drugs, though preliminary, the research focuses on the drug pricing system. Data generated from this limited research inform R&D outputs with incentives and disincentives as part of the totality of evidence generated to inform the risk-benefit profile of the Japanese drug pricing system. As part of the research design, adequate steps have been taken to ensure the validity of the data in this limited scope of the research focusing exclusively on the drug pricing system.

1.8 Thesis Structure

This thesis consists of seven research themes, including the literature review (**Figure 1.5**). The primary focus of this thesis is the Japanese pharmaceutical market. The rationale for also investigating

the Japanese drug pricing system is on the basis that R&D strategies discussed in this thesis depend highly on the drug pricing system and that these results, although preliminary, provide some insight into the direction of the Japanese pharmaceutical industry. Given the limited evidences on the Japanese pharmaceutical market and the possibility of the Japanese drug pricing system underestimating new drugs, this thesis will allow for evaluation of the characteristics of the Japanese pharmaceutical market including the drug pricing system among the pharmaceutical regulations in Japan.

Chapter 1 discusses the problem statement, the purpose of this research, as well as the research hypotheses.

Chapter 2 summarizes previous studies related to this thesis, and the current state of the Japanese pharmaceutical industry and related matters, clarifying the positioning of this thesis.

Chapter 3 elucidates the characteristics of the Japanese pharmaceutical market using the Gini coefficient and the Herfindahl-Hirschman Index. The top 100 top-line market data for prescription drugs in Japan and four major international markets are compared, and the uniqueness of the Japanese pharmaceutical market is quantitatively verified.

Chapter 4 investigates the current status and prospects of the Japanese anti-cancer drug market. The sales amount and prescription volume of anti-cancer drugs by category from 2010–2016 are analyzed, and categories with high sales potential in the current and future Japanese market are identified.

Chapters 3 and 4 discuss the R&D strategy of pharmaceutical companies using the “product portfolio” framework.

Chapters 5 and 6, focusing on the increased revenues that rare cancer drugs will bring to pharmaceutical companies as well as the contents of the labeling of anti-cancer drug combination therapy, propose new types of new drug development that Japanese pharmaceutical companies should pursue to achieve high sales. This involves the following two studies:

- A study of the sales of rare cancer drugs by pharmaceutical companies
- A study of the contents of the package insert of each drug used in combination anti-cancer drug therapy

Chapters 5 and 6 also present areas that pharmaceutical companies should focus on in relation to their R&D activities for anti-cancer drugs, using the “capabilities” framework.

Chapters 7 and 8 evaluate Japan’s NHI pricing system among pharmaceutical regulations in Japan through two studies, and investigate whether the current system can promote the Japanese pharmaceutical industry:

・ A study of NHI price calculation methods using projected sales amounts

・ A trend analysis of new molecular entities (NMEs) categorized by drug price calculation methods

Chapters 7 and 8 also discuss the impact of NHI pricing system among pharmaceutical regulations in Japan on the R&D activities of pharmaceutical companies using the “external” framework.

Finally, Chapter 9 presents a summary of this thesis. The research results from the seven themes are outlined; their academic contributions and implications for business are presented; and outstanding issues are discussed.

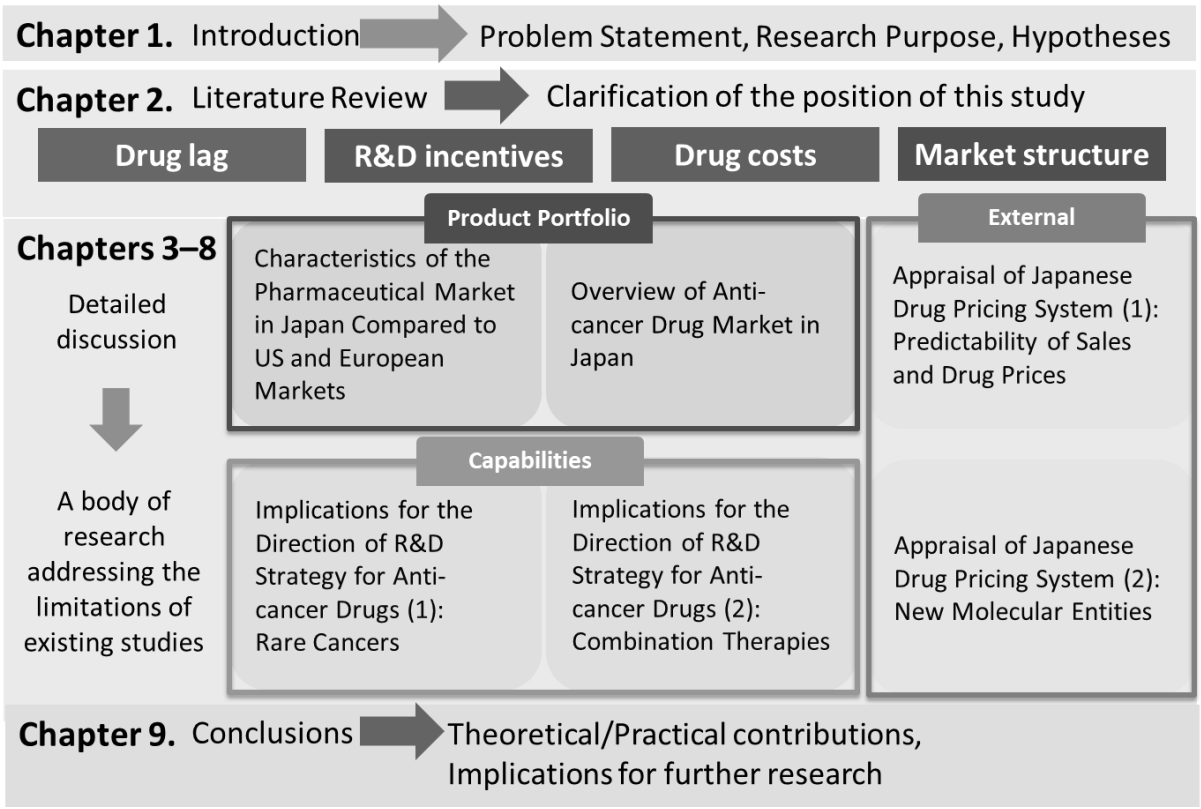


Figure 1.5. Thesis structure

1.9 Thesis Highlights

What is the current knowledge on the topic?

The mission of pharmaceutical companies is to contribute to the human health through R&D of innovative new drugs. This requires the definition of innovative drugs and R&D strategies for such drugs so that pharmaceutical companies can pursue R&D activities with the proper directions. However, there are limited studies that have investigated these topics scientifically.

What questions did this thesis address?

What drugs can be considered innovative new drugs?

Which therapeutic areas should be addressed in R&D projects?

Can the current drug pricing system in Japan among pharmaceutical regulations serve as a regulation to encourage R&D of those drugs?

What does this thesis add to our knowledge?

This thesis presents a definition of innovative drugs and possible R&D strategies for Japanese pharmaceutical companies to R&D innovative new drugs, based on the primary investigation on the characteristics of the Japanese pharmaceutical market and the preliminary assessment of the Japanese drug pricing system. The main findings are as follows: Innovative new drugs should include anti-cancer drugs. Several specific R&D strategies in this therapeutic area highlighting rare cancers and combination therapies are proposed. While only preliminary findings, the current drug pricing system should be considered as a potential disincentive for R&D of innovative new drugs.

How might this change pharmaceutical companies' R&D strategy?

This should allow for more innovative new drugs R&D by pharmaceutical companies and show one of the possible paths for the Japanese pharmaceutical industry. The findings facilitate R&D of innovative new drugs, such as anti-cancer drugs, in the pharmaceutical industry and enable the growth of Japanese pharmaceutical industry. Pharmaceutical companies should select and implement their appropriate strategies depending on their R&D capabilities between the possible strategies provided in this thesis.

2. Literature Review: Recommendations for Future Research

2.1 Introduction

2.1.1 The Japanese Pharmaceutical Industry

Despite being one of the largest markets in the world, Japan's pharmaceutical market continues to post the smallest average annual growth rate—approximately 1.0% between 2014 and 2018—among developed countries [26]. A complex regulatory process and a strict price control policy, including regular price cuts, have challenged pharmaceutical companies' R&D of innovative new drugs. Another reason for the stagnant market is the government's active promotion of generic drugs since 2007, as part of a wider initiative to control increasing health care expenditures [27]. Furthermore, in 2013, the government announced a 5-year plan to increase the proportion of generic drug prescriptions to over 60% of all prescriptions by 2018 [28], thereby accelerating the penetration of generic drugs. Moreover, the imminent expiry of certain drug patents is forcing Japanese companies to adapt to the changing market environment, leading them to either explore other business models or participate in strategic alliances and acquisitions.

In this context, since 2000, there has been growing expectation that the pharmaceutical industry will support Japan's growth and contribute to national innovation. The MHLW has articulated its vision for the pharmaceutical industry several times—in 2002, 2007, and 2013 [29], [30], [15] (**Table 2-1**).

Table 2-1. The MHLW's vision for the pharmaceutical industry

Title	Date	Sub-title
Pharmaceutical industry vision	April 9, 2002	Strengthen the international competitiveness of the pharmaceutical industry supporting the century of life
New pharmaceutical industry vision	August 30, 2007	Aim for an internationally competitive, innovative industry
Pharmaceutical industry vision 2013	June 26, 2013	Different actions to overcome international competition in the research and development of new drugs

In the 2002 vision document, in light of the intensifying competitive environment due to industrial

reorganizations—mainly in Europe and the US—the MHLW stated that there should be at least two or three Japanese companies with global product portfolios (“mega pharma”).

The 2007 vision document noted the increasingly competitive landscape of R&D in relation to antibody drugs and molecular targeted drugs instead of small molecule drugs—which, till then, had been considered “blockbuster drugs”—as well as changes in the global market environment. The MHLW stated that there should be at least one or two companies that could take on the role of “global mega pharma” and adapt to changes in the new drug development environment. Moreover, even small companies should grow by exploiting the results of innovative R&D activities (“global niche pharma”), and some companies should strengthen their international competitiveness by focusing R&D specifically on their specialties (“global category pharma”).

The 2013 vision document identified an environmental change whereby medical needs had expanded from lifestyle-related diseases to therapeutic areas with high UMN, such as oncology or neuroscience, and an increased focus on antibody drug R&D. The 2013 vision emphasized that the pharmaceutical industry should go beyond the categories reported in the past two visions, creating an entirely new business model, and that the Japanese pharmaceutical industry should deliver innovation in the life sciences area.

The 2013 vision also specified various industrial promotion actions such as the expansion of tax support for R&D and a reevaluation of the drug pricing system. The relationship between the drug pricing policy and industrial promotion is described in the next section.

2.1.2 The Japanese Drug Pricing System

In Japan, the government sets the initial drug prices. To control increasing health care costs, the government has been revising drug prices biennially. The latest pricing reform was in April 2020.

The drug pricing process is described in **Figure 2.1** [31]. When new drugs are to be launched, pharmaceutical companies must submit a price listing application, and the 1st Drug Pricing Organization discusses an appropriate pricing plan. The companies can express opinions on whether they agree with the decision. A pricing plan is then announced, and the drug price is fixed if there are no further objections. If an objection is raised, the price is re-evaluated at the 2nd Drug Pricing Organization, and based on this second discussion, the pricing plan is approved at a general meeting of the Central Social Insurance Medical Council, which leads to a price listing; this happens four times a year—in February, May, August, and November.

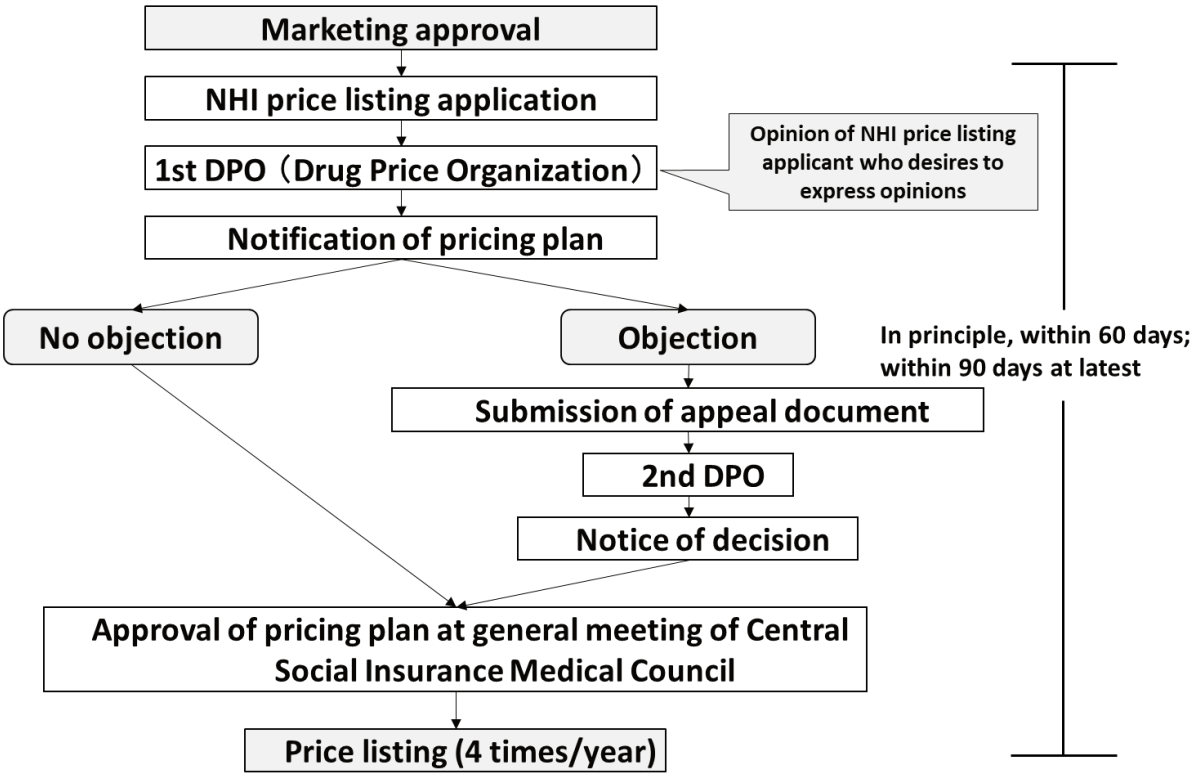


Figure 2.1. Drug pricing process in Japan

The government sets the initial price based on two primary methodologies: the "comparative method (CM)" and the "cost calculation method (CCM)," as described in **Figure 2.2** [31]. If the new drugs are similar to drugs already available in the market, the CM is applied, and a certain premium is awarded, if appropriate. If there are no similar drugs in the market, the CCM is used to set the price, considering certain costs (manufacturing, sales and general administration, operating profit, distribution and marketing, consumption tax, etc.).

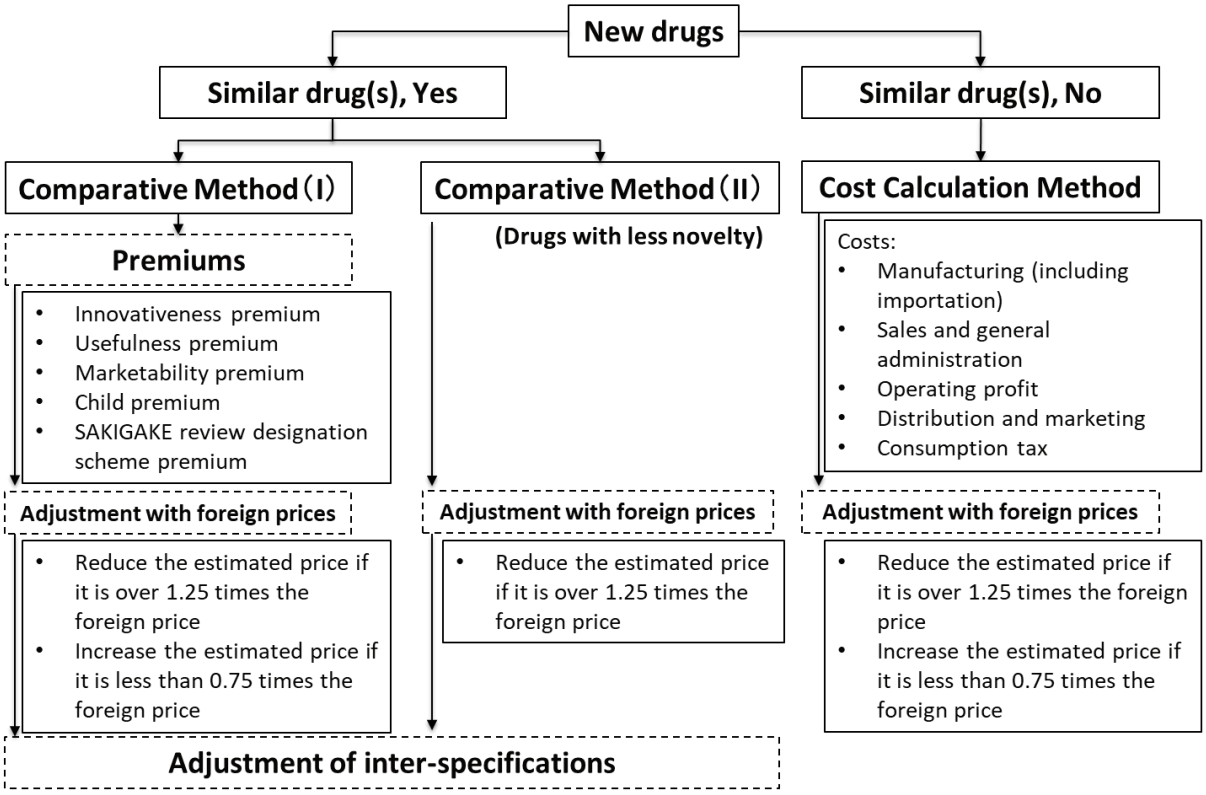


Figure 2.2. Price calculation methodologies for new drugs in Japan

Notably, there are two other drug pricing systems in Japan—the "price maintenance premium (PMP)" (**Figure 2.3**) and "re-pricing following market expansion" (**Figure 2.4**) [31].

The PMP adds price premiums to the pricing of innovative new drugs, and grants price protection for the duration of the period of exclusivity or patent enforcement. This system encourages pharmaceutical companies to develop new drugs early because there is a mechanism in place to obtain reimbursements that would reduce R&D costs.

The "re-pricing following market expansion" scheme reduces drug prices (by up to 25%) when the annual sales of a drug exceed its estimated figure to some extent. Furthermore, some drugs with large annual sales are treated as an exception to the rule, with their prices being reduced by up to 50%. This exceptional re-pricing was applied, for instance, to nivolumab, since the drugs used in the new indication of non-small cell lung cancer, for which there is a large patient population relative to the first indication of melanoma, are expensive; the drug price was revised downward by 50% on February 1, 2017 [32].

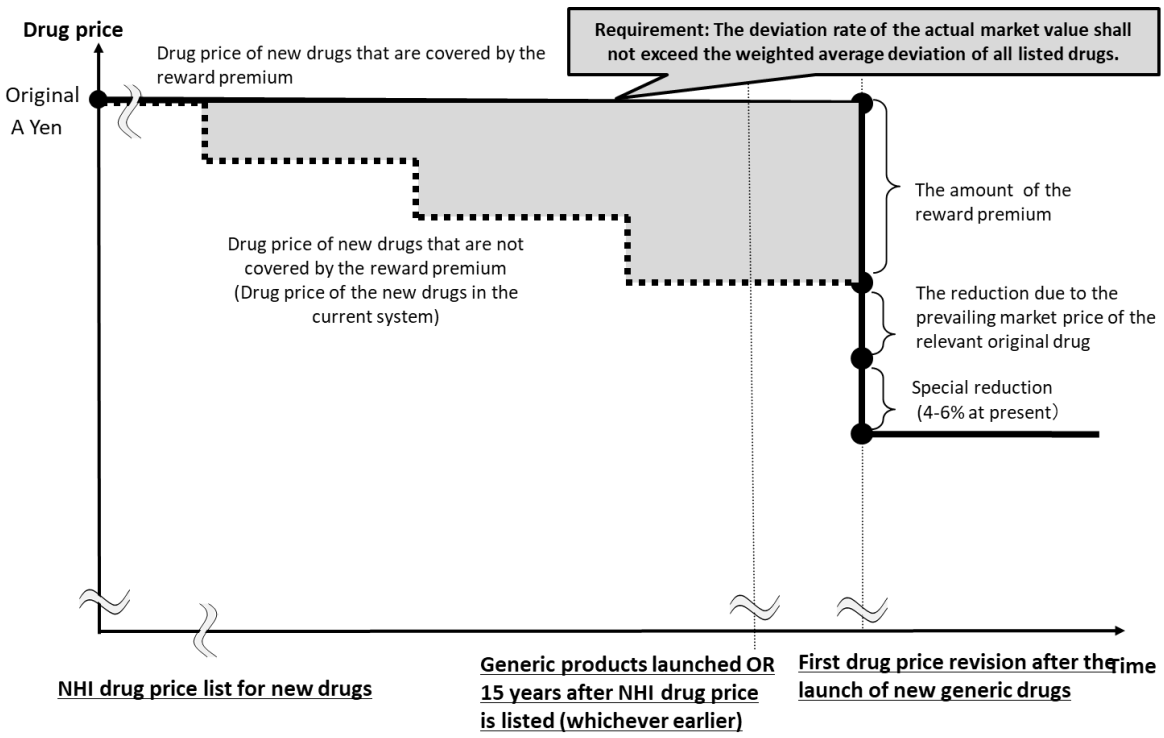


Figure 2.3. Price maintenance premium

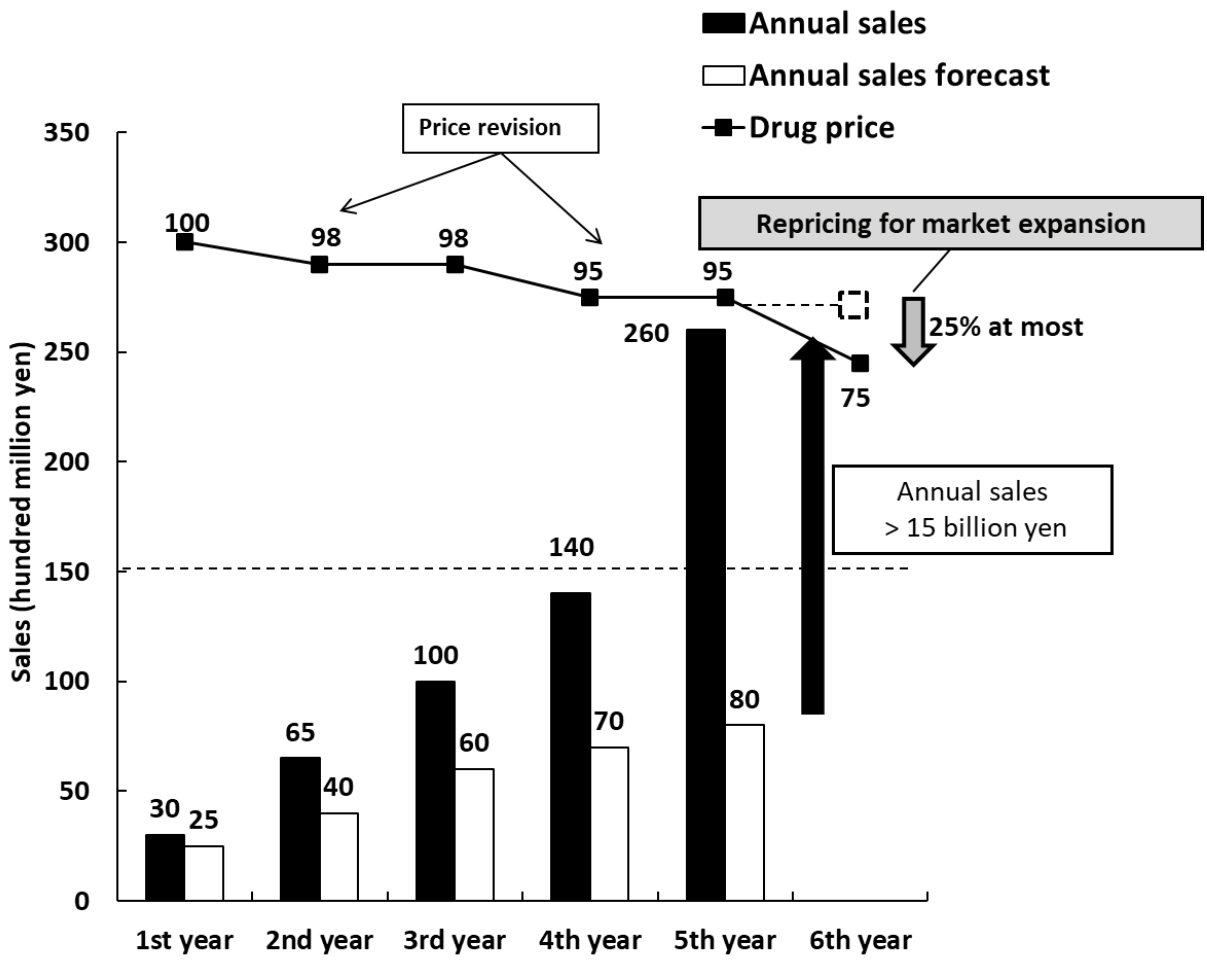


Figure 2.4. Re-pricing following market expansion

In summary, these pricing systems contribute to maintaining and improving R&D incentives for pharmaceutical companies and to sound health insurance finance.

2. 2 Scope and Justification of Review

In recent years, the promotion of the pharmaceutical industry has become a key policy issue in Japan. Factors that limit access to new drugs in Japan include problems in the Japanese clinical trial environment, such as high costs, a lack of clinical trial staff, and problems with regulatory matters. In this context, several efforts have been made to improve Japan's clinical trial environment and regulatory process, in order to shorten the drug lag. However, due to the wide variety of factors hindering access to new drugs, deriving a comprehensive solution to these issues requires examining them from a wider perspective.

Figure 2.5 depicts the issues involved in improving access to new drugs in Japan. The challenges can be broadly divided into two categories: “encouraging pharmaceutical innovation” and “shortening drug lag.”

Figure 2.6 shows a general overview of the drug lag, including the development lag and approval lag. To solve the drug lag problem, it is necessary to effectively initiate clinical trials in Japan and improve the approval process. In terms of “shortening the development lag,” the timing of the start of clinical trials seems to be strongly related to the characteristics and structure of the Japanese pharmaceutical market. With regards to “shortening the approval lag,” as discussed, improvement measures have been implemented, such as improving the clinical trial environment and the performance of review systems, and promoting global clinical trials.

If the R&D activities of pharmaceutical companies are economically rational, R&D activities in Japan should be prioritized by pharmaceutical companies, given that the resource investments for R&D can be sufficiently recouped by the launch of new drugs in the Japanese market. In other words, improving the clinical trial environment and shortening the drug lag will motivate pharmaceutical companies to develop new drugs in Japan.

Furthermore, the characteristics and structure of the Japanese pharmaceutical market are associated with the profits that pharmaceutical companies can potentially obtain from launching new drugs in Japan. If the profits do not sufficiently exceed the cost of new drug development, companies will place lower priority on R&D in Japan. In addition, the characteristics and structure of the Japanese pharmaceutical market are also considered to be a factor in determining the number of new drug launches. To increase the number of new drugs, it is necessary to increase the number of products developed in Japan. One effective method is to encourage both Japanese and global pharmaceutical companies to develop Japanese-origin new drugs. In this context, pharmaceutical innovation can be encouraged by “increasing the R&D activities of global companies in Japan,” “increasing the R&D activities of Japanese companies in Japan,” and “increasing the R&D activities of Japanese companies outside of Japan.” To achieve this, it is important to have an attractive market to recover R&D investments by launching the new drugs in Japan. Therefore, the above three activities can be reclassified into the core objective of “creating a dynamic market structure”—an environment that ensures adequate incentives for innovative drugs.

The Japanese market includes certain inherent factors that suppress growth in the new drug market, such as the constant decline in drug prices through regular price revisions. This factor may make it more

difficult for pharmaceutical companies to quickly recover their R&D investments. Therefore, a market structure that enables early recovery of R&D investments is needed. Therefore, it is necessary to "improve R&D incentives for innovative new drugs through the Japanese drug pricing system" and "suppress rising drug costs through the drug pricing system."

This sub-section discusses the relationship between new drug access and market factors, to understand the current status of new drug access and the characteristics and structure of the Japanese pharmaceutical market; it also compares the Japanese pharmaceutical industry to that of other countries. It is important to understand the complexities of the Japanese pharmaceutical market and the limitations and challenges that future studies must address, to make the pharmaceutical industry in Japan more productive.

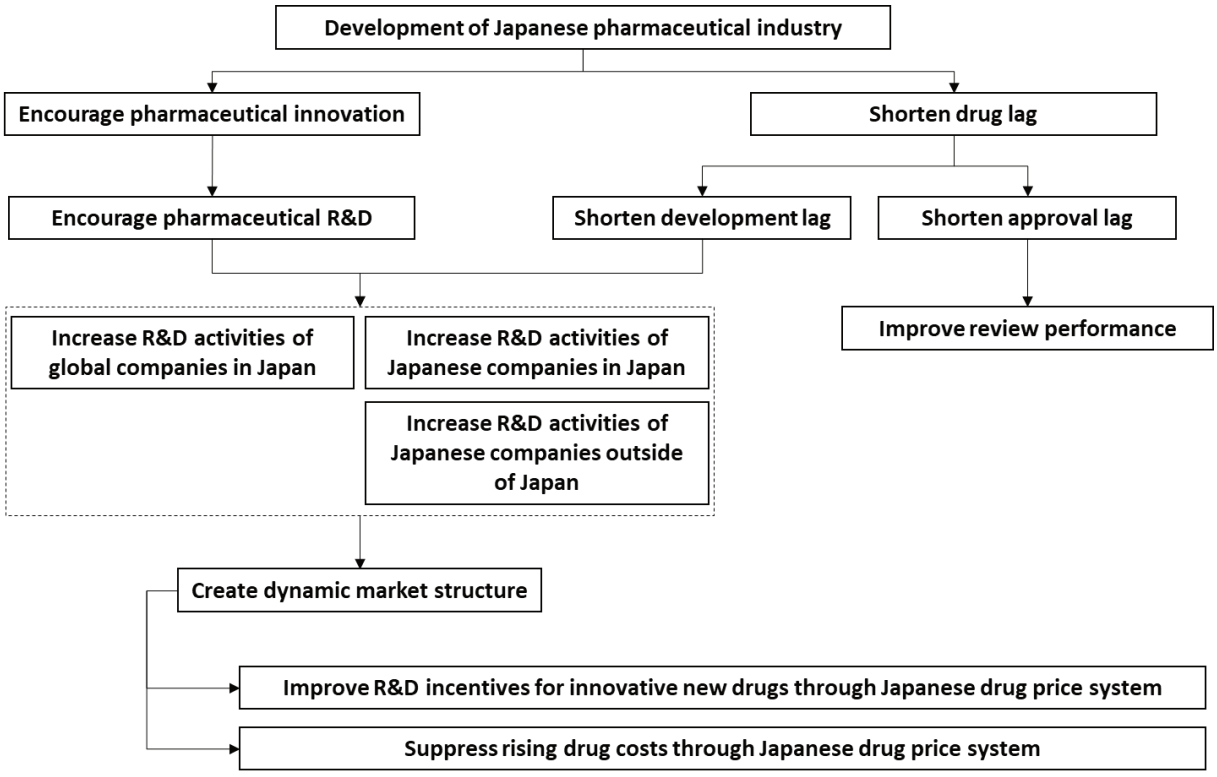


Figure 2.5. Scope of the literature review

2. 3 Drug Lag

There are two types of drug lags: the first is a development lag, or the time taken for clinical development; the second is an approval lag, or the time taken from the submission of a new drug application to its approval (**Figure 2.6**). **Table 2-2** presents the summary of a drug lag relating to new molecular entities (NMEs) in Japan [33]. Overall, the drug lag has been shortened and it is now less than 1 year. An overview of NMEs along with the line extension, is presented in **Figure 2.7**.

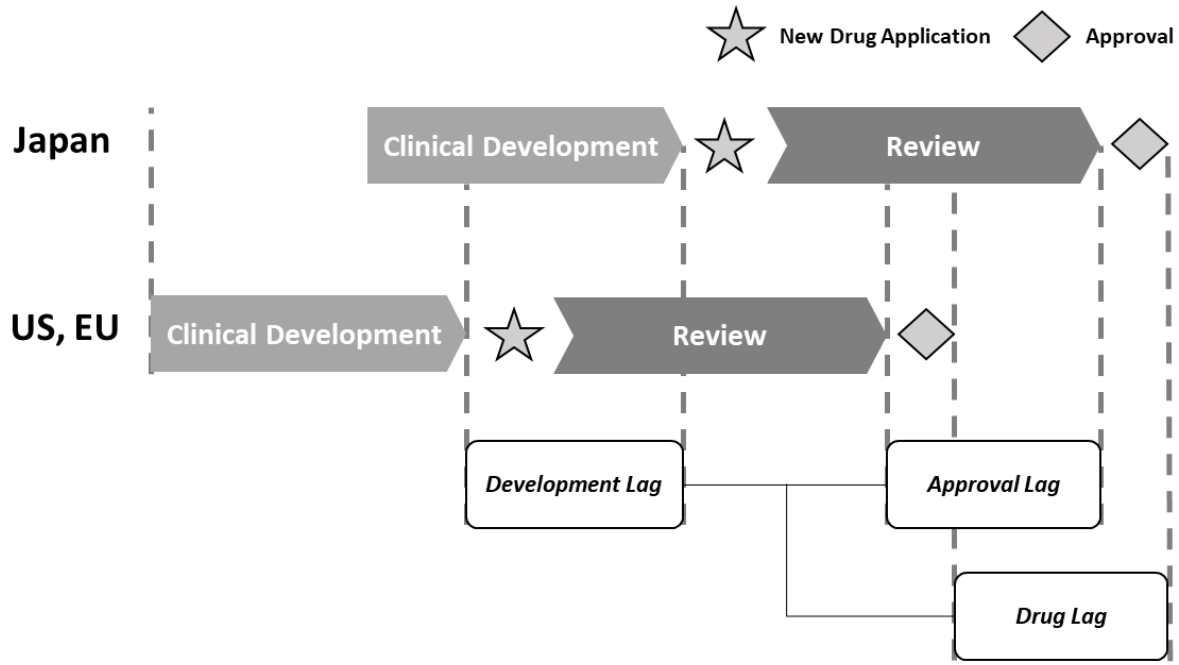


Figure 2.6. Framework of drug lag

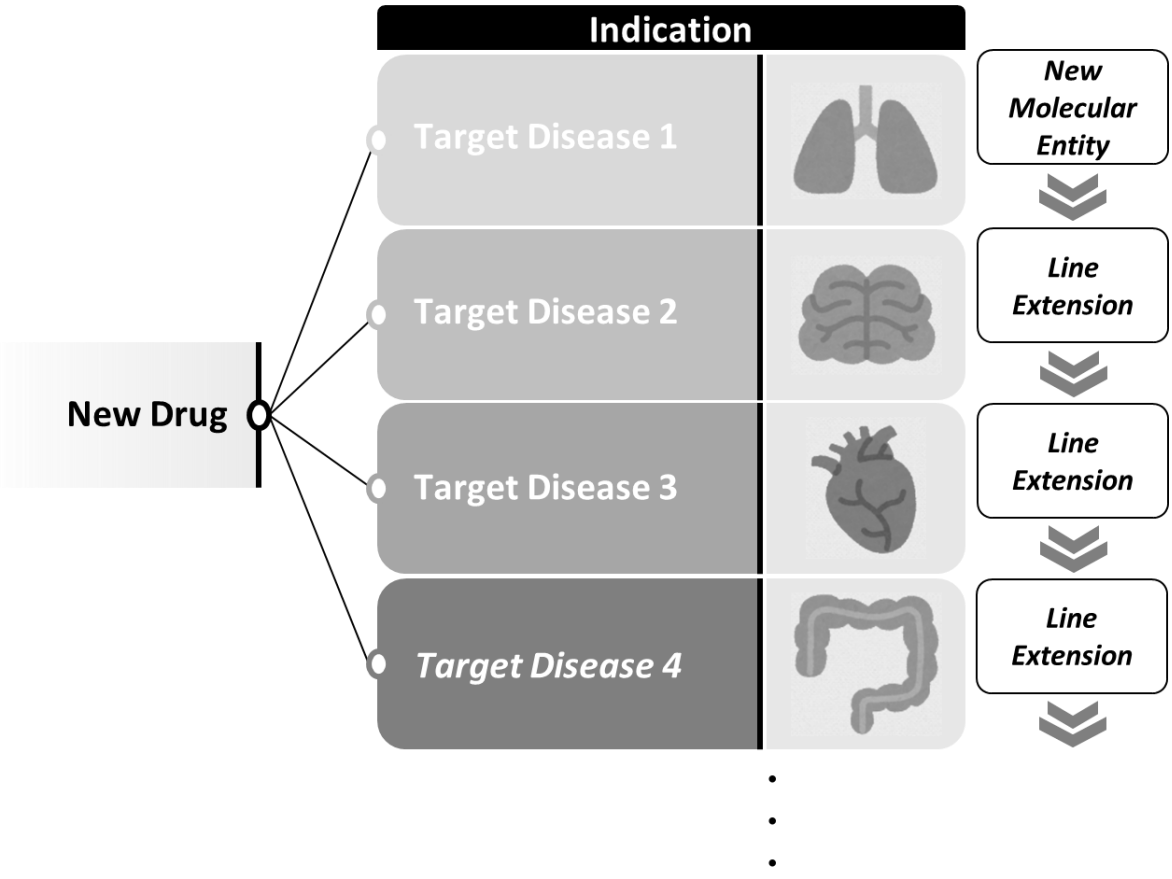


Figure 2.7. Outline of new molecular entity and line extension

However, the probability of the technical success of the clinical development of investigational drugs is extremely low. The success rate—from Phase 1 to approval—for lead indications in all therapeutic areas is reported to be 15.3% [3], while that for oncologic agents is even lower (3.4% [34] and 13.4% [35]). Indeed, the percentage of clinical development failures in oncology is reported to be 32%—highest among all therapeutic areas [36].

In this context, the Japanese health authorities—the MHLW and the PMDA—have implemented countermeasures to shorten the drug lag in Japan.

The following sections include detailed discussions on each lag.

Table 2-2. Drug lag for NMEs in Japan

	2014	2015	2016	2017	2018
Development lag (Year)	1.1	1.7	1.0	0.2	0.7
Approval lag (Year)	0	0	0	0.2	0.2
Drug lag (Year)	1.1	1.7	1.0	0.4	0.9

Development lag: Median time difference in new drug application submissions for NMEs between Japan and the US
Approval lag: Median time difference in regulatory review of NMEs between Japan and the US
Drug lag: Development lag + Approval lag.

2. 3. 1 Development Lag

The PMDA and the pharmaceutical industry has minimized this lag in recent years.

The PMDA has issued various guidance documents such as on global clinical trials [37], [38] and first-in-human clinical trials [39], to promote global clinical development in Japan. As a result, the number of global clinical trials has increased between 2008 and 2017 [40].

From the industry perspective, pharmaceutical companies have been globally implementing effective clinical development strategies, utilizing the aforementioned guidance issued by the PMDA. Pharmaceutical companies have been strategically utilizing Asian global clinical trials [41], [42] bridging strategies [43] and Japan's participation in global clinical trials [44]-[46]. As a result, several reports have indicated a decrease in Japan's drug lag in anti-cancer drug development, and an increase in the clinical development of oncologic agents, including cancer immunotherapy [47]-[49].

To summarize, the development lag in Japan has decreased because the delay in the initiation of clinical development, considered the key cause of the drug lag in Japan, has been mitigated as a result of various actions taken by the PMDA and pharmaceutical companies. However, certain drug-lag related problems continue to persist—specifically in relation to rare cancers [50]. Moreover, the R&D efficiency of the Japanese pharmaceutical industry has not improved despite the increasing R&D expenditure [51]. Pharmaceutical companies choose to delay the launch of new drugs in Japan to maximize profits worldwide, implying that the pharmaceutical companies will not select Japan as their first choice for new drug development [52]. This suggests that Japanese pharmaceutical companies should revisit their R&D activity management not only to diminish the drug lag, but also to promote the Japanese pharmaceutical industry.

2.3.2 Approval Lag

This lag has been addressed only by the PMDA.

To minimize the approval lag, the PMDA has enhanced resources so that reviewers can conduct a quick review of the new drugs [53]; this countermeasure has been reported to be effective in shortening the approval lag [54]. Indeed, a reduced review time has been reported for oncologic agents, which have the lowest success rate, as discussed previously [55]. A downward review-duration trend has also been reported for other therapeutic areas [56], [57].

Overall, the countermeasures pursued by the PMDA have been effective. Furthermore, the PMDA has shared its vision and strategy for the simultaneous development of new drugs on a global scale, increasing the number of global human resources [58].

Although arguable points remain, this topic has been comprehensively addressed by several studies. The next sections discuss the literature review results from the perspective of "encouraging pharmaceutical innovation", and identify areas for further research.

2.4 Encouragement of Pharmaceutical Innovation

This section first presents a definition of "pharmaceutical innovation" through a related literature review, before delving deeper into the topic.

A systematic literature review regarding the definition of "innovativeness" in drug development [59], uses the "counts of new products" to define pharmaceutical innovation. By contrast, a survey of physicians equates innovation with the development of "highly efficacious new drug classes that address previously clinical needs" [60]. Another article reports a similar definition, using the words "radical innovation" [61]. This survey research uses "number of NMEs that address UMN" as the definition of "pharmaceutical innovation" because it enables quantitative investigation and also encompasses all the previous definitions.

Japan is one of the leading countries in terms of new drug development and clinical information networks; most new drugs are developed by pharmaceutical companies [62], [63], suggesting that the pharmaceutical industry has a critical role in the delivery of innovative drugs in Japan. In 1986–2014, 54% of biologic NMEs and 24% of small-molecule NMEs were first-in-class (FIC) drugs, which use a new and unique mechanism of action for treating medical conditions [64]; this indicates that the biologic NME market has been evolving.

Based on these discussions, the following sections discuss how to increase the number of NMEs that

address UMN in Japan, by exploiting the characteristics of the Japanese R&D environment.

2.4.1 R&D activities by Pharmaceutical Companies

Sustaining a competitive advantage is critical to R&D strategy. There are numerous studies elucidating the characteristics that result in a competitive advantage for pharmaceutical companies and promote R&D activities. The technological capabilities of pharmaceutical companies are considered to play key roles in developing a competitive advantage [65]. Discussions on increasing companies' technological capabilities focus on two mechanisms: strategic alliances and mergers and acquisitions (M&A).

Strategic alliances facilitate a competitive advantage through resource congestion [66]. Strategic alliance partners are likely to be those that focus on new portfolio resources as organizational slack—defined as excess capacity—increases [67]. Partners can also include rival pharmaceutical companies [68], and their asset accumulations can be strengthened amid rapid technological changes in the industry [69]-[71], suggesting that strategic alliances can play a key role in the pharmaceutical industry by stimulating R&D activities.

The past few decades have witnessed numerous M&As in the pharmaceutical industry, such as Takeda's recent acquisition of Shire (in addition to many more M&As at a smaller scale). As M&A is known to be effective in increasing the R&D activities and strategic alliances of pharmaceutical companies, it is important to assess the productivity of companies following an M&A [12], [72]. M&As may lead companies to become multinational. A previous study reports an S-shaped relationship between multinationality and performance for a sample of Japanese companies [73], which is not the case with companies in the US [74]. Although the relationship between multinationality and performance demonstrates regional differences, the advantages of M&As, such as an increase in R&D performance, have been confirmed in Japanese pharmaceutical companies [75], suggesting that M&A is central to encouraging R&D activities.

To summarize, there are many articles discussing the "system" and "its mode of actions," such as strategic alliances and M&As, and their effects on the promotion of R&D activities. These are considered to be effective countermeasures for increasing R&D activities, especially considering the characteristics of the pharmaceutical industry, such as the importance of nonmarket strategies under regulatory bodies [76], informal collaboration structures within the industry [77], drastic changes in the drug discovery approach from "target based (target selectivity)" to "functional based (biological effect)" [78], and the emergence of biotech sectors [79]. However, detailed discussions are critically lacking.

There is no comprehensive, empirical, or concrete discussion on the optimal therapeutic area for the promotion of the pharmaceutical industry. This gap is even more evident in the context of the Japanese pharmaceutical industry, which has unique features such as a strict drug pricing policy. This warrants future studies to identify the right direction—specifically for the Japanese pharmaceutical industry.

2.4.2 Effects of Price Control Strategy on Pharmaceutical R&D

This section reviews the issue of Japan's drug pricing policy by referring to selected articles and emphasizes the need for the reconstruction of the drug pricing system. It discusses the factors influencing drug prices and policies as well as measures to reduce the rising costs of drugs, in order to sustain universal health insurance and promote innovation [80]. To ensure the soundness of health insurance finance, it is important to reduce unnecessary financial burdens on patients and increase incentives on drug prices so as to promote the R&D of pharmaceutical companies. Several articles have discussed the reform of the Japanese drug pricing system from both perspectives [16], [81]-[83].

A multitude of factors drive Japan's significant expenditure on pharmaceuticals. The major factors include the prices of branded medication [84] and the low penetration rates of generic drugs [85]. As described, there have been regular price revisions. This price cut policy has been reported as an effective countermeasure in controlling the rapid growth of medication expenditures. For instance, studies have empirically clarified this policy's effectiveness in the Chinese market, focusing on the oncologic agents available there [86] as well as in comparison with other Asia-Pacific regions [87]. Moreover, the regulation of drug prices in the Taiwanese market has been reported to have a positive impact on medication expenditures [88]. Recently, a critical review found little evidence of the positive effects of government drug price control policies in the context of R&D promotion [89]. Indeed, government drug price control delays the adoption of generic drugs [90]; this delay has also been reported in relation to new drugs [14], [91]-[93], lowering the investment in the pharmaceutical industry [94] by affecting companies' profitability [95]. In summary, the drug pricing system affects the R&D policy for both new and generic drugs. Higher drug prices for innovative products are known to have positive effects on R&D activities [96]. A nonlinear relationship between sales and R&D intensity has also been reported for European companies [97]. In this context, the price maintenance premium in Japan is an effective way to promote R&D. The premium rates are approximately 10% in the CM [98], accelerating the development of new drugs that can meet high medical needs, such as in the case of oncologic agents and drugs in neuroscience [99]-[101].

Another policy that assists with controlling drug costs is reference pricing. Many countries have adopted this system as a reimbursement system for pharmaceuticals. Under this policy, drugs are clustered and a reference price is defined for each cluster. Drugs can be clustered based on several criteria such as mode of action. The payer reimburses no more than the reference price for each drug in that cluster. If patients buy certain drugs at a price lower or equal to the reference price of that cluster, the drug is reimbursed up to the reference price value. If the purchased drug is priced higher than the reference price, patients pay the difference between the reference price value and the actual drug price. This system has two known challenges [102]. First, if there is no reference drug in the market, the drug will be clustered with other expensive procedures, which will have negative effects in terms of increasing health care expenditures. Second, if there is no innovation in pharmaceuticals, and existing drugs are old, the drug prices will be fixed at lower levels, which will decrease the profit of pharmaceutical companies. As evidence of the first perspective, an article focusing on France's market has reported that the magnitude of decrease in health expenditures might depend heavily on the degree of cost-reducing innovations [103]. Reference pricing policies such as minimum and linear policies are reported to lead to an increase in health care expenditures [104]. As evidence of the second perspective, fixed prices potentially cause the reference price system to discourage R&D activities by modeling and simulation [105]. Reference price was reported to be a function of R&D incentives only under certain conditions, suggesting that the reference price does not always produce competitive situations in which R&D activities are stimulated [106]. Similar discussions focusing on the effects induced by the reference price on the Japanese market focus on Germany's reference pricing system [107]; the reference price system does not always lower pharmaceutical companies' profits, indicating that it does not always lower R&D incentives. The results of a recent systematic review indicate that uncertainties remain in the association between reference pricing policy and R&D investments, indicating a strong need for further evidence generation [108].

Collectively, drug prices and the profits of pharmaceutical companies are known to have positive impacts on the R&D of new drugs, and the drug pricing policy plays a central role. Setting high drug prices is considered to encourage R&D such as through the price maintenance premium in Japan (**Figure 2.3**). However, further research is warranted to discuss the reference pricing system.

Previous articles have reported that the market prices of medical products in Japan are higher than those in the other developed countries such as the US [109]-[112], suggesting that Japan's competitive environment is well-organized, which is likely to stimulate new drug R&D [113]. Moreover, the hurdle

to new drugs in Japan is reportedly lower compared to that in European countries, with an average time of 66 days between marketing authorization and reimbursement [114]. Notably, there is transparency in the Japanese drug pricing system. Indeed, evidence of this transparency has been reported in studies investigating the mechanism of premium rewards in the CM [17]. Previous reports find that the CCM is applied mostly to oncologic agents and sets higher drug prices, resulting in higher sales for pharmaceutical companies [115], [116]. However, in addition to high price drugs, reasonably priced drugs are also widely prescribed by Japanese physicians as they are backed by significant clinical evidence; this is expected to mitigate the increasing health care expenditures in Japan [117]. If the current characteristics continue, the promotion of the Japanese pharmaceutical industry can be easily achieved. However, some remaining topics must be discussed. One such issue is re-pricing following market expansion (**Figure 2.4**). This system contradicts the price maintenance premium (**Figure 2.3**), hindering pharmaceutical companies' efforts to recover R&D costs, by reducing the prices of drugs of interest, including similar drugs [118]. Another topic is predictability. Previous research has stressed that the lack of predictability in drug pricing policy makes it challenging for pharmaceutical companies to implement R&D strategies, resulting in a drag lag [119]. In other words, if predictability can be assured, R&D incentives can be achieved even without raising drug prices. There are three types of predictability in Japan's drug pricing policy: predictability of rules (transparency), predictability of drug prices, and predictability of sales. The latter two predictabilities are the key areas of concern as the transparency of rules themselves is well assured in Japan. Pharmaceutical companies tend to value price predictability, as this will affect their profits. However, considering the impact on the overall health insurance system, the government considers not only drug prices but also sales to be important. As a result, drug prices are reduced if sales of a drug are significantly higher than the expected sales, for instance, due to line extension (**Figure 2.7**). In the future, if sales deviate significantly from the forecast and if the current rules cannot be applied, the government may set new rules to deal with the situation. Therefore, it is important that the government and the pharmaceutical industry work toward establishing the predictability of sales, rather than the predictability of drug price. In this context, it is critically important to create evidence to guide the discussion not only from the sales perspective but also the drug price perspective. Indeed, several previous reports have quantitatively focused on the predictability of drug price, evaluating premium rates in Japan, investigating the factors affecting the price gap between the actual market price and reimbursement price, and stressing the importance of the predictability of the drug pricing system [120], [121]. These papers generate another important insight as to the drug pricing

policy in Japan, in that, it will be increasingly important to have a drug pricing system that properly reflects the increases in drugs' clinical value. One methodology to consider is health technology assessment (HTA). Studies have intensively discussed how to establish an optimal HTA process in Japan [122]-[127]. In the future, in addition to the HTA method, it will be important to analyze the process of negotiations between pharmaceutical companies and the government to consider appropriate systems that can best manage incentives for pharmaceutical companies.

2.5 The Japanese Pharmaceutical Market

Although the perspectives are limited, some articles focus on the Japanese pharmaceutical market. This section discusses selected articles related to the promotion of the Japanese pharmaceutical industry.

Two reports have assessed the Japanese pharmaceutical market through a sample of the top-100 drugs by sales rank [128], [129], reporting certain unique characteristics of the Japanese topline market—drugs for lifestyle diseases such as hypertension are ranked top in the market, while drugs that can meet critical medical needs such as cancers or neuroscience diseases are not; this has been the trend since 1995 [19]. Despite some recent reports that indicate an upward trend in prescription volumes and the R&D for drugs related to cancers and neuroscience diseases [130]-[133], in the context of "innovativeness" discussed so far and the pharmaceutical industry vision documents issued by the MHLW (**Table 2-1**), the Japanese market may not be on the right path. One important factor in R&D investments is expected returns [134], [135] and R&D strategy strongly depends on a company's business strategy, which can delay new drug applications, especially in Japan. From the optimization perspective, pursuing the international harmonization of the Japanese pharmaceutical market with the global market trend, while not prioritizing the Japanese market [136], [137], is not a preferable strategy for the Japanese pharmaceutical industry. Nevertheless, innovation and global engagement are known to be key factors for sustainable growth [138], even in the Japanese pharmaceutical industry. Therefore, future studies clarifying the overall business strategy by incorporating the multiple perspectives discussed in this literature review, are strongly warranted, to help Japanese pharmaceutical companies make decisions on various business strategies, including R&D strategies, and fulfill their social responsibilities toward patients.

2. 6 Discussion and Conclusion

2. 6. 1 Summary of Current Perspectives

Although arguable points remain in relation to the topic of the “drug lag” in Japan, several studies have already intensively addressed this matter, finding that the countermeasures adopted by the PMDA and pharmaceutical companies have contributed to efficient clinical development in Japan.

There are numerous articles on the “R&D activities of pharmaceutical companies,” which discuss the “system” and “its mode of actions,” such as strategic alliances and M&As, and their effects on the promotion of R&D activities. These are considered to be effective countermeasures to increase R&D activities, considering the pharmaceutical industry’s characteristics. However, detailed discussions are critically lacking. There is no comprehensive, empirical, or concrete discussion on the optimal therapeutic area for the promotion of the pharmaceutical industry. The discussions are particularly lacking in the context of the Japanese pharmaceutical industry, which has certain unique characteristics such as a strict drug pricing policy.

Regarding the “effects of price control strategies on pharmaceutical R&D,” a positive correlation has been reported between drug price and R&D activities. For the Japanese market in particular, there are three types of drug pricing policy predictabilities that must be considered: predictability of rules (transparency), predictability of drug prices, and predictability of sales. As transparency of rules is well assured in Japan, the latter two predictabilities are the main discussion points. Pharmaceutical companies tend to value price predictability, as this will affect their profits. However, in light of the impact on the overall health insurance system, the government considers that the magnitude of sales to be an equally important consideration. Therefore, as this thesis argues, it is crucial that the government and pharmaceutical industry work together to establish the predictability of sales, rather than the predictability of drug price.

Although there are limited perspectives on the “Japanese pharmaceutical market,” there are some articles that quantitatively assess the Japanese market and pharmaceutical companies’ behaviors.

2. 6. 2 Current Challenges and Future Research Areas for the Japanese Pharmaceutical Industry

The issues involved in the promotion of the Japanese pharmaceutical industry are complex. Hence, all parties, including the pharmaceutical industry, the government, and patients and health care professionals, have a role to play in arriving at a solution (**Figure 2.8**).

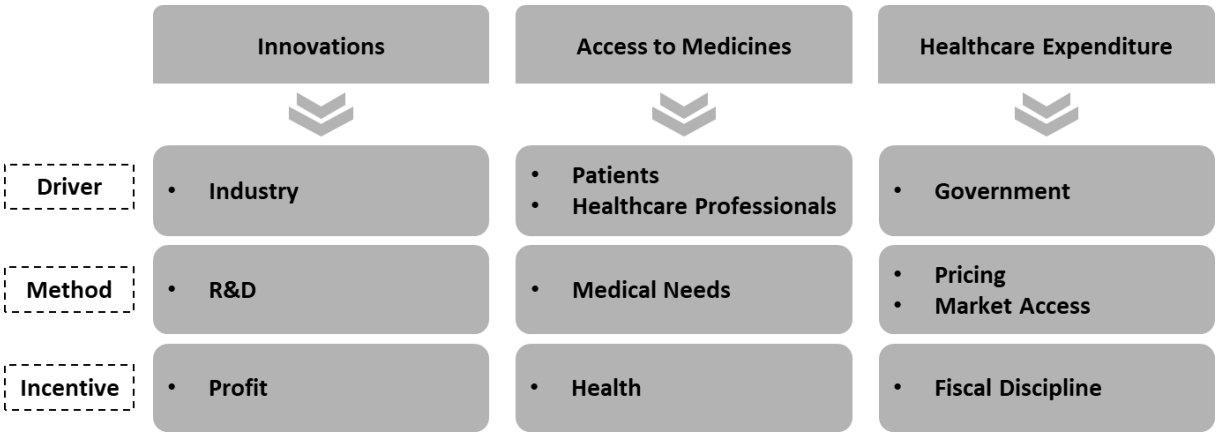


Figure 2.8. Three aspects determining the future direction of the Japanese pharmaceutical industry

The Japanese health care system must have a pricing scheme that balances medication accessibility with the cost of developing new medications. The pharmaceutical industry, the government, and patients and health care professionals can use a variety of strategies to combat the negative image of drug pricing and work with policymakers and others to fix some of the current issues. In this context, the following three under-researched topics warrant further study: “predictability of sales,” “predictability of drug prices,” and “definition of innovativeness,” specifically in therapeutic areas in the Japanese market (**Figure 2.9**).

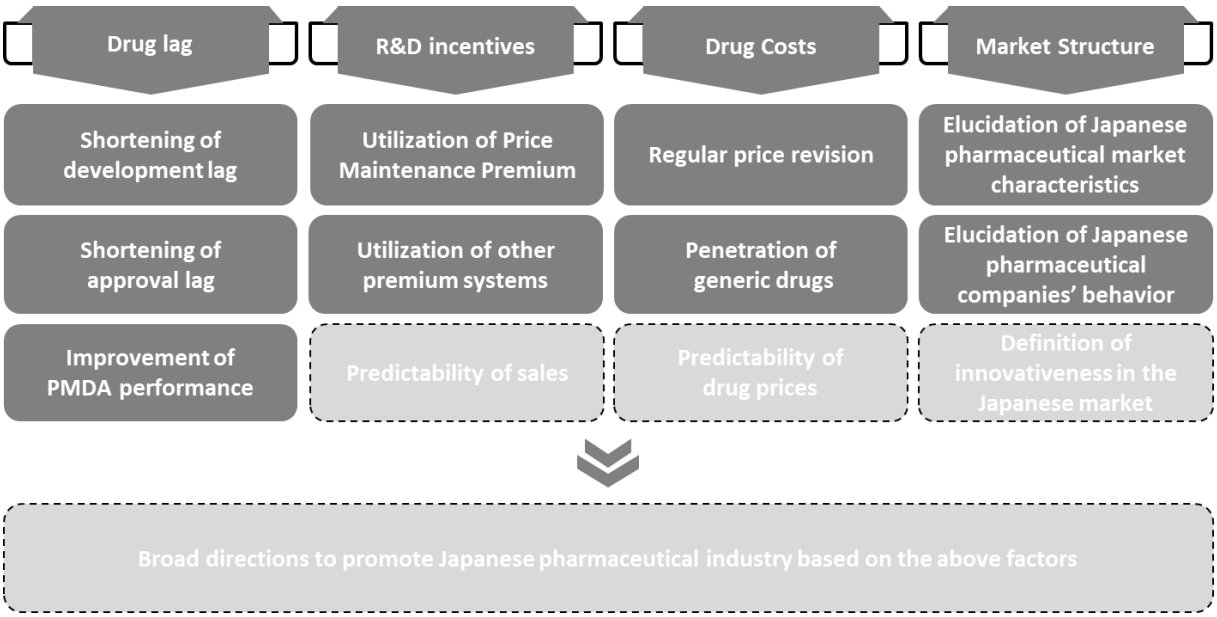


Figure 2.9. Areas of future studies

There is no detailed analysis of the first and second points, and for the third, drugs for "cancers" or "neuroscience diseases" appear to be among the therapeutic areas that are considered "innovative," although the evidence is limited. These three aspects are the focus of this thesis, in discussing the growth of the Japanese pharmaceutical industry. Additionally, the discussion regarding the overall actions to promote the Japanese pharmaceutical industry must consider the multitude of factors identified through this literature review.

3. Characteristics of the Japanese Pharmaceutical Market Compared to the US and European markets

3.1 Study Highlights

What is the current knowledge on the topic?

Although pharmaceutical industries across countries differ, largely due to the specific policies in each country, there is little empirical research on comparative market configurations using objective indicators. In this context, identifying differences in market configurations with a focus on the Japanese pharmaceutical market could provide useful new insights for pharmaceutical companies through suggestions on the types of drugs deemed “innovative”.

What hypotheses did this study address?

1. “Innovativeness” is applied to a therapeutic area as unique in the Japanese pharmaceutical market compared to the market structure of other countries around the world.
2. The structure of the Japanese market differs from that of global markets, and different drugs are often used to treat the same disease in different countries. This discrepancy is particularly pronounced in high UMN areas such as cancer and central nervous system diseases.

What does this study add to our knowledge?

This study elucidated there are more cardiovascular and fewer anti-cancer drugs among the best-selling drugs in the Japanese market; however, the promotion of anti-cancer drug development is evident and suggests that the Japanese market will rival overseas markets within a short period of time, given the increased clinical development of cancer immunotherapies and other anti-cancer drugs. These findings support the above two hypotheses.

How might this change pharmaceutical companies’ R&D strategy?

The findings should enable pharmaceutical companies to focus on anti-cancer drugs as one of the directions that will facilitate the optimization of R&D projects to achieve success in R&D of innovative new drugs.

3.2 Introduction

The pharmaceutical industry undertakes the R&D, production, and marketing of products that promote

better health worldwide. As disease prevalence varies greatly across the world, the pharmaceutical industry in each country understandably focuses on R&D and/or marketing strategies that meet that country's specific medical needs [139].

International comparisons of pharmaceutical market configurations can help pharmaceutical companies develop an optimal strategy for each country or region [128]. In 2014, global pharmaceutical revenues exceeded USD 1 trillion, with the US responsible for the largest portion [128]. However, in recent years, the Japanese pharmaceutical sector has shown the highest growth rates. In 2015, the Japanese market was the world's third largest as it continued to catch up to global markets [128]. In that same year, the combined market share of the US, the UK, France, Germany, and Japan in the global market was roughly 61.0% [128]. If the markets in each country had the same properties, pharmaceutical companies would find it easy to conduct global business. However, this is not the case, as the top-selling market categories vary in each country.

Several studies have reported market differences among countries. Danzon et al. focused on drug pricing policy, noting that strict price regulation in some countries systematically lowers prices of older molecules and globally diffused molecules, which tends to discourage R&D activities by pharmaceutical companies [110], [140]. Pricing differences have also been reported in studies focusing on European countries [141]. These differences are generally caused by differences in government policies and corporate strategies, and affect the entry strategies of pharmaceutical companies [93]. Nevertheless, most large pharmaceutical companies now conduct their business globally. One reason is that drugs as products are fully protected by patents for a certain period, which means that pharmaceutical companies can expect exclusive sales in nearly every market even when competitors' drugs in these markets have similar efficacy. Affecting market configuration are generic penetration differences among countries [142]-[144]. These generic entries not only affect the market share of off-patent drugs, but also intensify price competition [145]. Ultimately, sales of the original drugs generally decrease with the entry of generic drugs [146].

Today, governments in most developed countries are faced with the challenges of growing health care expenditures, and control pharmaceutical expenditures strictly through policy [118], [147]. For example, in Japan, the government introduced a new re-pricing rule for "huge-selling" drugs in 2016 [129], [148]. Under this new system, drug prices can be slashed by up to 50%. The system was applied to four drugs—clopidogrel, sofosbuvir, ledipasvir/sofosbuvir, and bevacizumab—in the initial round of price revisions in 2016 [129].

Although pharmaceutical industries across countries differ, largely due to the specific policies in each country, there is little empirical research on comparative market configurations using objective indicators. In this context, identifying differences in market configurations with a focus on the Japanese pharmaceutical market could provide useful new insights for pharmaceutical companies. Thus, the primary objective of this study is to identify similarities and differences in the market configuration in Japan relative to other developed countries using well-known economic indicators. This study began by establishing the cumulative shares of the 100 top-selling drugs in Japan, the US, the UK, France, Germany, and the global market to indicate the concentration of sales in each market. “Concentration” here is defined as the percentage of drugs in specific therapeutic areas in the total market of each country. Then, Lorenz curves and Gini coefficients for the 100 top-selling drugs in each market were derived. Finally, a comparison was undertaken of the sales and price trends for the 100 top-selling drugs in the targeted markets. The findings reveal differences in pharmaceutical market configurations, sales, and price trends among the countries of interest. “Market configuration” here is defined as the percentage of the drugs in each therapeutic area in each country’s market. It is expected that these findings will be of substantial value to pharmaceutical companies seeking to establish appropriate global business policies.

3.3 Methods

Database

The dataset for this study was obtained from IQVIA Solutions Japan K.K. This database summarizes the sales amount and prescription volume of each drug in an MS Excel file.

The 100 top-selling drugs in 2014 in Japan, the US, the UK, France, Germany, and the global market were selected as the drugs of interest. Data on the 100 top-selling drugs in 2015 in Japan were also used for specific comparative analyses of the Japanese pharmaceutical market.

Therefore, this study used population data, not sample data.

Drug classification and categories

The Anatomical Therapeutic Chemical (ATC) classification system, a pharmaceutical coding system operated by the World Health Organization [149], was used to categorize the drugs included in the study. The ATC level indicates the main anatomical group. Each group is designated by a single letter: **A** (alimentary tract and metabolism); **B** (blood and blood-forming organs); **C** (cardiovascular system); **D** (dermatologicals); **G** (genitourinary system and sex hormones); **H** (systemic hormonal preparations, excluding sex hormones and insulins); **J** (anti-infectives for systemic use); **L** (antineoplastic and immune-modulating agents); **M** (musculoskeletal system); **N** (nervous system); **R** (respiratory system); **S** (sensory organs); **T** (diagnostic agents); and **V** for various. **N/A** indicates "not applicable for ATC classification."

Inequality analysis

Chi-square tests were performed to determine if there was a statistically significant difference between ATC categories in each country.

Inequality in the sales distribution of the 100 top-selling drugs in each market was analyzed using the Gini coefficient. The Gini coefficient is an index commonly used to evaluate economic disparities [150]. (A Gini coefficient of 0 indicates perfect equality in the distribution; a Gini coefficient of 1 indicates perfect inequality.) In this case, the Gini coefficient was calculated using the following formula:

$$Gini\ coefficient = \frac{1}{2\mu n^2}\sum_{i=1}^{n}\sum_{j=1}^{n}|y_i - y_j|$$

where n is the number of drugs in the market (n=100), y_I represents sales of $drug_i$, μ is overall average sales, and $|y_i - y_j|$ is the absolute value of the difference in sales between $drug_i$ and $drug_j$. Gini coefficients can also be calculated from Lorenz curves, which are graphical representations of the equality (or inequality) in a distribution. The Lorenz curve is drawn by a straight diagonal line with an inclination of 1, which represents perfect equality; the Lorenz curve lies beneath it, showing the actual distribution. The area between the straight line and the curved line, expressed as a ratio of the area under the straight line, is the Gini coefficient, a measurement of inequality. The Lorenz curves for this study were constructed using the cumulative proportion of sales amounts for the 100 top-selling drugs in the market and the cumulative number of drugs.

The sales distribution bias in the 100 top-selling drugs by ATC classification was also analyzed using the Herfindahl-Hirschman Index (HHI), a measure often used to indicate the level of market concentration. In this case, HHI was calculated as the sum of the square of the market share of each ATC classification:

$$\text{Herfindahl} - \text{Hirschman Index} = \sum_{i=1}^{n} (Market\ share_i)^2$$

where n is the number of ATC classifications and Market share_1 and Market share_n represent the market shares of various ATC classifications. The maximum HHI value is 1, which, in this application, would indicate that the market is completely dominated by a single ATC classification. Lower index values would indicate a less “oligopolistic” market.

Price was calculated as sales amount/sales volume, which is the weighted average of price per standard unit defined by IQVIA Solutions Japan K.K.

3.4 Results

Cumulative market shares

The cumulative market share of the 100 top-selling drugs in each country is shown in **Figure 3.1**. In the US market, the 100 drugs comprise over 50% of the total market. In Germany, France, and Japan, these drugs comprise approximately 40% of the market. Based on degree of concentration, the countries can be ranked as follows: US > UK > Germany > France > Japan > Global.

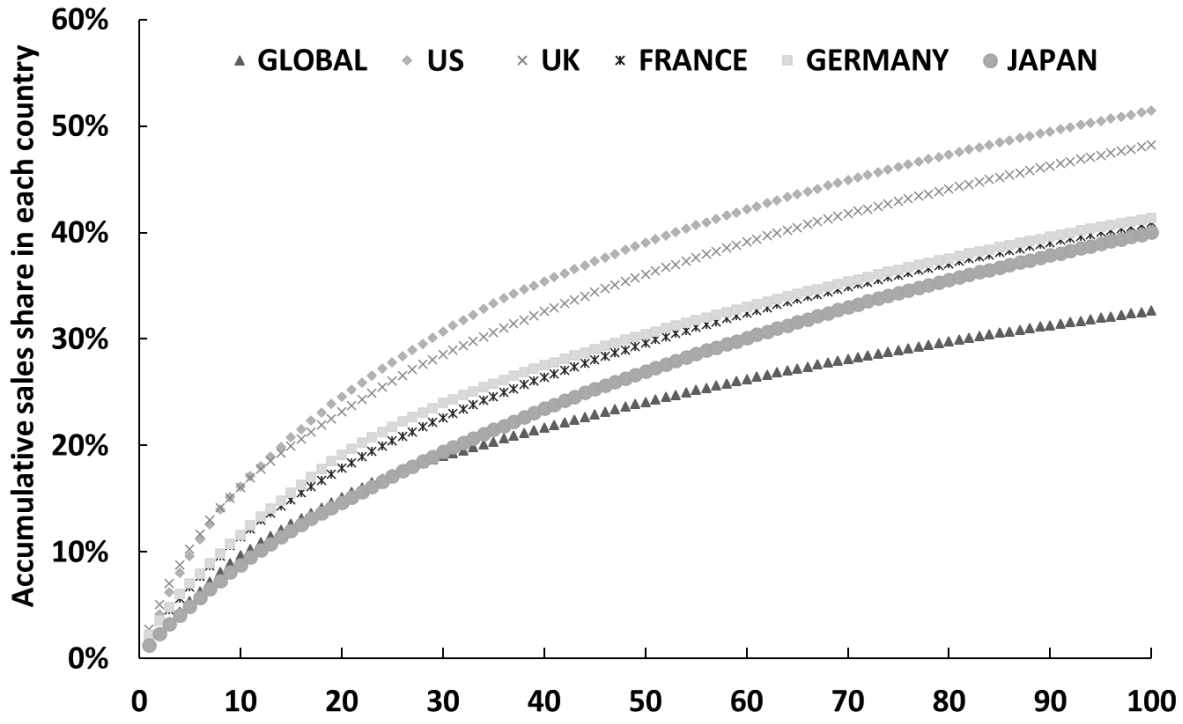
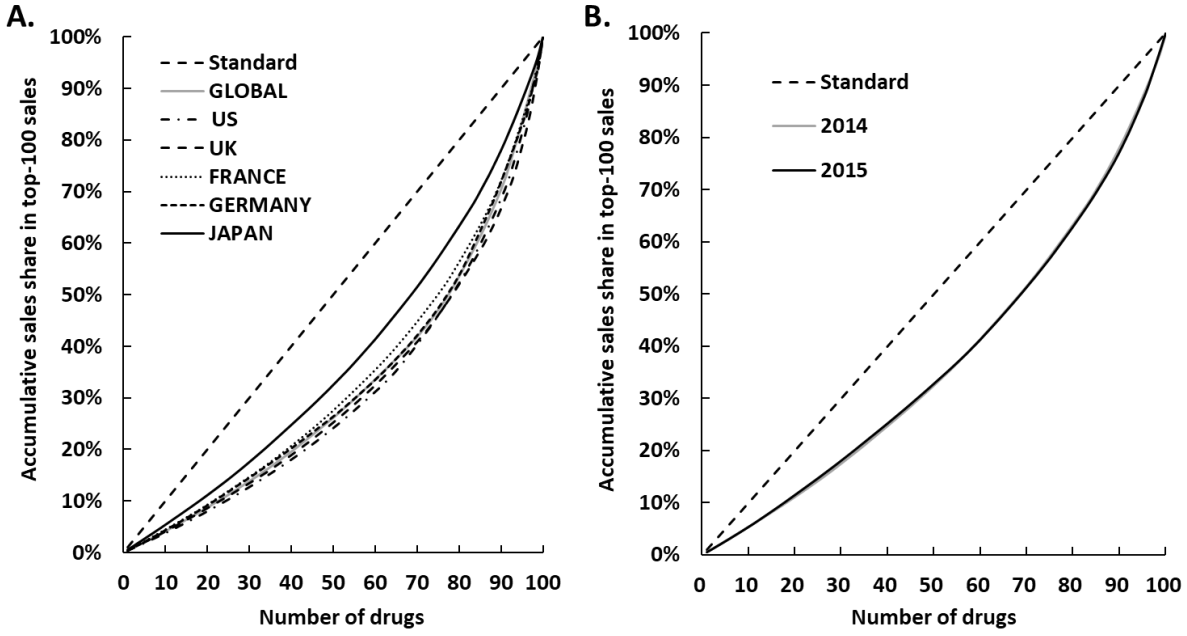


Figure 3.1. Cumulative market shares of the 100 top-selling drugs in 2014

Sales distribution of the 100 top-selling drugs

The Lorenz curves and Gini coefficients for the 100 top-selling drugs in 2014 in each country are shown in **Figure 3.2**. In the case of Japan, results for 2015 also appear in the figure. The standard curves (i.e., the 45° line) shown in **Figure 3.2A** and **Figure 3.2B** represent cases in which the sales of all 100 top-selling drugs in a given market are identical. The Lorenz curve of the Japanese pharmaceutical market is closest to the standard curve, indicating that market disparities in sales among the 100 top-selling drugs are relatively small in the Japanese pharmaceutical market. Moreover, the Gini coefficient for the Japanese pharmaceutical market is the lowest among the countries in the study. As

shown in **Figure 3.2B** and **Figure 3.2C**, the Lorenz curves and Gini coefficients in the Japanese pharmaceutical market were nearly the same in 2014 and 2015, indicating that the 2014 differences between Japan and other countries in the study were not a chance occurrence. The differences in sales distributions grew larger in the following order: the US > the UK > Global > Germany > France > Japan.



C.

Year	2014						2015
Country	GLOBAL	US	UK	FRANCE	GERMANY	JAPAN	JAPAN
Gini coefficient	0.361	0.389	0.384	0.336	0.355	0.253	0.253

Figure 3.2. Sales distribution of the 100 top-selling drugs

A. Lorenz curves for each market in 2014. B. Lorenz curves for Japan in 2014 and 2015. C. Gini coefficients for each market.

The bias in sales distributions by ATC classification

Table 3-1 shows the number of the drugs included in this study, based on their ATC classification. The chi-square test reveals a significant difference in **C** drugs, consistent with previous research [128].

Table 3-1. Number of drugs by ATC classification among the 100 top-selling drugs

Year		2014						χ^2, *p value*
Country		GLOBAL	US	UK	FRANCE	GERMANY	JAPAN	
ATC Code	A	9	13	12	9	13	13	$\chi^2 = 1.7$, *n.s.*
	B	8	5	6	13	6	8	$\chi^2 = 5.4$, *n.s.*
	C	7	8	8	4	4	19	$\chi^2 = 18.4, p < 0.05$
	D	0	0	1	1	0	0	$\chi^2 = 4.0$, *n.s.*
	G	4	4	1	1	0	2	$\chi^2 = 7.0$, *n.s.*
	H	2	3	1	1	1	3	$\chi^2 = 2.6$, *n.s.*
	J	16	16	13	17	14	6	$\chi^2 = 6.0$, *n.s.*
	L	29	24	29	31	38	18	$\chi^2 = 8.1$, *n.s.*
	M	3	2	1	2	3	5	$\chi^2 = 3.5$, *n.s.*
	N	11	12	20	14	14	11	$\chi^2 = 4.2$, *n.s.*
	R	8	10	10	4	4	9	$\chi^2 = 4.8$, *n.s.*
	S	1	1	1	2	2	2	$\chi^2 = 0.80$, *n.s.*
	T	1	0	0	0	0	1	$\chi^2 = 4.0$, *n.s.*
	V	0	1	1	0	0	1	$\chi^2 = 4.0$, *n.s.*
	N/A	1	1	1	1	1	0	$\chi^2 = 2.0$, *n.s.*
Total		100	100	100	100	100	98*	*n/a*

n.s.: not significant, n/a: not applicable

* Some drugs were counted together as these drugs are sold by two different manufacturers in Japan

The 2014 market share of drugs in each ATC classification in each country, as well as the corresponding HHI, is reported in **Table 3-2**. Based on HHI calculations, the bias in the sales distribution related to ATC classification is largest in Germany, followed, in descending order, by France, the Global market, the UK, the US, and Japan. Market share values by ATC classification for Japan are also reported for 2015, as is HHI. In several significant cases, the share values for 2015 are lower than in 2014 (for example, **C** and **L**). This is also true of HHI. The sales share of category **C** drugs in Japan is

quite high compared to other countries in the study, while the sales share of **L** (relative to other countries) is quite low. The market share of category **A** drugs is relatively low in European countries compared to the US and Japan.

Table 3-2. Market share and HHI of the 100 top-selling drugs by ATC classification

Year		2014						2015
Country		GLOBAL	US	UK	FRANCE	GERMANY	JAPAN	JAPAN
ATC Code	A	14.7%	17.5%	9.2%	6.9%	9.7%	13.1%	11.9%
	B	5.3%	3.0%	4.6%	12.3%	7.4%	9.8%	10.1%
	C	7.1%	7.0%	6.1%	5.6%	2.5%	22.1%	17.5%
	D	0%	0%	0.5%	0.5%	0%	0%	0%
	G	2.5%	2.3%	1.2%	0.6%	0%	1.4%	2.4%
	H	0.9%	1.3%	1.4%	0.5%	0.5%	2.7%	2.4%
	J	12.7%	14.1%	9.2%	17.0%	10.5%	4.7%	12.5%
	L	32.2%	27.1%	30.4%	33.7%	46.2%	18.6%	16.6%
	M	1.7%	2.1%	0.4%	0.9%	2.3%	4.9%	5.8%
	N	11.5%	13.8%	18.3%	12.0%	12.2%	10.6%	8.5%
	R	8.7%	9.4%	13.4%	5.4%	5.0%	8.0%	6.5%
	S	1.5%	1.0%	5.2%	4.0%	3.1%	1.5%	1.5%
	T	0%	0%	0%	0%	0%	0.6%	1.0%
	V	0.4%	0.6%	0%	0%	0%	0.7%	0.7%
	N/A	0.7%	1.0%	0%	0.7%	0.5%	1.5%	2.5%
HHI		0.172	0.159	0.170	0.185	0.259	0.134	0.115

Comparison of market trends

Comparisons of sales (monetary value), sales volumes, and prices across 2013 and 2014 are shown in **Table 3-3**. Most of the targeted drugs in the UK, the US, Germany and the global market show an

increase in sales; by contrast, just over half of the drugs in France and Japan show an increase. Price change patterns vary rather sharply among the countries. While the prices of nearly all of the top-100 drugs in the US (N=89) and the UK (N=84) show an increase, price increases are recorded for far fewer drugs in France (N=34), Germany (N=57), and Japan (N=40). Sales volume changes show relatively small differences.

Table 3-3. Comparison of market trends

A. Number of drugs in top-100 sales according to the 2014/2013 sales ratio

Country	GLOBAL	US	UK	FRANCE	GERMANY	JAPAN
(2014 sales / 2013 sales) number of drugs (out of 100 drugs)						
≥100%	75	87	92	52	66	56
≥125%	21	28	23	16	22	12
≥150%	8	11	9	13	10	7
≥200%	6	8	3	7	7	4

B. Number of drugs in top-100 sales according to price and sales volume increase

Country	GLOBAL	US	UK	FRANCE	GERMANY	JAPAN
Number of drugs with a price increase (of 100 drugs)	57	89	84	34	57	40
Number of drugs with a sales volume increase (of 100 drugs)	68	55	80	64	68	60

Changes in sales amount, volumes, and prices by classification

Directional changes in sales amount, sales volume, and prices by ATC classification are shown in

Table 3-4. The sales of nearly all group **A** drugs show an increase in all countries except Japan. However, there is a decrease in the prices of a majority of the group **A** drugs in Japan, France, and Germany, while the prices tend to be higher in the UK, the US, and the global market. Group **L** accounts for the largest number of top-100 drugs in all countries except in Japan (where group **C** dominates). Sales of these drugs have generally increased in all countries and the global market. The price of these drugs has increased in the UK and the US, but decreased in Germany, France, and Japan.

Table 3-4. Directional changes in sales amount, volume, and drug prices

A. Sales amount

Country		GLOBAL	US	UK	FRANCE	GERMANY	JAPAN
Sales amount (Increase/Decrease)							
ATC Code	A	9 / 1	12 / 1	12 / 0	8 / 1	11 / 2	5 / 8
	B	5 / 3	4 / 1	6 / 0	6 / 7	4 / 2	5 / 3
	C	4 / 3	6 / 2	7 / 1	2 / 2	2 / 2	11 / 10
	D	0 / 0	0 / 0	0 / 1	0 / 1	0 / 0	0 / 0
	G	2 / 2	3 / 1	1 / 0	0 / 1	0 / 0	1 / 1
	H	2 / 0	3 / 0	1 / 0	1 / 0	1 / 0	3 / 0
	J	12 / 4	15 / 1	10 / 3	10 / 7	9 / 5	5 / 1
	L	24 / 5	22 / 2	28 / 1	16 / 15	23 / 15	11 / 7
	M	2 / 0	2 / 0	1 / 0	0 / 2	3 / 0	2 / 2
	N	6 / 5	10 / 2	18 / 2	7 / 7	11 / 3	6 / 5
	R	6 / 2	7 / 3	6 / 0	3 / 1	0 / 4	4 / 5
	S	1 / 0	1 / 0	2 / 0	1 / 1	1 / 1	2 / 0
	T	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 1
	V	1 / 0	1 / 0	0 / 0	0 / 0	0 / 0	1 / 0
	N/A	1 / 0	1 / 0	0 / 0	0 / 1	0 / 1	0 / 1
	Total	75 / 25	87 / 13	92 / 8	54 / 46	65 / 35	56 / 44

B. Sales volume

Country		GLOBAL	US	UK	FRANCE	GERMANY	JAPAN
Sales volume (Increase/Decrease)							
ATC Code	A	10 / 0	9 / 4	10 / 2	9 / 0	12 / 1	6 / 7
	B	6 / 2	3 / 2	4 / 2	8 / 5	4 / 2	5 / 3
	C	3 / 4	1 / 7	6 / 2	3 / 1	2 / 2	12 / 9
	D	0 / 0	0 / 0	0 / 1	0 / 1	0 / 0	0 / 0
	G	2 / 2	0 / 4	1 / 0	1 / 0	0 / 0	1 / 1
	H	2 / 0	2 / 1	1 / 0	1 / 0	0 / 1	3 / 0
	J	11 / 5	10 / 6	10 / 3	10 / 7	9 / 5	5 / 1
	L	21 / 8	17 / 7	25 / 4	19 / 12	24 / 14	11 / 7
	M	2 / 0	1 / 1	0 / 1	0 / 2	2 / 1	3 / 1
	N	5 / 6	7 / 5	16 / 4	9 / 5	11 / 3	6 / 5
	R	4 / 4	3 / 7	5 / 1	3 / 1	0 / 4	5 / 4
	S	1 / 0	1 / 0	2 / 0	1 / 1	1 / 1	2 / 0
	T	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 1
	V	0 / 1	0 / 1	0 / 0	0 / 0	0 / 0	1 / 0
	N/A	1 / 0	1 / 0	0 / 0	0 / 1	0 / 1	0 / 1
	Total	68 / 32	55 / 45	80 / 20	64 / 36	65 / 35	60 / 40

C. Price

Country		GLOBAL	US	UK	FRANCE	GERMANY	JAPAN
Drug price (Increase/Decrease)							
ATC Code	A	8 / 2	12 / 1	11 / 1	2 / 7	3 / 10	2 / 11
	B	3 / 5	3 / 2	6 / 0	4 / 9	4 / 2	4 / 4
	C	5 / 2	8 / 0	7 / 1	1 / 3	2 / 2	2 / 19
	D	0 / 0	0 / 0	1 / 0	1 / 0	0 / 0	0 / 0
	G	3 / 1	4 / 0	1 / 0	0 / 1	0 / 0	2 / 0
	H	1 / 1	2 / 1	1 / 0	1 / 0	1 / 0	2 / 1
	J	8 / 8	13 / 3	10 / 3	8 / 9	7 / 7	4 / 2
	L	13 / 16	23 / 1	24 / 5	9 / 22	14 / 24	11 / 7
	M	1 / 1	1 / 1	1 / 0	1 / 1	2 / 1	2 / 2
	N	6 / 5	11 / 1	14 / 6	6 / 8	5 / 9	3 / 8
	R	7 / 1	10 / 0	6 / 0	1 / 3	1 / 3	4 / 5
	S	0 / 1	0 / 1	2 / 0	0 / 2	1 / 1	2 / 0
	T	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 1
	V	1 / 0	1 / 0	0 / 0	0 / 0	0 / 0	1 / 0
	N/A	1 / 0	1 / 0	0 / 0	0 / 1	1 / 0	1 / 0
	Total	57 / 43	89 / 11	84 / 16	34 / 66	41 / 59	40 / 60

A drug whose value in 2014 was above that in 2013 is counted as an “increase”; a drug whose value was lower in 2014 is counted as a “decrease.”

3. 5 Discussion

The present study reveals a number of market differences among the targeted countries, including differences in the level of drug market concentration. Concentration is higher in the US and the UK than in Germany, France, and Japan; the degree of concentration is lowest in the global market. One reason for such differences is the fact that pharmaceutical companies in the US freely determine drug prices, generally resulting in higher drug prices relative to prices in other countries, which can affect market configuration. The calculated Gini coefficients indicate that sales disparities (i.e., differences in sales totals among the various drugs) in Japan are considerably smaller than those in other countries, at least among the 100 top-selling drugs targeted in the study.

Several factors may explain such market differences. For example, the penetration of generics is relatively lower in Japan than in other developed countries, partly because of concerns relating to low quality, leading to recalls [129]. Moreover, Japan has unique drug pricing systems that include strict re-pricing of “huge-sales drugs” [99], [100], [129].

The present study also reveals differences in market configurations by ATC classification. HHI shows a lower bias in market share according to ATC classification in Japan than in the other countries. Nevertheless, the sales share of group **C** drugs is relatively high in the Japanese market, while the sales share of group **L** drugs is relatively low. However, the sales share of off-patent drugs in group **C** is substantial. Given the enactment of several policies that aim to enhance the penetration of generics in this therapeutic area [128], the sales share of group **C** drugs is likely to decline in the near future (the sales share of this group is lower in 2015 than in 2014)—an occurrence that is consistent with a previous report [151]. It is also notable that the sales share of group **L** drugs in Japan has decreased in 2015 (compared to 2014), warranting further investigation to determine the reasons for this decline as well as for the very high sales share of group **L** drugs in Germany.

The present study has identified differences in market trends in sales amount, sales volume, and prices for the 100 top-selling drugs. Most drugs in the UK, the US, and the global market show an increase in sales. By contrast, only about half of the drugs in Germany, France, and Japan show an increase. As for the price, most drug prices in the US and the UK display an increase, while over half the drug prices in France and Japan record a decrease. As has been noted, drug prices in Japan are reviewed every other year and are either maintained or reduced, except in the case of drugs that show additional usefulness [152].

The present study also reveals that the price of drugs in group **L** has been increasing in the US and the

UK, while it has been decreasing in France and Germany. Group **L** accounts for a large share of drug sales in these countries. Such differences tend to reflect variations in policies in each country. There are several studies providing evidence that the anti-cancer drug market share in Japan, especially after 2015, has been expanding dramatically, rivaling the global market [130], [132], [133], [153].

The present study reveals certain unique characteristics of the Japanese market. In Japan, the 100 top-selling drugs comprise approximately 40% of the total market (**Figure 3.1**), suggesting the existence of complex regulatory and pricing processes. Notably, this perspective is consistent with the fact that the Gini coefficient for the Japanese pharmaceutical market is the lowest among the countries in the study, and the coefficient for the Japanese pharmaceutical market is nearly the same for 2014 and 2015 (**Figure 3.2**). In addition, more **C** and fewer **N** and **L** drugs are among the top 100 best-selling drugs in the Japanese market (**Table 3-2**). However, the emerging growth of **N** and **L** drugs is evident from their sales amount, sales volume, and price (**Table 3-3** and **Table 3-4**), indicating that the Japanese market has been catching up to other developed countries, given the increasing clinical development of anti-cancer drugs, including cancer immunotherapy, as compared with other therapeutic areas [47]-[49]. To summarize, pharmaceutical companies will face some challenges in Japan mainly in terms of its complex regulatory and drug pricing processes. However, the Japanese market is currently transitioning to a global market, and the perspectives obtained from this research will provide the foundations for a successful business strategy for pharmaceutical companies.

However, the study has certain limitations. The scope of the study is limited to drugs in the top-100 in sales and uses data for these drugs only from 2014 and 2015. In particular, considering that the market share of the drugs of interest in each country is different (**Figure 3.1**), the perspectives obtained from this research are limited. Further study with a comprehensive marketing dataset is needed to extend our understanding of market configuration differences, along with our understanding of the internal and external business environment, including global and local business strategies for pharmaceutical companies. Such research will require comprehensive marketing data that will enable researchers to conduct pricing simulations to explore the relationships between market configurations and pricing systems. Furthermore, correlation analyses involving price transitions and sales volume transitions in each country are needed to clarify the association between drug prices and sales increases in various countries. Such perspectives should inform marketing strategies and policies regarding the product life cycle of drugs. In addition, studies that consider the demographic structure of the diseased populations in individual countries is warranted, as such profiles are likely to be reflected in the prescription patterns.

This study mainly investigates the differences in market trends in five developed countries and the global market. The individual market configurations, especially in the Japanese pharmaceutical market, ae identified. In 2015, the Japanese pharmaceutical market was the world's third largest. The business policies of Japanese pharmaceutical companies have continued to shift to global business policies, in sharp contrast to the previous era [19]. An understanding of the market differences among countries is clearly essential for pharmaceutical companies to formulate effective business policies for the Japanese market and beyond.

It should be noted that the data used in this study were only for 2014 and 2015. In particular, it is necessary to empirically investigate whether the trends identified in this study continue to hold in the current market. Given the recent trends in R&D, there is a high probability that the trends found in this study are also present in the current market. Moreover, due to issues with data availability, this study could only cover the top 100 markets in each country. In other words, further study is warranted to confirm the applicability of the results from this study to the entire market.

3. 6 Conclusions

There are more cardiovascular and fewer anti-cancer drugs among the top 100 best-selling drugs in the Japanese market; however, the promotion of anti-cancer drug development is evident, considering the increasing clinical development of anti-cancer drugs, including cancer immunotherapy, in comparison with other therapeutic areas, suggesting that the Japanese market will rival overseas markets in the near future (**Figure 3.3**).

- ✓ The market deviation of the 100 top-selling drugs, as indicated by the HHI and Gini coefficient, is the smallest in Japan.
- ✓ The Japanese market is dominated by cardiovascular drugs, unlike the global market where drugs for the treatment of central nervous system diseases and anti-cancer drugs dominate.
- ✓ If the current market trend continues, given the increasing clinical development of anti-cancer drugs than other therapeutic areas, the Japanese market is expected to shift to a market structure similar to that of overseas markets in the future, suggesting that the Japanese market is currently in a transitional period.

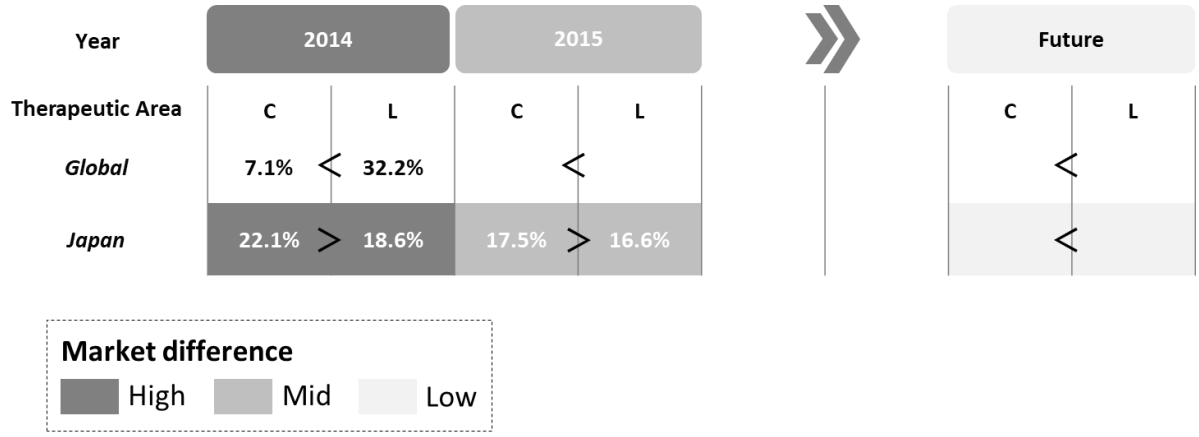


Figure 3.3. Visual abstract

In the following sections, three studies focusing on anti-cancer drugs that should play an important role in long-term R&D and should be recognized as “innovative” are presented, which should be supported by favorable performance of the companies focusing on anti-cancer drugs, according to the annual reports of the pharmaceutical companies [21]. In the next section, the current status and outlook of the Japanese anti-cancer drug market with extensive analyses of marketing data are presented, assuming that the results supporting the conclusions of this study should be submitted.

4. Overview of Anti-cancer Drug Market in Japan

4.1 Study Highlights

What is the current knowledge on the topic?

Anti-cancer drugs are critical for pharmaceutical companies to determine their future R&D. This requires the clarification of the market trends of anti-cancer drugs. There are no reports of specific surveys regarding the prescription trends for all available anti-cancer drugs in Japan in terms of sales amount or prescription volume.

What hypotheses did this study address?

3. One therapeutic area that is likely to witness innovative new drugs is oncology.

What does this study add to our knowledge?

This study showed the market size of anti-cancer drugs has been growing, the sales and prescription volume of molecularly targeted drugs have been increasing, and the market penetration of generic drugs has been increasing in area of chemotherapeutics. This allowed effective R&D of anti-cancer drugs and enabled improved refinements in the selection of suitable characteristics of anti-cancer drugs for R&D. These findings support the above hypothesis.

How might this change pharmaceutical companies' R&D strategy?

Based on the drug profile of anti-cancer drugs identified as suitable for market penetration in this study, new drugs and generics should be developed in appropriate markets. The findings should facilitate the selection of suitable characteristics of anti-cancer drugs to achieve success in R&D of innovative anti-cancer drugs.

4.2 Introduction

Both the number of deaths and morbidity from cancer continue to increase, mainly due to the aging of the population. Globally, approximately 14 million new cases and 8 million deaths were reported in 2012 [154]. Since the introduction of chemotherapy, new therapeutic modalities have been developed, such as signaling inhibitors and molecularly targeted therapeutics [155]. As the understanding of the molecular biology of cancer progresses, new therapies such as cancer stem cell targeted drugs [156] and oncolytic virus therapy [157] have been successively developed . Similar to trends in clinical

development abroad, the clinical development of anti-cancer drugs in Japan is being promoted on an unprecedented scale [47], [55]. In addition, the Japanese government has been indirectly promoting the clinical development of new drugs in therapeutic areas where medical needs are extremely high, such as anti-cancer drugs, through regulations such as the NHI drug pricing system [99], [100], [118], [131].

On one hand, it is expected that the influx of new drugs over the past few years will further improve treatment outcomes, and on the other, there is widespread concern regarding escalating drug costs. In the US, expensive anti-cancer drugs, including molecularly targeted drugs, account for a majority of drug costs in cancer treatment, and these drug costs are expected to continue to increase as new therapies are continuously introduced in the future [158]. The same trend can be anticipated for Japan. However, there are no reports of specific surveys regarding the prescription trends for all available anti-cancer drugs in Japan in terms of sales amount or prescription volume. Thus, it can be said that there is little basis for discussion on how to conserve medical resources and improve patient outcomes. Accordingly, this section analyzes the trend of anti-cancer drug prescriptions in Japan from 2010 to 2016 and presents data that will serve as a basis for future health care economic considerations to develop more efficient and cost-effective cancer treatments. Specifically, the prescription patterns of anti-cancer drugs in Japan will be clarified and the findings will offer suggestions for the future direction of cancer treatment.

A discussion regarding generic drugs is inevitable in health economics and health policy research. Due to an aging population and rising health care costs, regulators in developed countries have promoted the use of generic drugs to improve their fiscal health. The generic drug must have the same quality, efficacy, and safety profile as the corresponding original drug, and bioequivalence between the corresponding original drug and the generic drug must be demonstrated [28]. With regard to the drug price, the generic drug is cheaper than the brand-name drug. Since both drugs are clinically compatible, there are reports on several policy evaluations advocating the active use of generics for health care and fiscal health [159]-[162].

In Japan, modified dispensing to generics was introduced in 2006, allowing pharmacists to change a brand-name product to a generic product with the permission of the prescribing physician [163]. Since 2008, changes have been made to allow pharmacists to dispense generics at their discretion, unless prohibited by the prescribing physician [164]. In addition, since 2007, generic drugs have been allowed to be listed on the NHI drug price list twice a year (in May and November) to promote the spread of generic drugs [165]. However, even with these policies, the penetration of generics has not been as great as in other developed countries.

As aforementioned, Japan has an NHI price system that promotes the clinical development of innovative drugs—the "PMP" (**Figure 4.1**); however, it is believed that competition with generic drugs may lead to the reduction of drug costs by further promoting the development of innovative drugs by companies and controlling the drug costs of original drugs whose patents have expired [166]. Therefore, the penetration of generics in the anti-cancer drug market could be an effective measure to control the rising drug costs [167]. However some generic drugs can easily penetrate the market, while others face challenges in doing so, because each drug has a different mechanism of action, even if all the drugs under consideration are anti-cancer drugs.

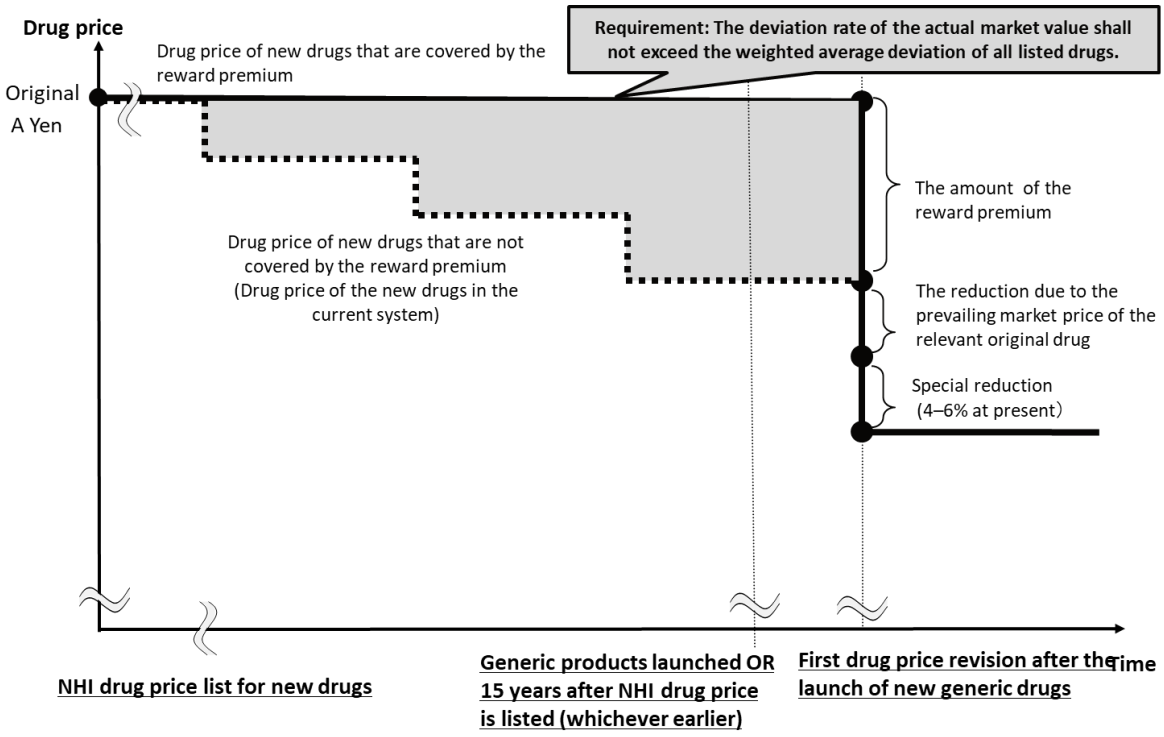


Figure 4.1. Price maintenance premium (reshown, see Chapter 2, Section 2.1)

Therefore, this section quantifies the percentage of generic anti-cancer drugs in each ATC category in Japan. Subsequently, a market analysis of generic anti-cancer drugs in Japan is conducted based on the ATC classification, to identify the characteristics of generic drugs that support or hinder their penetration. Market analysis is also conducted for brand-name products to determine the characteristics that support their penetration in the Japanese pharmaceutical market.

In conclusion, the findings from this section reveal the requisites for effective market penetration of

anti-cancer drugs in Japan through an assessment of the market conditions of both brand-name and generic anti-cancer drugs.

4.3 Methods

Database

The dataset used in this study was created from publicly available information obtained from IQVIA Solutions Japan K.K. Data on the number of prescriptions, including sales amount, of all anti-cancer drugs between 2010 and 2016 in Japan were selected. This database presents the information in an MS Excel file.

Therefore, this study used population data, not sample data.

Information collection regarding each anti-cancer drug

The drugs of interest are categorized according to the third level of the ATC Classification System as shown in **Table 4-1**.

First, **L** drugs of ATC classification are selected as anti-cancer drugs (**Table 4-1A**). Then the anti-cancer drugs of interest are categorized based on the second level; based on the second and third levels of classification (**L01** and **L02,** respectively) (**Table 4-1B**).

Table 4-1. ATC classification system

A. First level

Code	
A	Alimentary tract and metabolism
B	Blood and blood-forming organs
C	Cardiovascular system
D	Dermatological agents
G	Genitourinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Anti-infectives for systemic use
K	Transfusions
L	Antineoplastic and immunomodulating agents
M	Musculoskeletal system
N	Nervous system
P	Anti-parasitic products, insecticides, and repellents
R	Respiratory system
S	Sensory organs
T	Diagnostic medicines
V	Various

B. Second and Third level in L

Code		
L01	A	Alkylating agents
	B	Antimetabolites
	C	Plant-based neoplastics
	D	Antineoplastic antibiotics
	F	Platinum antineoplastics
	G	Antineoplastic mAbs
	H	Protein kinase inhibitors
	X	Other antineoplastics
L02	A	Cytostatic hormones
	B	Cyto hormone antagonists

Statistical analysis

The overall size of the anti-cancer drug market, the top 30 anti-cancer drugs by sales amount, the number of available anti-cancer drugs in each year, sales amounts, prescription volumes, and the changes in sales amounts and prescription volumes over 2010–2016, were investigated. These analyses were carried out in three stages: the overall anti-cancer drug market, brand-name drugs, and generic drugs.

4.4 Results

Overall anti-cancer drug share in Japan

Table 4-2. shows the change in the sales amount and prescription volume of anti-cancer drugs from 2010 to 2016. The anti-cancer drug market has continued to expand every year from 2010 to 2016, with the sales amount exceeding JPY 1 trillion in 2015. There is no significant change in prescription volume during this period.

Table 4-2. Anti-cancer drug market share in Japan

Year	Sales Amount (JPY)	Prescription volume
2010	793,047,550,314	435,735,617
2011	833,441,918,069	425,033,179
2012	857,737,058,482	418,349,885
2013	897,448,275,100	415,496,678
2014	952,095,535,980	416,757,815
2015	1,050,457,777,269	430,716,538
2016	1,176,171,997,394	438,331,860

Top 30 anti-cancer drugs in Japan by sales volume

The top 30 anti-cancer drug categories by sales volume are shown in **Table 4-3**. Overall, there is no significant change in the top-selling drug category. However, it is notable that the sales volume of **L01G** (Mab antineoplastics) and **L01H** (Protein kinase inhibitors) drugs has been increasing since 2010. Particularly, drugs in the **L01H** category have been recording the highest sales volume since 2014.

Table 4-3. Top 30 anti-cancer drugs in Japan by sales volume

	Year	2010	2011	2012	2013	2014	2015	2016
ATC Codes	L01A	1	1	1	1	1	1	1
	L01B	6	6	5	6	5	5	5
	L01C	3	3	3	3	1	1	1
	L01F	1	1	1	1	1	1	1
	L01G	5	6	5	5	6	6	8
	L01H	5	6	7	6	8	8	8
	L01X	1	1	1	1	1	1	1
	L02A	4	4	4	4	3	3	3
	L02B	4	2	3	3	4	4	2

Number of anti-cancer drugs

The number of drugs available in each category of anti-cancer drugs in Japan from 2010 to 2016 is presented in **Table 4-4**. Overall, the number of all drugs has increased. Notably, the number of drugs in the **L01G** (Mab antineoplastics) and **L01H** (Protein kinase inhibitors) categories has increased drastically compared to drugs in other categories.

Table 4-4. Number of anti-cancer drugs in each category

	Year	2010	2011	2012	2013	2014	2015	2016
ATC Codes	L01A	11	10	10	12	11	13	13
	L01B	53	55	54	56	64	70	66
	L01C	24	27	31	42	48	51	51
	L01D	25	24	24	25	25	24	23
	L01F	16	16	17	18	29	29	30
	L01G	6	7	8	10	11	15	16
	L01H	10	10	13	18	30	37	44
	L01X	21	22	21	21	22	24	25
	L02A	27	25	23	24	26	25	26
	L02B	43	47	67	70	71	89	98
	Total	236	243	268	296	337	377	392

Sales amounts

Sales amounts changes in each ATC category between 2010 and 2016 are presented in **Figure 4.2**. The sales amount of drugs in the **L01A** (Alkylating agents), **L01C** (Plant-based neoplastics), **L01G** (Mab antineoplastics), **L01H** (Protein kinase inhibitors), **L01X** (Other antineoplastics), and **L02B** (Cyto hormone antagonists) categories has gradually increased. Among them, sales of drugs in the **L01G** (Mab antineoplastics) and **L01H** (Protein kinase inhibitors) categories has increased drastically.

By contrast, sales of drugs in the **L01B** (Antimetabolites) and **L02A** (Cytostatic hormones) categories has gradually decreased. There is no dramatic change in the sales of drugs in the **L01D** (Antineoplastic antibiotics) and **L01F** (Platinum antineoplastics) categories.

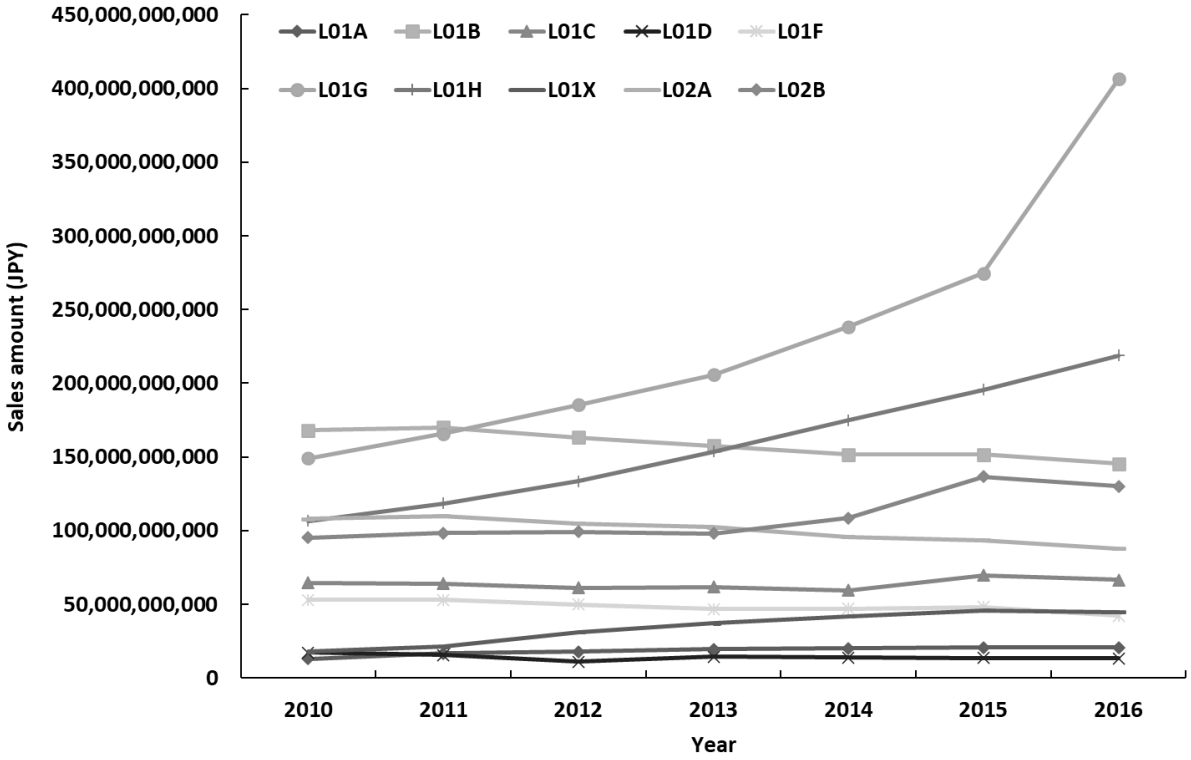


Figure 4.2. Sales amount in each category

Prescription volumes

Changes in the prescription volumes in each ATC category between 2010 and 2016 are presented in **Figure 4.3**. The prescription volumes of drugs in the **L01F** (Platinum antineoplastics), **L01G** (Mab antineoplastics), **L01H** (Protein kinase inhibitors), and **L02B** (Cyto hormone antagonists) categories has gradually increased. Among them, the prescription volumes of drugs in the **L01G** (Mab antineoplastics) and **L01H** (Protein kinase inhibitors) categories has increased drastically.

By contrast, prescriptions of drugs in the **L01A** (Alkylating agents), **L01B** (Antimetabolites), **L01C** (Plant-based neoplastics), **L01D** (Antineoplastic antibiotics), **L01X** (Other antineoplastics), and **L02A** (Cytostatic hormones) categories have gradually decreased.

The categories with both increased sales amounts sand prescription volumes are as follows; **L01G** (Mab antineoplastics), **L01H** (Protein kinase inhibitors), and **L02B** (Cyto hormone antagonists).

The categories with decreased sales amounts and prescription volumes are **L01B** (Antimetabolites) and **L02A** (Cytostatic hormones).

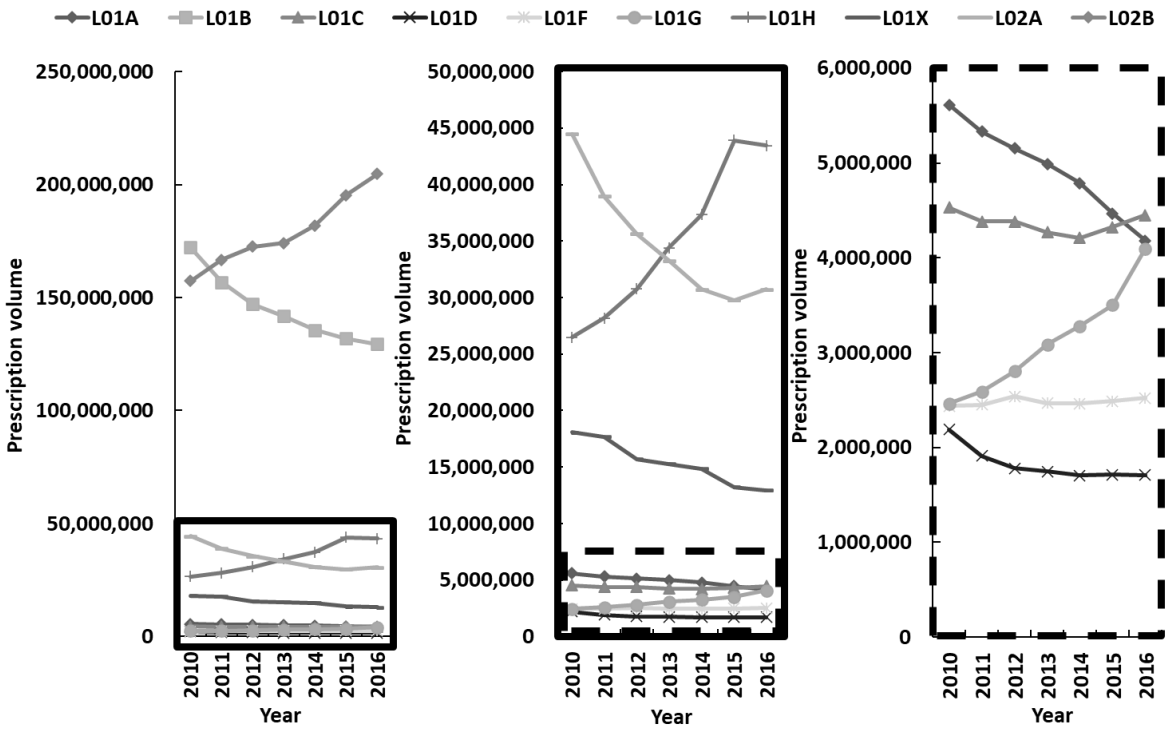


Figure 4.3. Prescription volume in each category

Overall anti-cancer drug share in Japan categorized by brand-name drug and generic drug

The size of the Japanese anti-cancer drug market (sales amount) according to the ATC code is shown for both brand-name drugs (**Figure 4.4**) and generic drugs (**Figure 4.5**). The top five drug categories for brand-name drugs are **L01G** (Antineoplastic mAbs), **L01H** (Protein kinase inhibitors), **L01B** (Antimetabolites), **L02B** (Cytostatic hormone antagonists), and **L02A** (Cytostatic hormones). Among them, a downward trend can be seen in relation to **L01B** and **L02A**. For the other categories whose sales are less than JPY 60 billion, the sales amount of **L01X** (Other antineoplastics) and **L01A** (Alkylating agents) has increased, while a downward trend can be confirmed for **L01C** (Plant-based neoplastics), **L01F** (Platinum antineoplastics), and **L02B**. Among generic drugs, the top five drug categories are **L02B**, **L01C**, **L01F**, **L01B**, and **L02A**. In the remaining categories, the sales of **L01H** have increased since 2013, while there is no drastic change in the sales of **L01D** (Antineoplastic antibiotics). There are no generic penetrations in **L01A**, **L01G**, and **L01X**. Overall, the brand-name drug categories that have experienced decreased sales were all affected by generic penetration.

The size of the Japanese anti-cancer drug market (prescription volume) according to the ATC code is shown for both brand-name drugs (**Figure 4.6**) and generic drugs (**Figure 4.7**). The top five drug categories for brand-name drugs are **L01B**, **L02B**, **L01H**, **L02A**, and **L01X**, and a downward trend

could be confirmed for all except **L01H**. In the other categories, the prescription volume has been decreasing for drugs in **L01A**, **L01C**, **L01D**, and **L01F**, while that for drugs in **L01G** has been increasing. Among generic drugs, the top five drug categories are **L02B**, **L02A, L01B**, **L01C**, and **L01F**. An upward trend is observed in all these categories. For the other categories, an upward trend can be confirmed for **L01H** and **L01D**. Furthermore, the prescription volume since launch has increased for all categories, except **L01A**, **L01G**, and **L01X**.

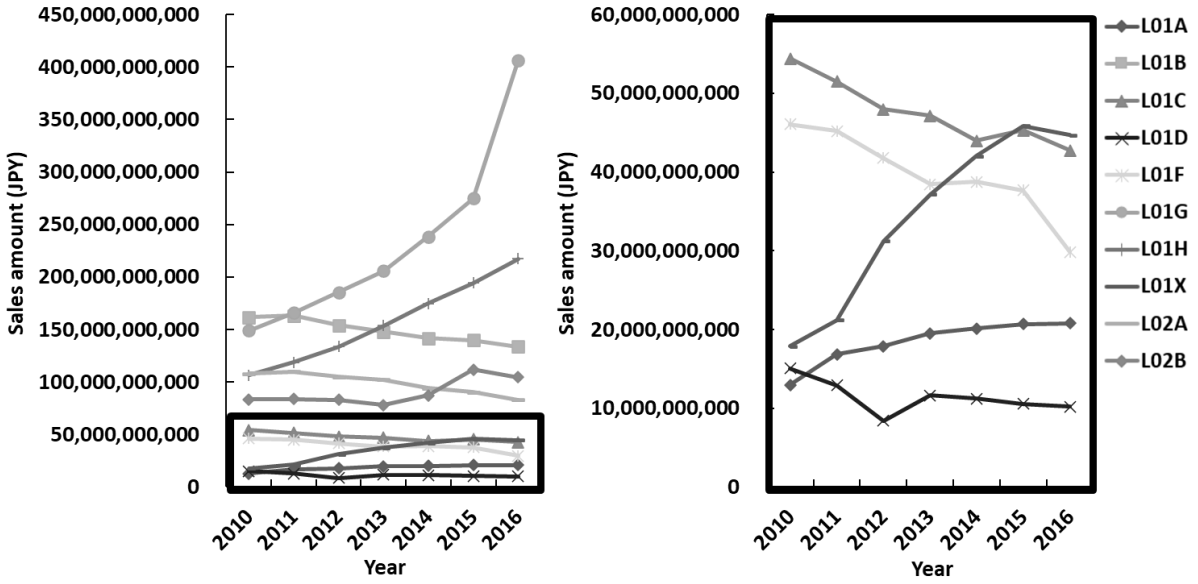


Figure 4.4. Japanese anti-cancer brand-name drug market according to ATC code (sales)

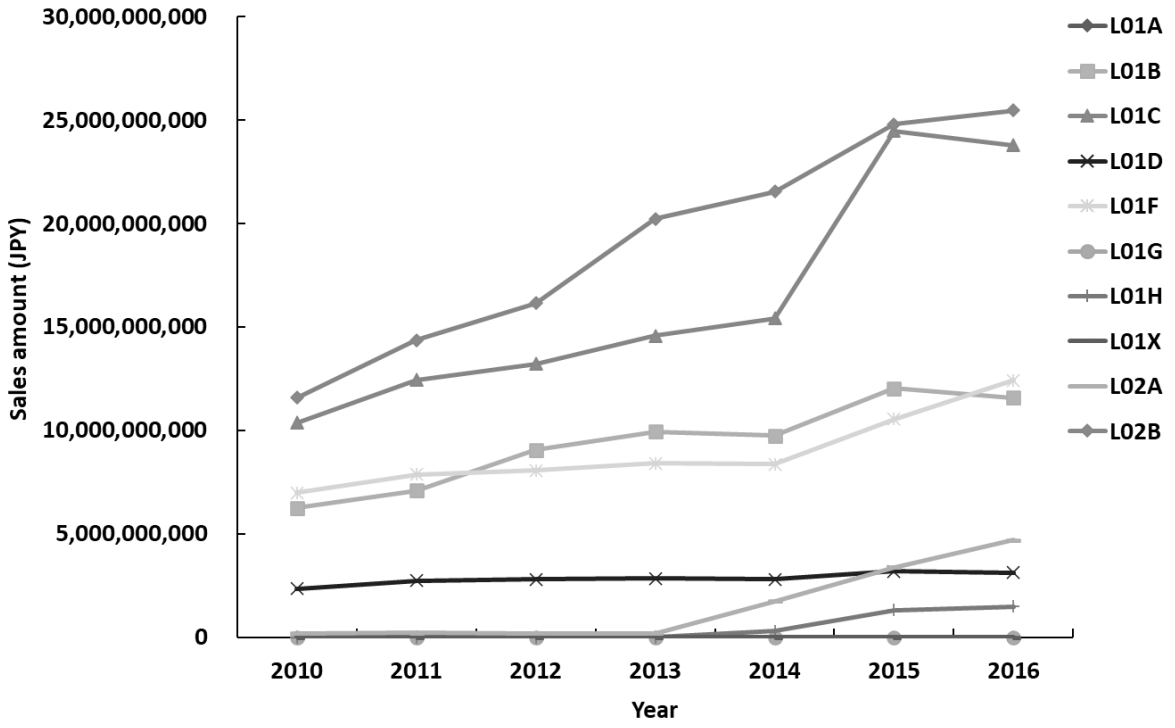


Figure 4.5. Japanese anti-cancer generic drug market according to ATC code (sales)

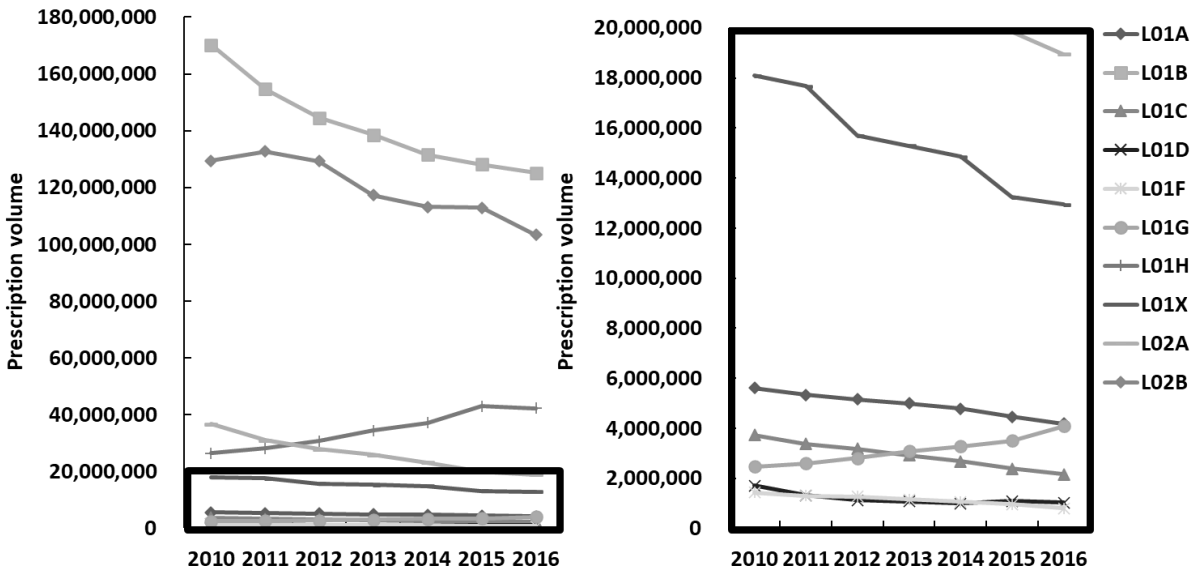


Figure 4.6. Japanese anti-cancer brand-name drug market according to ATC code (prescription volumes)

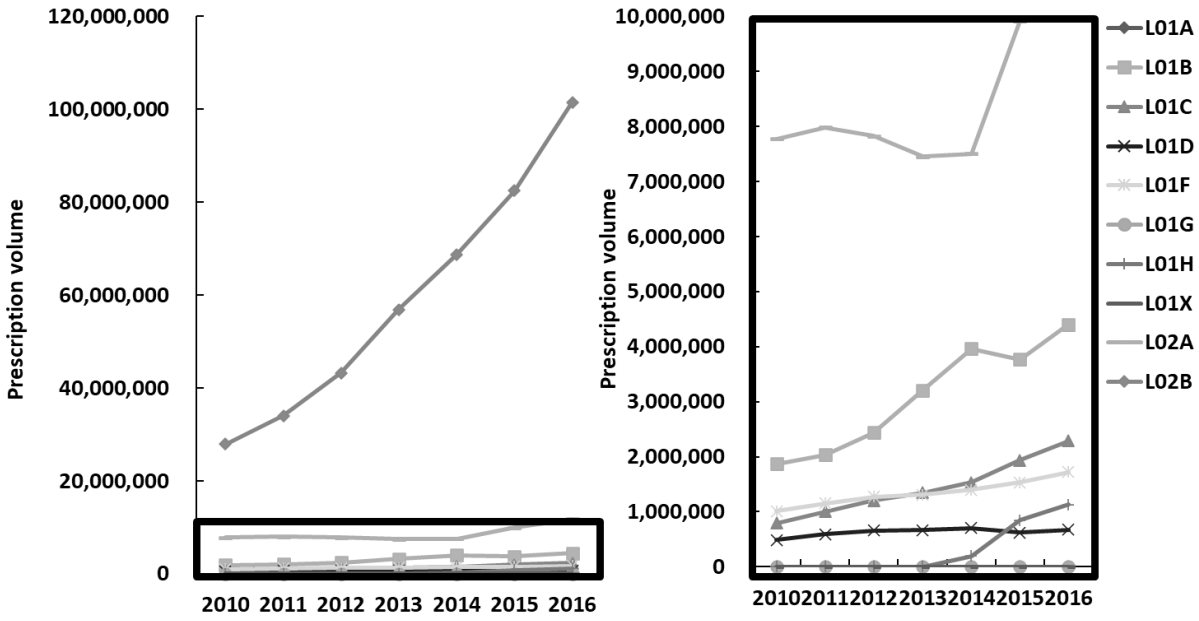


Figure 4.7. Japanese anti-cancer generic drug market according to ATC code (prescription volumes)

The ratio of generics in the overall market

The ratio of generics in the entire market (consisting of both brand-name and generic drugs) in Japan according to the ATC code is shown in **Figure 4.8**. Based on the sales amounts, the ratio of generics has increased in all the categories, with the sales amounts being largest in the **L01C**, **L01F**, **L01D**, **L02B**, **L01B**, **L02A**, and **L01H** categories (in descending order). In terms of prescription volumes, again, the ratio has increased in all categories, with prescriptions being highest for drugs in the **L01F**, **L01C**, **L02B**, **L01D**, **L02A**, **L01B**, and **L01H** categories (in descending order). Similar trends have been confirmed in all the categories affected by generic penetration.

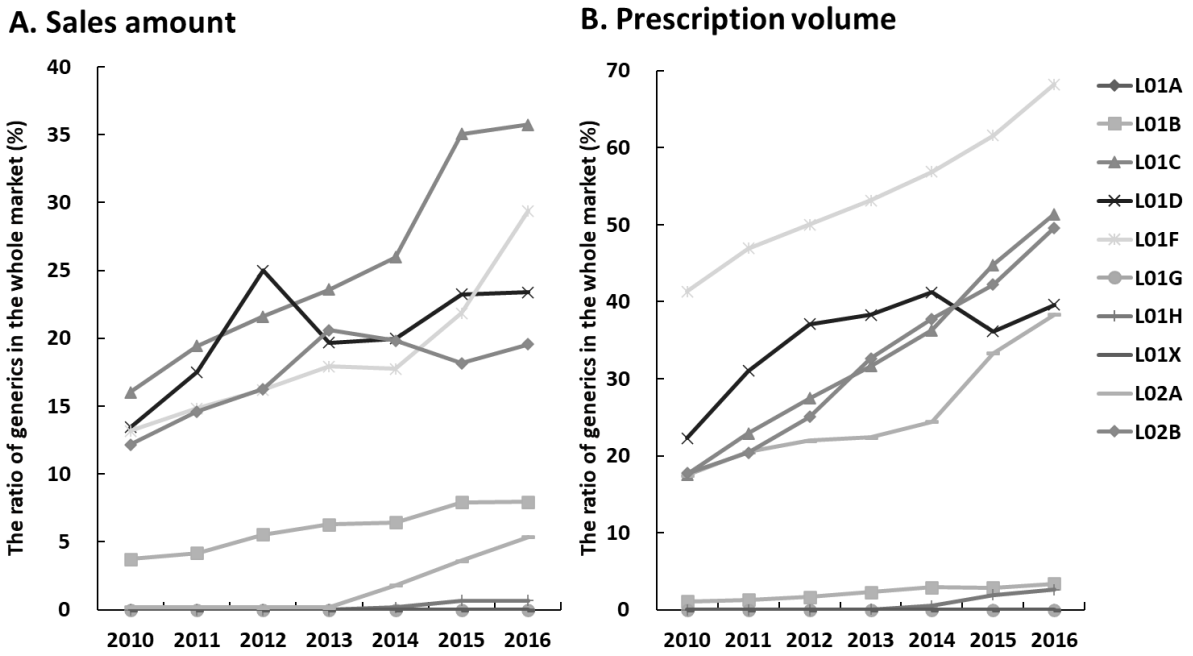


Figure 4.8. The ratio of generics in the whole market (brand + generic) in Japan according to ATC code

4. 5 Discussion

The present study demonstrates that novel anti-cancer drugs, specifically antibody drugs and protein kinase inhibitors for molecular targeted therapy, are becoming the main treatment options for cancer drug therapy in Japan. The present study also suggests that the frequency of prescribing these drugs may be expected to increase in the future, similar to trends in other developed countries [168]. Moreover, molecularly targeted therapies may impose an even greater economic burden on cancer patients and health care finances in the future [169], [170].

Increased options for molecularly targeted therapies are known to be a major factor in increasing health care costs [171]. There are also several anti-cancer drugs that, despite being expensive, do not have clinical significance over other existing therapies [172]. In other words, it is difficult to completely control the increase in medical costs, but if the right drugs are not prescribed to the right patients, medical costs may continue to rise unnecessarily.

In recent years, precision medicine, which analyzes and selects the optimal treatment method for each individual patient, has grown in popularity. Precision medicine is said to reduce health care costs by providing tailor-made treatments for each patient [173]. Therefore, significant research funds are currently being invested in precision medicine, and research is underway [174], [175], with an increasing number of clinical trials (known as basket and umbrella trials) [176]-[178]. In 2017,

Pembrolizumab was approved for high microsatellite instability (MSI-H) colorectal cancer (CRC) and non-CRC cancers in the US [179]. To date, no anti-cancer drug has shown a 100% response rate. This indicates that an adequate patient population in which the anti-cancer drug is highly effective has not yet been identified. Therefore, there is a need for further promotion of precision medicine to classify patient populations, and establish and provide optimal treatment and disease prevention for each population.

The results of the present study are consistent with previous reports and demonstrate that the clinical development of anti-cancer drugs in recent years has focused on molecularly targeted therapeutics and that the highest percentage of such therapeutics are used in cancer drug therapy [128], [130], [180], [181].

It is possible to control the increase in medical costs if precision medicine or related regulations are properly introduced; otherwise, costs may continue to rise. In Japan, there are few cost-effectiveness analyses of cancer treatment because the majority of health care costs are controlled by the government through the insurance system [182]. However, cancer treatment is known to impose a great financial burden on patients, families, and society compared to treatments for other diseases [183].

In the US, as of July 18, 2017, there were 81 biomarkers—objective indications of medical status, observed from outside the patient, and which can be measured accurately and reproducibly—listed in the package insert of medical products [184], and the number of medical institutions offering genomic testing has increased since 2015 [185]. In Japan, some of these biomarkers have been used to predict treatment effects. It is expected that additional biomarkers will be identified and that the optimization (individualization) of cancer treatment will similarly progress in Japan (**Figure 4.9**).

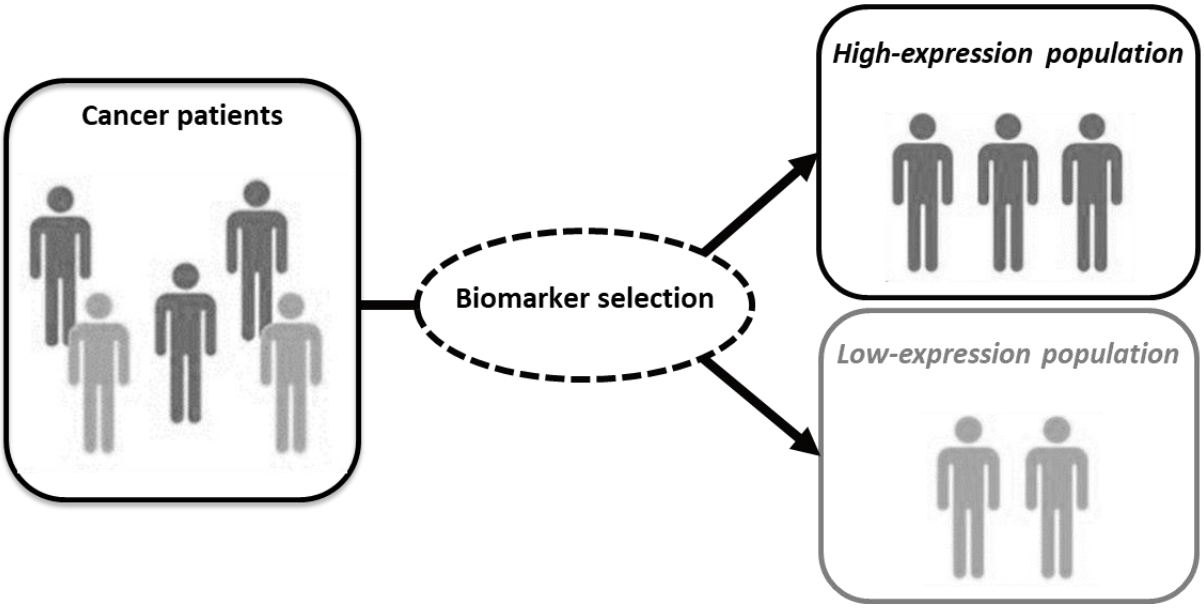


Figure 4.9. Future directions in cancer therapy

With regard to the promotion of the use of generics, another measure to control health care costs, this study reveals the optimal drug characteristics for the penetration of generics in the Japanese anti-cancer drug market. From the perspective of the number of original drugs on patent expiration, the barriers to market entry are relatively low for platinum agents; plant-based antineoplastic agents; hormone antagonists; and antibiotic antineoplastic agents, including conventional chemotherapeutic agents—but high for hormonal agents; protein kinase inhibitors; and metabolic antagonists, including hormone therapies, molecular targeting agents, and hematologic oncology agents. The low barriers to entry for generics indicate that the market is highly competitive. Therefore, there are many generic drugs on the market for “platinum preparations,” “plant-based antineoplastic drugs,” “hormone antagonists,” and “antibiotic antineoplastic drugs.” By contrast, the markets for “hormone products,” “protein kinase inhibitors,” and “metabolic antagonists“ have significant room for generics to enter. From the aforementioned, it can be seen that the switch from conventional chemotherapy drugs to generic drugs is already complete. Therefore, the future development of generic drugs should focus on markets other than chemotherapeutic agents. Notably, this study reveals a lack of penetration of generic drugs in relation to “alkylating agents,” “antibody drugs,” and “others.” In particular, most of the “antibody drugs“ and “protein kinase inhibitors“ have active patents. However, if generics are able to enter these areas, pharmaceutical companies may be able to generate high volumes of sales.

The dissemination of generic drugs is challenged by the lack of confidence in the quality of generic

drugs, lack of clinical trial data on efficacy and safety, and unknown safety profile of the drug. However, while research on generic alternatives to anti-cancer drugs remains limited, the number of studies on generics themselves has increased annually since 1984 [186]. It has also been reported that there are no safety concerns regarding the quality of generic drugs marketed in Japan [187]. Furthermore, some reports argue that if the elution of the generic drug is comparable to that of the original drug, it is unlikely that there will be a significant difference in the therapeutic efficacy of the two drugs [188]. Accordingly, Japan's generic drug market is expected to expand in the future, and further market entry will make it possible to control medical costs. This study reveals the optimal drug characteristics for the development and market penetration of generic anti-cancer drugs in the future, and the findings provide a foundation for their promotion.

The present study has the following limitations. It has not been verified whether the drug profiles to be developed for original and generic drugs are linked to the profitability of pharmaceutical companies. In addition, the present study only reports the trend in Japan, and further investigation is required to determine if the same trend exists in global markets by analyzing the market data of anti-cancer drugs in each country.

4.6 Conclusions

Since there are certainly optimal drug profiles in Japan's growing anti-cancer drug market, it is necessary to detect areas with significant sales potential, so that anti-cancer drugs can be launched in appropriate markets where there truly are high-needs patients (**Figure 4.10**). Importantly, the findings here were consistent with the main conclusions of Chapter 3.

- ✓ The anti-cancer drug market has grown annually from 2010 to 2016 and its market size was over 1 trillion in 2015. The market for molecularly targeted therapeutics has more than doubled in size compared to 2010.
- ✓ In cancer treatment, molecularly targeted therapies are now the mainstay of drug therapy, and sales and prescription volumes have been increasing. The market penetration of generics in the area of chemotherapeutic agents has also been increasing.
- ✓ Based on the drug profile of anti-cancer drugs identified as suitable for market penetration in this study, new drugs and generics should be developed in appropriate markets.

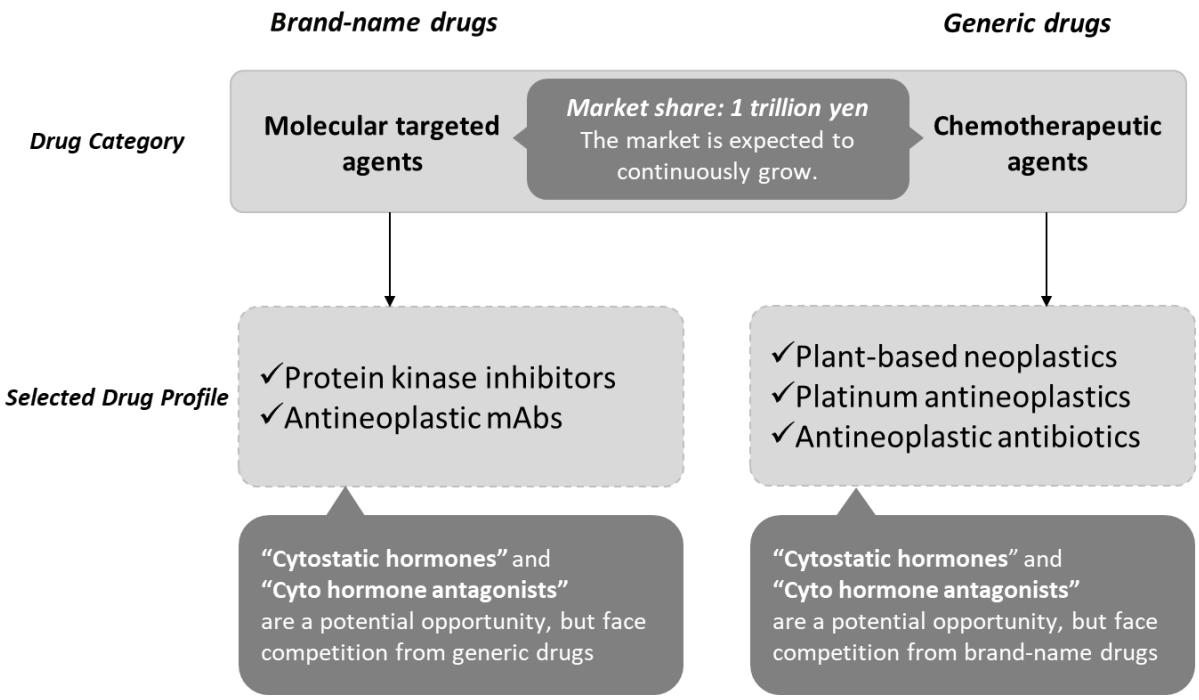


Figure 4.10. Visual abstract

Given the findings in this study are consistent with the primary conclusions of Chapter 3, it is evident that anti-cancer drugs will play an important role in the Japanese market in terms of future R&D. The drug lag of all NMEs in Japan is getting shorter [33], and a similar shortening of the drug lag of anti-cancer drugs has also been reported [48]. However, given that the lag has not been completely eliminated, albeit in a shortening trend, that anti-cancer drug sales are relatively low in the Japanese market, and that it is only recently that the number of R&D projects for anti-cancer drugs in Japan has reached the level comparable to the rest of the world, Japan lags behind the Western countries in anti-cancer drug approvals. Therefore, possible implications for future directions are critically needed so that the Japanese pharmaceutical market can continue to promote R&D activities. However, no practical suggestions have been presented for pharmaceutical companies to follow R&D strategies. Accordingly, in the following two studies, actual cases will be presented in the context of rare cancers and combination therapies. "Product Strategy" will be mainly discussed in Chapter 5 on "Rare Cancers" and Chapter 6 on "Combination Therapies," because the insights on "Product Strategy" should provide direct implications for "R&D Strategy."

5. Implications for the Direction of R&D Strategy of Anti-cancer Drugs (1): Rare Cancers

5.1 Study Highlights

What is the current knowledge on the topic?

Anti-cancer drugs will play an important role in the Japanese market. This requires practical applications of R&D strategies for pharmaceutical companies to follow according to their R&D capabilities. There are limited studies in rare cancers describing them in that perspective.

What hypotheses did this study address?

4. Utilizing pharmaceutical regulations and considering the characteristics of anti-cancer drugs with the potential for high sales will enable the development of new drugs with high sales potential in Japan.

What does this study add to our knowledge?

"Product Strategy" on rare cancers was mainly discussed, because the insights on "Product Strategy" should provide direct implications for "R&D Strategy." This study found that, in the area of rare cancers, even if the drug is not FIC, it will have high sales if its clinical positioning with existing drugs can be clarified in clinical trials and expanding the indication to a cancer type with a large number of patients after launching the drug for a rare cancer results in high sales. These findings support the above hypothesis.

How might this change pharmaceutical companies' R&D strategy?

This study fills a research gap by directly testing the profitability of rare cancer drugs and revealing the potential capabilities of rare cancer drugs to acquire market share and recover their R&D costs. This insight allows efficient R&D of rare cancer drugs in pharmaceutical companies.

5.2 Introduction

Rare cancers are defined as cancers with an incidence of less than 6 per 100,000 persons per year [189]. Although each rare cancer is obviously "rare" in itself, when the numbers of each type are combined, they constitute up to 22% of all new cancer cases [189]. Scientific and clinical knowledge of the pathology of rare cancers is lacking because of the limited number of patients, who are thus treated

differently across the country and are unlikely to receive evidence-based treatment [190]. As a result, the treatment satisfaction is still low, and the prognosis is likely to be poor relative to that for more common cancers [191]. Despite these high UMN, rare cancer drug development has stagnated because (1) the knowledge about rare cancers is insufficient, (2) conventional trial designs demand unfeasibly large numbers of patients, and (3) rare cancer drugs are generally thought to be less profitable than conventional drugs [192]. However, recent advances have been promoting rare cancer drug development.

Registries for rare cancers are required to measure the dispersity of rare cancer patients. The MASTER KEY (Marker Assisted Selective ThErapy in Rare cancers: Knowledge database Establishing registrY) Project has been initiated to collect genetic, treatment, and prognostic information to enable a large-scale comprehensive database [193]. SCRUM-Japan (Cancer Genome Screening Project for Individualized Medicine in Japan) has also been initiated as a genomic screening project for lung cancer and gastrointestinal cancer [194]. These projects, led by the National Cancer Center, are expected to accelerate the global development of rare cancer drugs through reliable, integrated databases in Japan.

The Orphan Drug Act was passed in the US in 1983 to facilitate the development of orphan drugs, defined as drugs that are not developed by the pharmaceutical industry for economic reasons but that respond to a public health need. Japan established similar regulations. The review time for orphan drugs is significantly shorter than that for non-orphan drugs in Japan [47]. Studies have reported the specific characteristics of pivotal research on orphan drugs, including non-randomized, non-controlled, and Phase II studies [195]. A systemic analysis of study design for rare cancer drug approvals in the US revealed a 69% approval response rate [196]. Study designs applicable to rare cancer clinical trials have been discussed in order to identify the most efficient clinical development; this include umbrella studies, basket studies, N-of-1 studies, adaptive design, and Bayesian design [197]. Discussions about these innovative trial designs are ongoing in Japan to promote personalized medical care [198].

Profitability is considered one of the most important factors in pharmaceutical product development. Several papers have examined Japanese pharmaceutical characteristics and prognoses. It is reported that Japan’s unique pricing system indirectly encourages the development of anti-cancer drugs and leads to higher prices compared to other drugs [99], [100], [118]. Moreover, the development of anti-cancer drugs with novel modes of action has been encouraged at the global level, including in Japan, and the Japanese pharmaceutical market will rival the global market, in which anti-cancer drugs may be the most profitable among all therapeutic areas [128]-[130]. However, no systematic empirical research has

examined how rare cancer drugs produce profits. One paper investigated the profitability of orphan drugs for neurological diseases in Japan, but neurological diseases was the study's sole focus [131]. Based on these insights, however, this study hypothesizes that rare cancer drugs can be profitable in Japan.

The development of rare cancer drugs faces three hurdles (**Figure 5.1**). The first and second have been mitigated through the countermeasures discussed above. For the third, there is no relevant evidence on which countermeasures could be based. Thus, the primary objective of this study was to examine whether the development of drugs targeted to treat rare cancers can meet both the patients' and pharmaceuticals' needs in Japan, using the prescription data on selected drugs prescribed to treat rare cancers between 2010 and 2016.

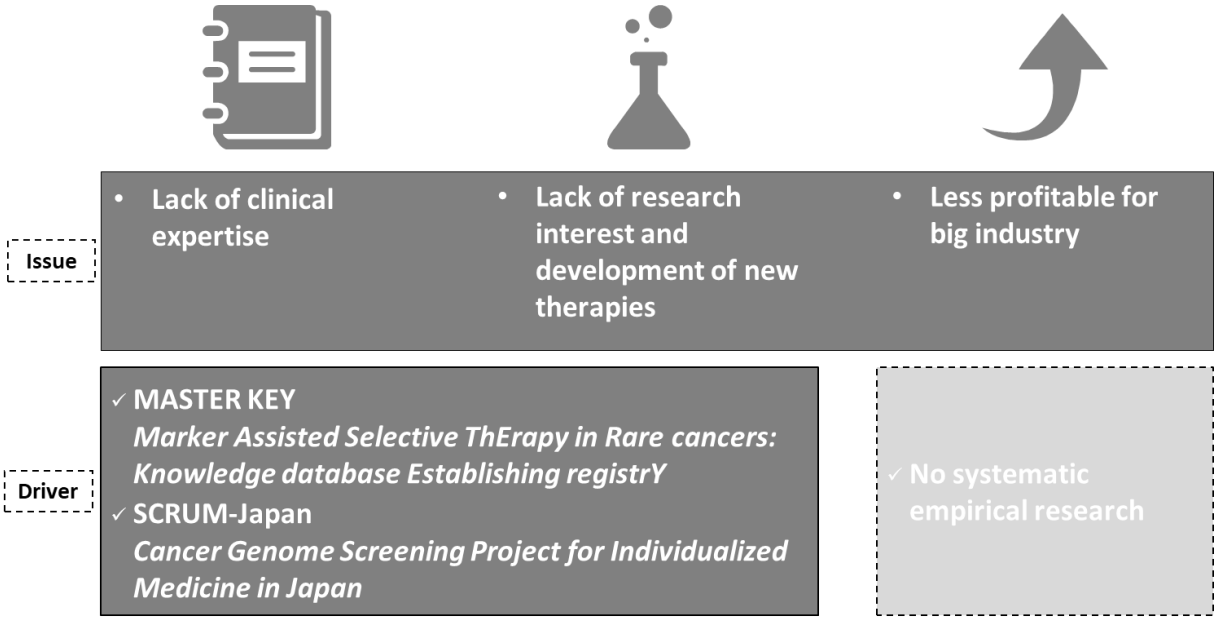


Figure 5.1. Specific challenges for rare cancer drugs

To the best of our knowledge, no study has used empirical data on prescription patterns to examine the profitability of drugs for rare cancers in Japan. The insight obtained by investigating recent prescription patterns will help stimulate the development of rare cancer drugs, primarily by pharmaceutical companies working in collaboration with clinicians and academia.

The primary objective of this research was to clarify whether it can be profitable for pharmaceutical companies to research and develop rare cancer drugs and thus address urgent UMN in Japan, thereby providing direction for future rare cancer drug development by pharmaceutical companies, clinicians,

and academia.

5.3 Methods

Database

The study's dataset was created using publicly available information obtained from the IQVIA Solutions Japan K.K. Market database. Data on the total sales amounts and prescription volumes of the selected anti-cancer drugs between 2010 and 2016 in Japan were analyzed. Therefore, the study used population data, not sample data.

Selection of rare cancer drugs

The selected rare cancer drugs were characterized to evaluate their potential market position in Japan's anti-cancer drug market. Specifically, drugs for chronic myelogenous leukemia (CML) and neuroendocrine tumor (NET) were selected (**Table 5-1**).

Table 5-1. Selected rare cancer drugs

Drugs	Indications	Approval dates
Imatinib	1. Chronic myelogenous leukemia 2. KIT (CD117) positive gastrointestinal stromal tumor 3. Philadelphia chromosome-positive acute lymphoblastic leukemia 4. FIP1L1-PDGFRα positive, hypereosinophilic syndrome, chronic eosinophilic leukemia	1. November 21, 2001 2. July 17, 2003 3. January 31, 2007 4. February 22, 2012
Dasatinib	1. Chronic myelogenous leukemia 2. Relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia	1. January 21, 2009 2. January 21, 2009
Nilotinib	1. Chronic myelogenous leukemia in chronic phase or transition phase	1. January 21, 2009
Ponatinib	1. Chronic myelogenous leukemia resistant to or intolerant to prior therapy 2. Relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia	1. September 28, 2016 2. September 28, 2016
Sunitinib	1. Gastrointestinal stromal tumor resistant to imatinib 2. Unresectable or metastatic renal cell carcinoma 3. Pancreatic neuroendocrine tumor	1. April 16, 2008 2. April 16, 2008 3. August 10, 2012
Everolimus	1. Unresectable or metastatic renal cell carcinoma 2. Neuroendocrine tumor 3. Unresectable or recurrent breast cancer 4. Renal angiomyolipoma with tuberous sclerosis 3. Subependymal giant cell astrocytoma with tuberous sclerosis	1. January 20, 2010 2. December 22, 2011 3. March 17, 2014 4. November 21, 2012 3. November 21, 2012
Streptozocin	1. Gastroenteropancreatic neuroendocrine tumor	5. September 26, 2014

The drug selection was performed on the basis of feasibility. The drugs for diseases that can receive relatively long-term pharmacotherapy among rare cancers were selected so that the prescription pattern could be investigated periodically. The indications and approval dates for the drugs of interest were selected by referring to the package inserts and interview forms available on the PMDA website [199].

Drug price of selected rare cancer drugs

The drug prices of the selected rare cancer drugs were calculated by dividing the sale amounts by the prescription volumes between 2010 and 2016. The MHLW website was consulted to identify the drugs that received pricing premiums [200].

Generic medicines of interest for this study

Imatinib generic medicines, which are the only generic medicines for CML, were selected for this study to investigate the prescription patterns of generic medicines for CML and NET. Since no generic medicines were available in NET, only imatinib for CML was selected for study.

5.4 Results

Prescription drug trends for rare cancers

The prescription patterns of the drugs for CML are shown in **Figure 5.2**. The prescription trends of each drug are similar, both in sales amounts and prescription volumes. The sales and prescription volumes of imatinib have been decreasing every year, while those of dasatinib and nilotinib have been increasing every year. The data on ponatinib cover only 2016; therefore, no trend has been confirmed. Dasatinib has the largest market share in CML drugs.

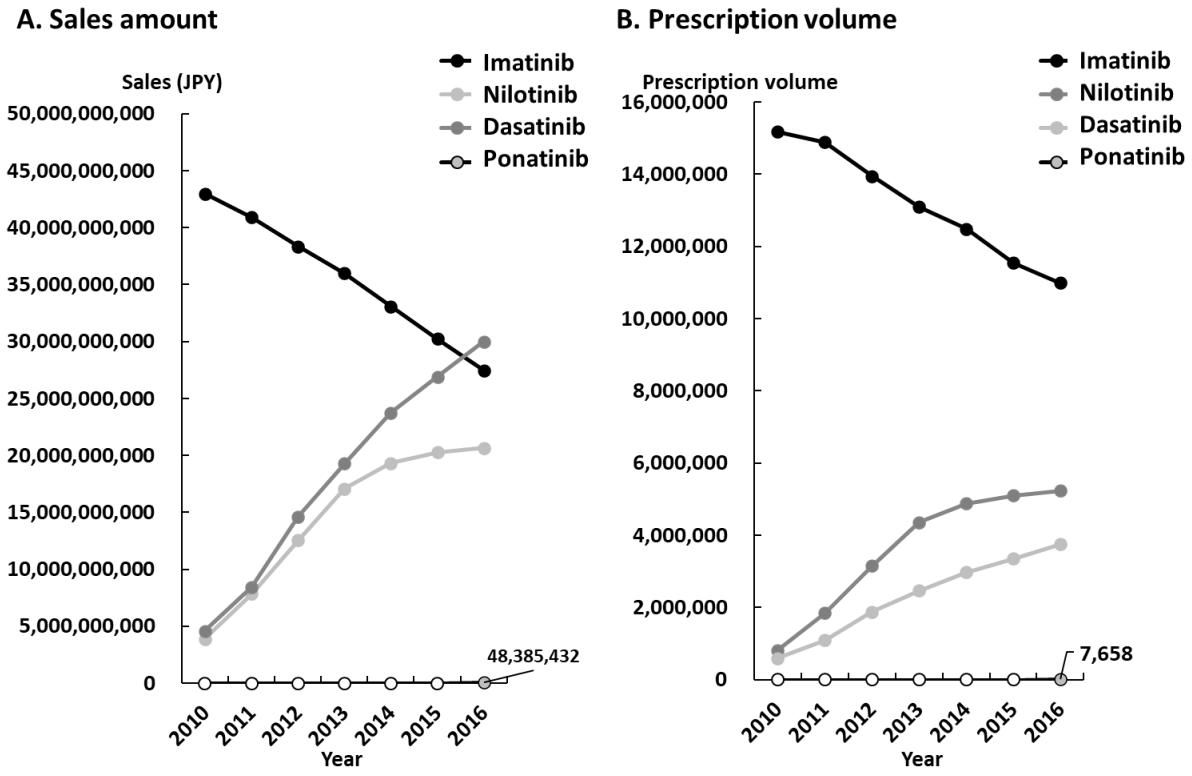


Figure 5.2. Prescription pattern of drugs for chronic myelogenous leukemia

White circles indicate that no data are available

The prescription patterns of the NET drugs are shown in **Figure 5.3**. The prescription trends of each drug are also similar, both in sales amounts and prescription volumes. The sales and prescription volumes of sunitinib and everolimus have been increasing every year. An increasing trend was also confirmed for streptozocin, although for a limited period. Everolimus has the largest market share in NET drugs.

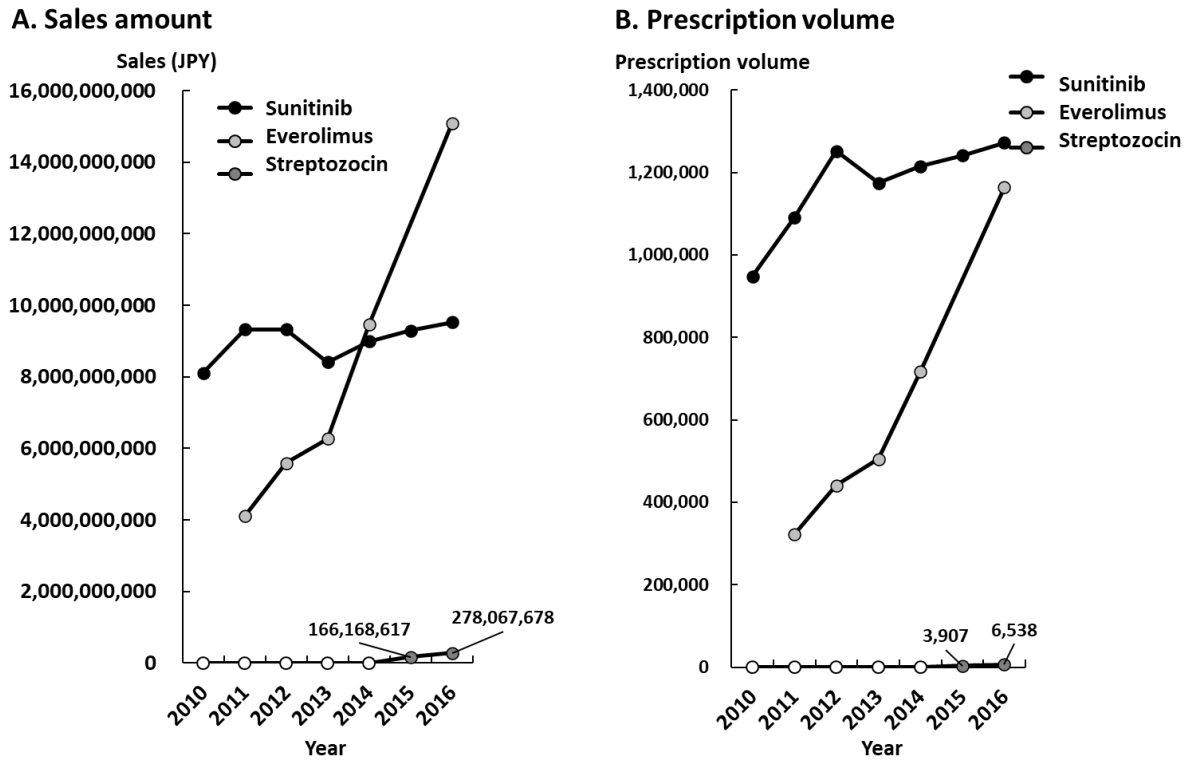


Figure 5.3. Prescription pattern of drugs for neuroendocrine tumors

White circles indicate that no data are available

Prescription drug trends for imatinib generic medicines

As described above, the only generic medicine available is imatinib; the other rare cancer drugs of interest have no generic versions. The prescription patterns of imatinib (original), imatinib (generic), and imatinib (original and generic) are shown in **Figure 5.4**. The sales and prescription volumes of imatinib (generic) have been increasing since 2013, when the first generic medicines were launched. However, those of imatinib (original) and imatinib (original and generic) have been decreasing.

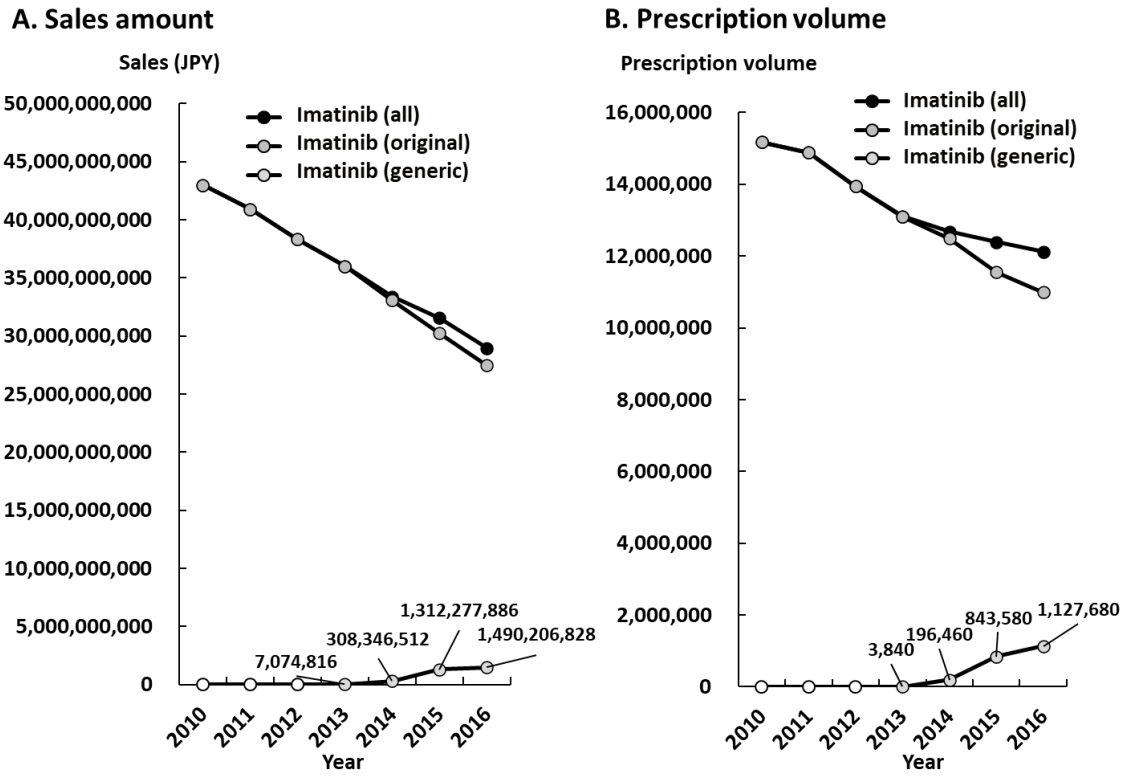


Figure 5.4. Prescription pattern of imatinib (original), imatinib (generic), and imatinib (original and generic)

White circles indicate that no data are available; “imatinib (all)” indicates imatinib (original and generic)

The number of imatinib generic medicines available in CML is shown in **Figure 5.5**. The first generic medicines were launched in 2013, and the numbers of generic medicines increased to 17 in 2016.

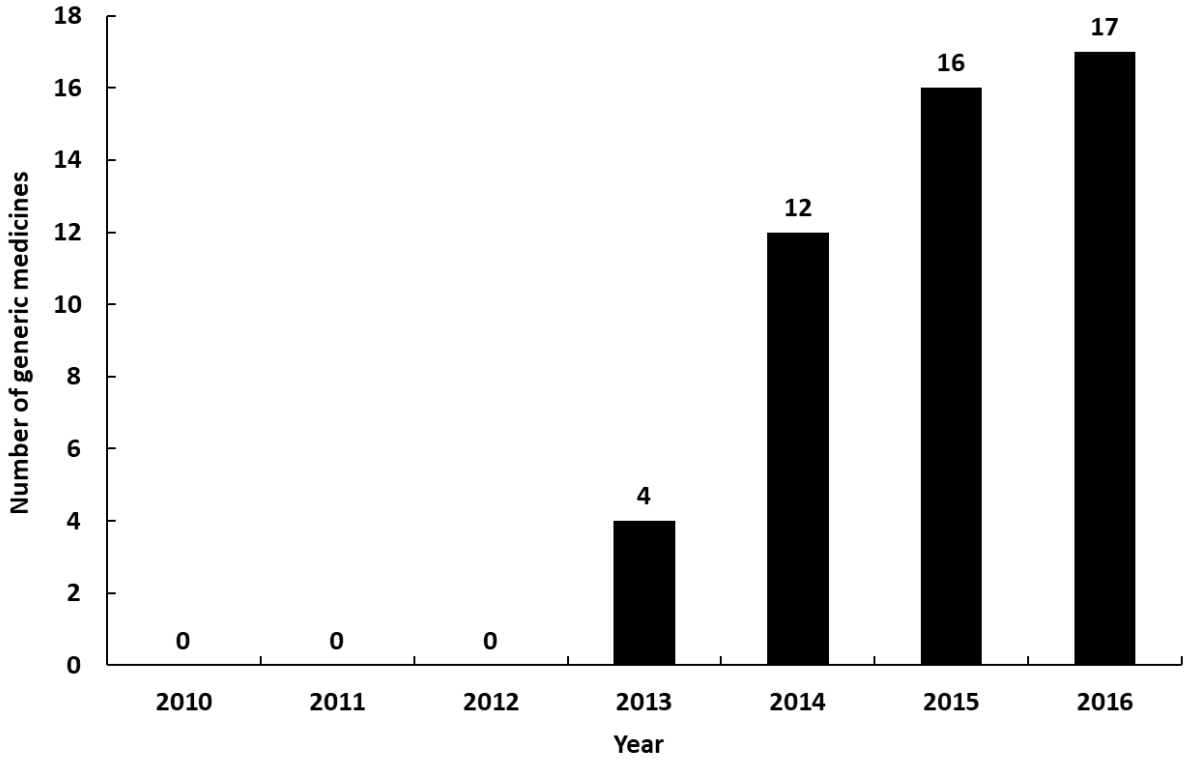


Figure 5.5. Number of imatinib generic medicines available between 2010 and 2016

Drug prices of rare cancer drugs

The calculated drug prices are shown in **Table 5-2**. For CML drugs, the highest price was for dasatinib and the lowest was for imatinib. The prices of imatinib and nilotinib were lower in 2016 than in 2010. On the other hand, prices for dasatinib were higher. The rates of change from 2010 to 2016 were 88.3% (imatinib), 88.5% (nilotinib), and 105.0% (dasatinib).

Table 5-2. Calculated drug prices of selected drugs for rare cancers

	2010	2011	2012	2013	2014	2015	2016
Imatinib	2,831.8	2,749.0	2,749.0	2,749.0	2,648.2	2,617.4	2,499.6
Dasatinib	4,718.7	4,235.9	3,984.1	3,907.9	3,955.1	3,964.1	3,940.5
Nilotinib	7,601.9	7,699.6	7,787.3	7,823.5	7,966.6	8,016.5	7,984.5
Ponatinib	n/a	n/a	n/a	n/a	n/a	n/a	6,318.3
Sunitinib	8,546.3	8,546.3	7,451.2	7,161.8	7,401.3	7,482.4	7,482.4
Everolimus	n/a	12,711.1	12,677.8	12,400.4	13,180.3	n/a	12,956.4
Streptozocin	n/a	n/a	n/a	n/a	n/a	42,531.0	42,531.0

n/a: Data not available
Drug prices have been calculated by dividing sales amounts by prescription volumes in each year and are presented in JPY.

Of the NET drugs, the highest-priced was streptozocin and the lowest-priced was sunitinib. The 2016 prices are lower than those in 2010 (sunitinib) and 2011 (everolimus), whereas prices are higher for everolimus. The rates of change from 2010 (sunitinib) and 2011 (everolimus) to 2016 are 87.6% (sunitinib) and 101.9% (everolimus).

Drug prices of imatinib generic medicines

The calculated drug prices of imatinib generic medicines are shown in **Table 5-3**. In 2016, the highest price was 1,555 JPY and the lowest was JPY 1,171, indicating that the generic drug prices were set between JPY 1,171 and 1,555, almost half of the price of imatinib (original).

Table 5-3. Calculated drug prices of imatinib generic medicines

	2010	2011	2012	2013	2014	2015	2016
GE1	n/a	n/a	n/a	1,842	1,552	1,575	1,284
GE2	n/a	n/a	n/a	1,842	1,555	1,540	1,338
GE3	n/a	n/a	n/a	1,842	1,558	1,540	1,339
GE4	n/a	n/a	n/a	1,842	1,581	1,540	1,256
GE5	n/a	n/a	n/a	n/a	1,661	1,754	1,555
GE6	n/a	n/a	n/a	n/a	1,540	1,540	1,345
GE7	n/a	n/a	n/a	n/a	1,769	1,651	1,359
GE8	n/a	n/a	n/a	n/a	1,540	1,540	1,224
GE9	n/a	n/a	n/a	n/a	1,540	1,540	1,235
GE10	n/a	n/a	n/a	n/a	1,386	1,386	1,216
GE11	n/a	n/a	n/a	n/a	1,386	1,386	1,210
GE12	n/a	n/a	n/a	n/a	1,386	1,386	1,298
GE13	n/a	n/a	n/a	n/a	n/a	1,386	1,309
GE14	n/a	n/a	n/a	n/a	n/a	1,386	1,202
GE15	n/a	n/a	n/a	n/a	n/a	1,429	1,341
GE16	n/a	n/a	n/a	n/a	n/a	1,386	1,171
GE17	n/a	n/a	n/a	n/a	n/a	n/a	1,207

GE: Generic medicine

n/a: Data not available

Drug prices were calculated by dividing sales amounts by prescription volumes in each year and are presented in JPY.

5. 5 Discussion

This study demonstrates that the rare cancer drugs whose indications focus on CML and NET can leverage strong sales in Japan. The study identifies two types of profitable models for developing rare cancer drugs: (1) For CML, sales amounts can be assured if the clinical positioning becomes clear with the existing drugs through well-designed clinical trials even though it is a "follower" drug. (2) For NET, obtaining a rare cancer label can stimulate drug development for the more common cancers, leveraging greater profits.

Of the CML drugs, imatinib was the FIC drug. Then, dasatinib, nilotinib, and ponatinib were launched as follower drugs (**Table 5-1**). They are all Tyrosine-Kinase inhibitors. However, dasatinib, nilotinib, and ponatinib show increasing prescription trends although it is difficult not to consider the patent expiration of imatinib, resulting in the penetration of generic medicines (**Figure 5.2**, **Figure 5.4**, and **Figure 5.5**). The indications of all of the imatinib generic medicines were CML and Philadelphia chromosome-positive acute lymphoblastic leukemia [199], and the patients with these cancers receive long-term therapy, with the prices of the generic medicines being almost half that of the original imatinib (**Table 5-3**). Therefore, the markets in the above two indications are highly competitive. However, the other two indications (gastrointestinal stromal tumor and hypereosinophilic syndrome/chronic eosinophilic leukemia) are dominated by imatinib (original), which serves as a brake on the decline in sales amounts and prescription volumes. Nilotinib [201] and ponatinib [202] could induce stronger clinical responses and a focus on CML resistant to or intolerant to prior therapy, which gives them a clinical position distinct from that of imatinib [203], [204]. Overall, stable sales can be assured even in rare cancers if the clinical positioning can be clearly established.

Of the NET drugs, sunitinib, streptozocin, and everolimus increased their sales and prescription volumes by obtaining the NET indication (**Figure 5.3**). Everolimus drastically increased sales and prescription volumes by obtaining the indication for unresectable or recurrent breast cancer. This "from niche market to mass market" strategy is considered to be a profitable model for rare cancer drug development, considering the recent advances in molecular biology research for cancer treatment and given that most of the candidate drugs under clinical development are molecular targeted drugs, which are unlikely to be affected by generic medicine penetration [132], [133].

The indication for rare cancer can be obtained based on early-phase clinical data by an effective use of biomarkers in clinical trials, such as basket and umbrella trails, as genomic medicine advances [191], [205], [206]. Using biomarkers can assist in accurate appraisals of clinical efficacy and safety data in

clinical trials or can be used as surrogate markers to evaluate efficacy and safety data, especially in early-phase trials [207]. In addition, stratifying patients using biomarkers can enhance efficacy and safety. These innovative clinical trial designs can boost the clinical development of rare cancer drugs.

However, it is necessary to mention the approval of nivolumab in Japan while proposing this profitable model. It raises concerns about the sustainability of Japan's health care system, as it may be damaged through the use of nivolumab owing to the high price set when the indication for melanoma was approved [208]. The agents in immune-oncology (IO) have transformed cancer therapy via the durable response rate, and the number of new clinical trials worldwide in 2017 was reported to be 469 [209], which includes many trials investigating combination therapy with other immune modulators, targeted therapy, chemotherapy, and radiation therapy [210]. Similar financial issues may occur in the Japanese health insurance system after the approval of the other IO therapies. Indeed, it was reported that cancer patients can suffer "financial toxicity" due to cancer therapy, although this was reported outside of Japan [211]. Considering the increasing health care expenditures, the potential financial burdens that IO agents may impose on the nation, rather than on cancer patients, have to be discussed. Health technology assessment is considered to be a potential solution for rising health care expenditures [212]. It can play a critical role in keeping health care sustainable in Japan while ensuring patients' access to innovative new drugs. Future strategies should include efforts to adequately appraise rare cancer care and refine the health insurance system, while also seeking opportunities to develop rare cancer drugs by stimulating industry-sponsored clinical trials through the proper incentive systems. This study provides important insights by which pharmaceutical companies can ensure the profitability of rare cancer drugs so as to ensure patients' timely access to innovative rare cancer care.

Two drugs (nilotinib and dasatinib) of the four drugs available for CML and all drugs (sunitinib, everolimus, and streptozocin) available for NET received premium rewards in their drug pricing in 2018 ("Price maintenance premium"). This indicates that prices higher than those for drugs designed for common cancers can be set for rare cancer drugs. Wakutsu et al. reported that the benefits brought by this premium reward system encouraged clinical development by allowing pharmaceutical companies to recover their R&D costs at an early stage [213]. However, Wakutsu et al. also stressed that the benefits can be limited, especially for orphan drugs, suggesting that financial support is strongly needed in this disease area to deliver new drugs efficiently [213]. In Japan, drug prices are set by the government and are revised every other year. One of the drug profiles associated with price cutting in regular drug price revisions is reported to be having follower drugs on the market [151]. This may also be true of rare

cancer drugs, thus posing as a negative factor for the development of rare cancer drugs. Indeed, for CML, downward trends in drug prices of Tyrosine-Kinase inhibitors were confirmed for imatinib and nilotinib (**Table 5-2**). Therefore, intensive discussions are required about drug pricing and the balance between the profitability of rare cancer drugs and overall health care expenditures in Japan.

This study has several limitations. In discussing profitability, R&D costs must be considered. However, this study did not consider that issue. Furthermore, it is difficult to conclude that rare cancer drugs can be profitable based only on the results obtained from this study, as the target indication should be expanded to cover all rare cancers. The dataset on the drugs examined in this study was not stratified by CML or NET, and the prescription data included all the indications for each drug. Future research should estimate the R&D costs for new drugs through mathematical models or proper simulations and investigate the prescription trends of all rare cancer drugs available in Japan, while adequately stratifying the data by each rare cancer indication.

Despite these limitations, the study fills a research gap by directly testing the profitability of rare cancer drugs (though only the drugs for CML and NET) and revealing the potential capabilities of rare cancer drugs to acquire market share and recover their R&D costs.

5. 6 Conclusions

Rare cancer drugs are associated with higher market value and greater profits, suggesting that further clinical development programs in this area should be encouraged to meet the high UMN (**Figure 5.6**).

- ✓ The study of drugs for the indication of CML found that, even if the drug is not FIC, it will have high sales if its clinical positioning with existing drugs can be clarified in clinical trials.
- ✓ The study of NET drugs found that expanding the indication to a cancer type with a large number of patients after launching the drug for a rare cancer results in high sales.
- ✓ Although there are some limitations to this study, analyzing the sales amounts and prescription volumes of rare cancer drugs produces a quantitative determination of whether such drugs can produce high sales for pharmaceutical companies.

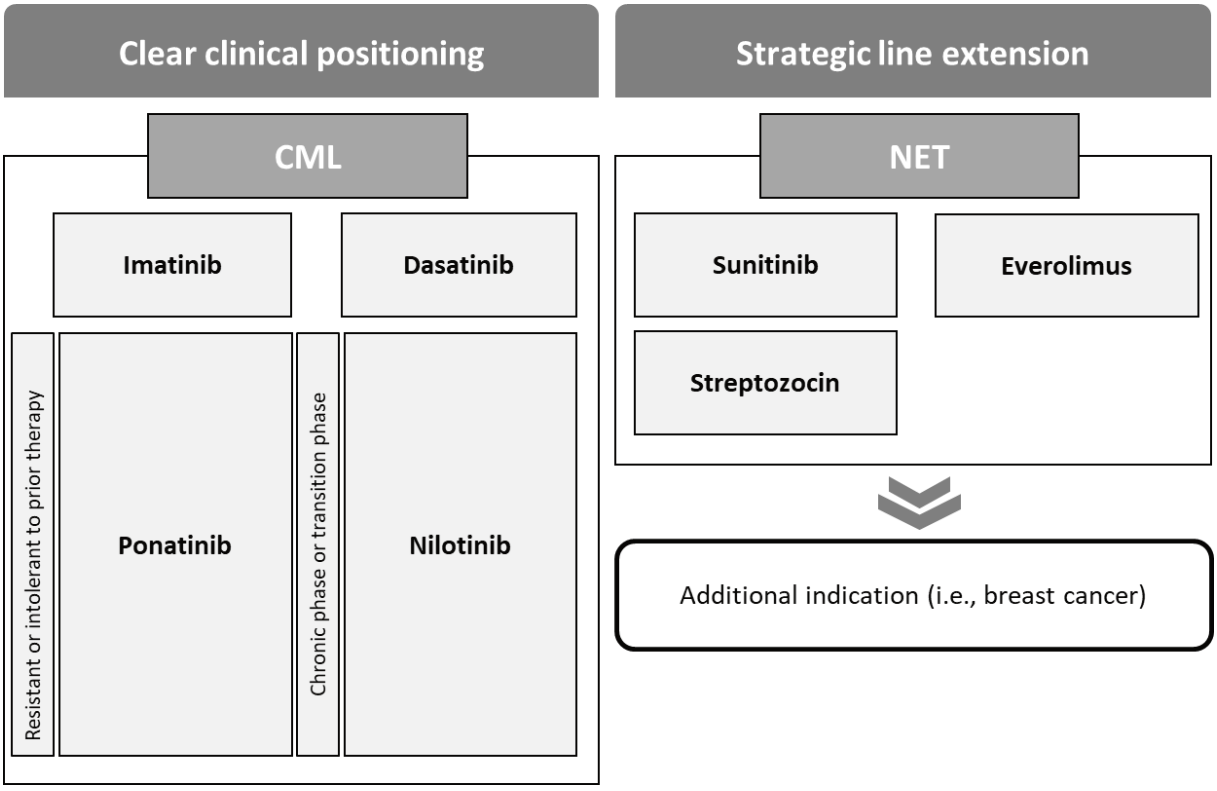


Figure 5.6. Visual abstract

In this section, the implications for R&D strategies for anti-cancer drugs that should be considered "innovative" have been presented, particularly for rare cancers. In the next section, the findings on combination therapies are presented.

6. Implications for the Direction of R&D Strategy of Anti-cancer Drugs (2): Combination Therapies

6.1 Study Highlights

What is the current knowledge on the topic?

Anti-cancer drugs will play an important role in the Japanese market. This requires practical applications of R&D strategies for pharmaceutical companies to follow according to their R&D capabilities. There are limited studies in combination therapies describing them in that perspective.

What hypotheses did this study address?

4. Utilizing pharmaceutical regulations and considering the characteristics of anti-cancer drugs with the potential for high sales will enable the development of new drugs with high sales potential in Japan.

What does this study add to our knowledge?

"Product Strategy" on combination therapies was mainly discussed, because the insights on "Product Strategy" should provide direct implications for "R&D Strategy." This study identified key features of Broad Label approval that could maximize the prescription opportunities of anti-cancer drugs. This allowed effective R&D in combination therapies and enabled increased accuracy of the targeted approval label. These findings support the above hypothesis.

How might this change pharmaceutical companies' R&D strategy?

This should facilitate R&D in the areas of high likelihood of obtaining a Broad Label, if there are multiple clinically comparable regimens and a clinical trial is conducted to evaluate the clinical benefit of adding new anti-cancer agents to one of the major regimens, and should enhance the characterization of anti-cancer drug profiles when planning clinical trials.

6.2 Introduction

Anti-cancer drug therapy is a form of treatment using cytotoxic anti-cancer agents, endocrine agents, molecularly targeted drugs, and immune checkpoint inhibitors. Recent advances in molecular biology have elucidated the mechanisms by which anti-cancer drugs exert their antitumor effects, lead to cell death, and cause drug resistance. Pharmacotherapy is expected to evolve further cancer treatments and

new therapeutic strategies are expected from empirical administration to a personalized approach to medicine [214].

Currently, the effect of single anti-cancer agents in most tumors is limited. Combination therapy is used to achieve the maximum therapeutic effect. The objectives are to enhance the therapeutic effects of each anti-cancer drug interaction, to broaden the spectrum of anti-cancer activities in a variety of cancers, and to avoid or delay the emergence of drug-resistant cells. The principles of combination therapy regimens include the selection of drugs with proven efficacy against the target tumors, the avoidance of concomitant anti-cancer drugs that are cross-tolerant due to resistance, and the selection of drugs with non-overlapping toxicity to maintain a higher dose intensity. In addition, each anti-cancer agent should be administered based on its ideal dosing schedule, and the interval between anti-cancer agents should be kept to a minimum. In addition, careful consideration should be given to the interaction between concomitant anti-cancer agents. Thus, pharmacokinetic and pharmacodynamic interactions, including the order of administration, should be taken into account in combination therapy [214].

In the field of cancer immunotherapy, based on recent advances in life sciences and various findings from clinical trials, immune checkpoint inhibitors have been successfully developed and are now being positioned as a new, scientifically based therapy. However, the therapeutic effect of immune checkpoint inhibitors is seen only in a limited proportion of patients who are treated with these agents, as there are some cancer types that respond to immune checkpoint inhibitors (hot tumors) and others that respond poorly (solid tumors), owing to differences in the anti-tumor immune response in the tumor microenvironment [215]. It is probably difficult to cure cancer with a single round of immunotherapy. However, as the biology of tumor microenvironment—including the surrounding blood vessels, immune cells, fibroblasts, signaling molecules, and the extracellular matrix—has been clarified [216]-[218], clinical trials are being carried out to investigate the efficacy and safety of a combination of immunotherapies or a combination of immunotherapy and existing chemotherapy [219].

As combination therapy is becoming a mainstay of cancer treatment, it is necessary to specify the regimen used in combination therapy in the package insert. Without such a provision, concomitant drugs without clinical trial evidence may be used, which may lead to off-label use. Off-label uses of anti-cancer drugs have indeed been reported, particularly with molecularly targeted drugs, anti-angiogenic drugs, and checkpoint inhibitors [220]. Concomitant drug provisions are based on evidence from clinical trials in the “Dosage and Administration” section [221], [222]. In order to promote the optimal use of innovative drugs with novel mechanisms of action based on the latest

scientific perspectives, the guidelines are developed in parallel with the review of approval to indicate the requirements, perspectives, and considerations of both patients and medical institutions concerning the use of such drugs [223]. However, the “Dosage and Administration“ section in package inserts does not define the combination therapies that have been evaluated for efficacy and safety in clinical trials as summarized in the Common Technical Document at the time of approval application. For example, a comparison of the dosage and administration of Avastin for colorectal cancer between the US and Japan shows that, in the US, only concomitant drugs that have been studied in clinical trials are allowed as an approved combination regimen [224], while in Japan, concomitant drugs are allowed to be used in combination with other anti-cancer agents” and are not limited to combination therapies used in clinical trials [225], as shown in **Figure 6.1**. A study examining the content of concomitant drug descriptions for anti-cancer drugs approved in Japan between April 2006 and March 2017 reported that the number of regimens included in the Common Technical Document may be related to the description given in the package inserts [226].

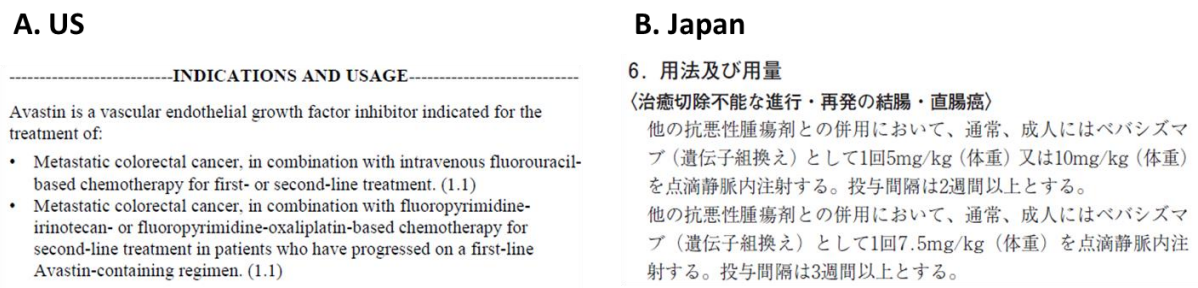


Figure 6.1. Avastin® package inserts

There are several reports on package inserts in Japan. One examines the timing of package insert revisions by categorizing the subject of analysis according to drug lag period [227]. Another compares the indications on reference labels between the US, Japan, and the European Union [228]. Another compares package inserts between the US, the United Kingdom, China, South Korea, and Japan with respect to information provided in the drug-drug interaction section [229]. Another compares pharmacokinetics information between China, Japan, and the US with respect to anti-cancer drugs [230]. Another studies the operational aspects of Japanese package inserts [231], and another proposes improvements in package inserts based on previous studies [232].

Thus, no recent studies review the descriptions of anti-cancer drug combination therapy in package

inserts. As mentioned, one of the principles of a combination therapy regimen is to select a drug whose efficacy has been validated for the target cancer. However, this is not indicated in the descriptions given in package inserts. Specifically, in cases where multiple concomitant drugs have been evaluated in clinical trials, there are some patterns in which concomitant drugs are specified beyond the scope of the drugs evaluated in the trials, such as Avastin in Japan; in such a case, only one drug is specified as a concomitant drug, and some of the patterns of the concomitant drugs evaluated in clinical trials are specified as they are. These three patterns are defined as “Broad Label,” “Narrow Label,” and “Same Label,” in the order presented in **Figure 6.2**.

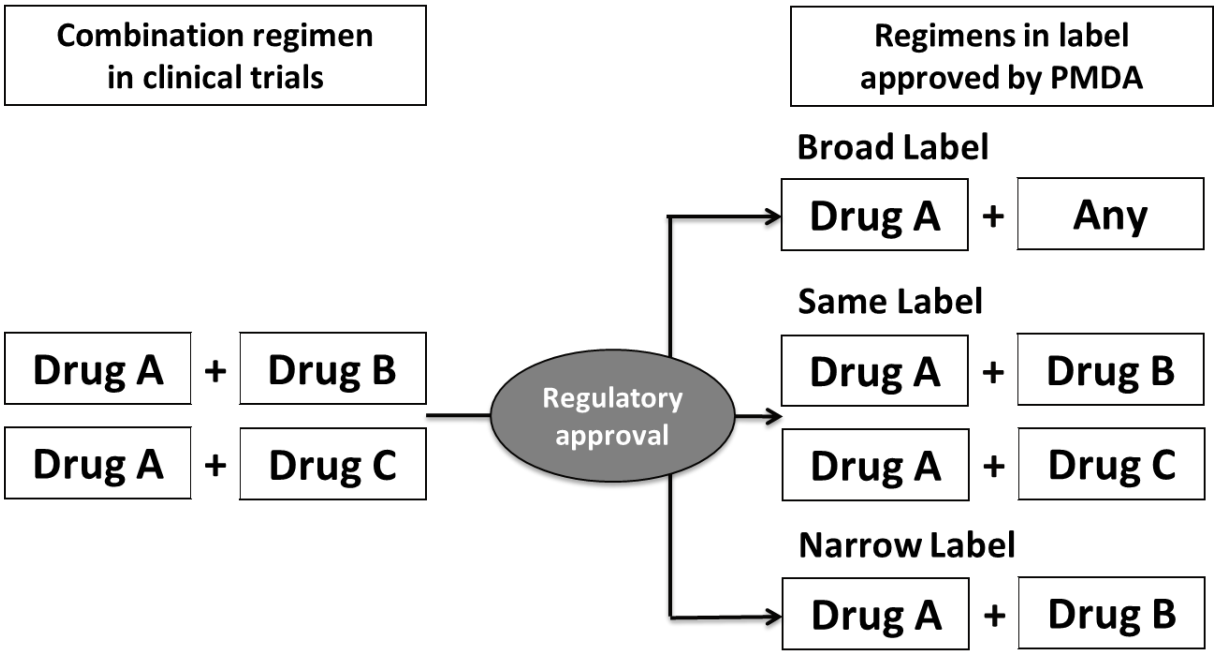


Figure 6.2. Groups of approval records

To solve the problem posed by the need to use anti-cancer drugs approved in Japan but not approved for certain indications for certain types of cancer, a committee has been established to expedite the acquisition of the indications of anti-cancer drugs needed for combination therapy [233]. However, no in-depth study has investigated which drugs are classified into the three patterns described above, and it is not known what characteristics each pattern has. In particular, it is very important to investigate the Broad Label since this pattern does not necessarily have an unfavorable aspect; pharmaceutical companies can maximize their chances of drug prescription because there are no restrictions on concomitant drugs; physicians can prescribe multiple anti-cancer drugs based on the latest evidence that

is yet unapproved in Japan.

This study investigated anti-cancer drugs approved in Japan between April 2006 and March 2020 under the condition that the drug be dosed in combination with some other anti-cancer drugs, and attempted to elucidate the characteristics of the Broad Label, which is an important consideration for the approval of anti-cancer combination therapy in Japan. The results should help pharmaceutical companies determine the best R&D strategy for maximizing prescription opportunities for their products used in combination therapy, which is the mainstay of anti-cancer therapy.

6.3 Methods

Drugs of interest

The study drugs were selected from the "List of Approved New Drugs" on the PMDA website [234] for all anti-cancer agents approved in Japan between April 2006 and March 2020. A total of 186 anti-cancer drug approvals were selected as the target drugs, excluding those without clinical trials in the Common Technical Document and those for public knowledge-based applications. Therefore, the study used sample data, not population data.

Statistical analysis

The study examined the review reports of each drug on the PMDA website and classified those approved for combination therapy and for monotherapy. Then, the study compared the package insert of the drugs approved for adjunctive therapy with the review report and classified them as Broad Label, Narrow Label, and Same Label. The number of regimens assessed in clinical trials included in the Common Technical Document for those drugs was investigated, and the differences in each category were examined using Tukey's test.

A multinomial logistic regression analysis was then conducted to examine the factors influencing each category. The objective variables were set to "Broad Label," "Narrow Label," and "Same Label," and the explanatory variables were set to the following binary variables: Type of cancer (Solid vs. Blood), Approval characteristics (new molecular entity vs. indication expansion), Company (Global vs. Japanese), Review category (Priority review [Yes vs. No], Expedited review [Yes vs. No], Conditional approval [Yes vs. No], SAKIGAKE designation [Yes vs. No], and Orphan drug designation [Yes vs. No]). Although the regression analysis was exploratory, the level of scientific verification was critically limited. However, a certain level of justification for the variable selection was confirmed because it was

based on previous studies focusing on anti-cancer drugs [50], [55].

Multinomial logistic regression analysis, which can model the probabilities for binary classification problems, was conducted. When a response variable was categorical, the relationship between the logarithm of the odds and explanatory variables was modeled as follows:

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 x_1 + \cdots + \beta_i x_i$$

where p, x, β, and i are the predicted probability, explanatory variable, regression coefficient optimized by a maximum likelihood estimation, and number of explanatory variables, respectively. This logistic regression approach can be extended to a multiclass classification problem, and the group membership probabilities are given as a log-linear function of x for any class K, including the baseline category:

$$P(y = k|x) = \frac{exp\left(\beta_0^k + \beta_1^k x_1 + \cdots + \beta_i^k x_i\right)}{\sum_{j=1}^{K} exp\left(\beta_0^j + \beta_1^j x_1 + \cdots + \beta_i^j x_i\right)}$$

where K is the number of classes. New unknown data were classified into group k, in which the obtained probability is the largest.

The study established a classification model that could discriminate between the three label description types (Broad, Same, and Narrow). Multinomial logistic regression analyses were conducted to explore the factors that provided the clearest discrimination.

6.4 Results

Of the 188 drugs, 63 were listed for combination therapy and 125 for monotherapy, as shown in **Table 6-1**.

Table 6-1. Characteristics of study drugs

A. Approved therapies (all drugs of interest)

Variable	N
Approved therapy	
Monotherapy	125
Combination therapy	63
Type of cancer	
Solid	125
Blood	63
Approval characteristics	
New molecular entity	91
Indication expansion	97
Company	
Global	106
Japanese	82
Review category	
Priority review	28
Expedited review	4
Conditional approval	3
SAKIGAKE designation	4
Orphan drug designation	94
Label category	
Broad	16
Same	166
Narrow	6

B. Approved therapies (monotherapy)

Variable	N
Type of cancer	
Solid	86
Blood	39
Approval characteristics	
New molecular entity	70
Indication expansion	55
Company	
Global	72
Japanese	53
Review category	
Priority review	18
Expedited review	2
Conditional approval	3
SAKIGAKE designation	4
Orphan drug designation	66
Label category	
Broad	0
Same	125
Narrow	0

C. Approved therapies (combination therapy)

Variable	N
Type of cancer	
Solid	39
Blood	24
Approval characteristics	
New molecular entity	21
Indication expansion	42
Company	
Global	34
Japanese	29
Review category	
Priority review	10
Expedited review	2
Conditional approval	0
SAKIGAKE designation	0
Orphan drug designation	28
Label category	
Broad	16
Same	41
Narrow	6

The regimen category of clinical trials in each approved therapy is shown in **Table 6-2**. Of the drugs whose regimen of clinical trials includes combination therapy, 16 were Broad Label, 41 were Same Label, and six were Narrow Label for combination therapy drug approvals; all approvals were Same Label for monotherapy drug approvals.

Table 6-2. Regimen category of clinical trials in each approved therapy

Approved therapy	Regimen of clinical trials		Total
	Monotherapy	Combination therapy	
Monotherapy	102	23*	125
Combination therapy	0	63**	63
Total	102	86	188

* Broad: 0, Same: 23, Narrow: 0.
** Broad: 16, Same: 41, Narrow: 6.

The results of Tukey's test revealed significant differences in the numbers of regimens included in the application for approval between the labels. These were, on average, 2.0 regimens for Broad Label, 1.1 regimens for Same Label, and 3.7 regimens for Narrow Label, as shown in **Figure 6.3**.

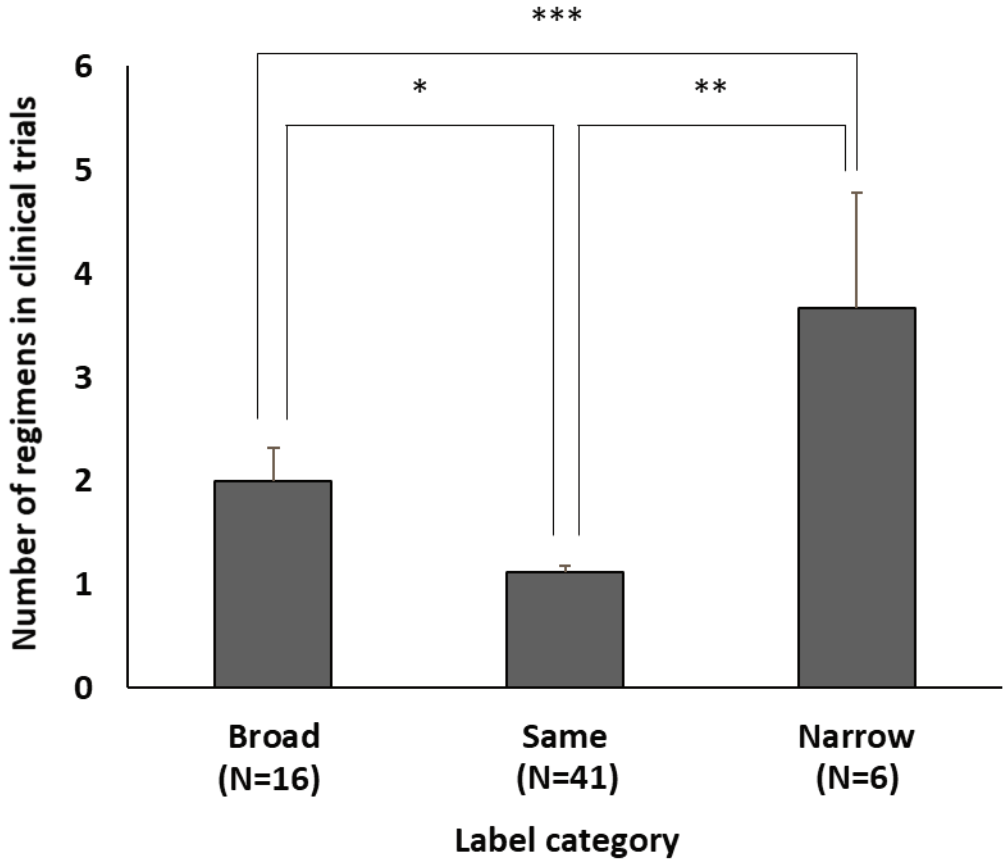


Figure 6.3. Number of regimens in clinical trials in each label category

The significance of the difference between the value of each label category was determined by one-way ANOVA with Tukey's post hoc test, at $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Multinomial logistic regression analysis was conducted based on the variables as shown in **Table 6-3**. The results are shown in **Table 6-4**. Trends could be confirmed for some variables. However, no significant differences were confirmed for any of the variables evaluated.

Table 6-3. Variables for multinomial logistic regression analysis

Variable	
Label category	
Same	1
Broad	2
Narrow	3
Approval characteristics	
Indication expansion	0
New molecular entity	1
Type of cancer	
Blood	0
Solid	1
Company	
Global	0
Japanese	1
Priority review	
No	0
Yes	1
Expedited review	
No	0
Yes	1
Orphan drug designation	
No	0
Yes	1

Table 6-4. Results of multinomial logistic regression analysis

	Partial regression coefficient	Standard error	*p*	Odds ratio	95% CI	
					Lower limit	Upper limit
Broad Label						
Approval characteristics	0.066	0.694	0.936	1.057	0.271	4.115
Company	-0.377	0.641	0.557	0.686	0.195	2.412
Type of cancer	-0.107	0.742	0.885	0.898	0.210	3.846
Priority review	0.277	0.970	0.775	1.320	0.197	8.833
Expedited review	-16.992	2005.920	0.993	0.000	0	-
Orphan drug designation	0.295	0.741	0.691	1.343	0.314	5.741
Narrow Label						
Approval characteristics	-1.215	0.995	0.222	0.297	0.042	2.087
Company	1.381	1.197	0.248	3.980	0.381	41.546
Type of cancer	-0.346	1.468	0.814	0.707	0.040	12.561
Priority review	-0.285	1.131	0.801	0.752	0.082	6.906
Expedited review	-0.392	0.000	-	0.676	0.676	0.676
Orphan drug designation	1.514	1.464	0.301	4.546	0.258	80.097

Reference: Same Label.

Since the exploratory multinomial logistic regression analysis did not identify any factors that significantly contributed to the Broad Label (or Narrow Label) drugs, the drug names and indications for which the respective labels obtained approval are shown in **Table 6-5** for a case analysis of individual drugs. Among the 16 records in Broad Label, 12 approvals were line extensions. Among the six records in Narrow Label, four approvals were NMEs.

Table 6-5. Drug names and indications in the Broad/Narrow Labels

A. Broad Label

Drug	Approval
Atezolizumab	・ Unresectable, advanced, or recurrent non-small cell lung cancer
Abemaciclib	・ Hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer **
Bevacizumab	・ Unresectable, advanced, or recurrent colorectal cancer *, **
	・ Unresectable, advanced, or recurrent colorectal cancer *
	・ Non-squamous non-small cell lung cancer
	・ Ovarian cancer
	・ Advanced or recurrent cervical cancer
Bortezomib	・ Multiple myeloma *
	・ Multiple myeloma *
	・ Mantle cell lymphoma
Daratumumab	・ Multiple myeloma
Fulvestrant	・ Breast cancer
Mogamulizumab	・ CCR4-positive adult T-cell leukemia/lymphoma
Palbociclib	・ Unresectable or recurrent breast cancer **
Pertuzumab	・ HER2-positive breast cancer **
Rituximab	・ CD20-positive chronic lymphocytic leukemia

Approvals were granted for NMEs or line extensions.
* Two different approval records exist.
** NME

B. Narrow Label

Drug		Approval
Aflibercept	・	Unresectable, advanced, or recurrent colorectal cancer *
Bevacizumab	・	Unresectable or recurrent breast cancer
Cabazitaxel	・	Prostate cancer *
Lapatinib	・	Unresectable or recurrent breast cancer with confirmed HER2 overexpression *
Panobinostat	・	Relapsed or refractory multiple myeloma *
Ramucirumab	・	Unresectable, advanced, or recurrent colorectal cancer

Approvals were granted for NMEs or line extensions.
* NME

6.5 Discussion

This study investigates the classification of anti-cancer drugs approved in Japan between April 2006 and March 2020 into three labels: Broad Label, Same Label, and Narrow Label (**Figure 6.2**). As the description of the package insert, especially the dosage and administration section, is considered to be based on clinical trial results, the number of regimens submitted at the time of application for approval was investigated to determine if there was a significant difference in the number for each label. The results show that the number of regimens increased in the following order: Narrow > Broad > Same (**Figure 6.3**). Including a combination regimen series with more than two regimens seems to be a reasonable way to obtain approval for combination therapy without facing a restriction in the combination use of other anti-cancer drugs for reimbursement.

A multinomial logistic regression analysis based on previous studies was conducted to explore the factors that contribute to each label. No significant differences were found for any of the variables. Because the number of drugs in each label was small and the validity of the variable selection was limited, the case analysis of the drugs in the Broad Label and Narrow Label is discussed below.

While no causal relationship was confirmed, it is notable that the Broad Label had more line extensions (12 out of 16) while the Narrow Label had more drugs approved as NMEs (4 out of 6; **Table 6-5**), suggesting that Broad Label seems to be granted primarily at the time of line extension and that the

condition of first approval as an NME may have an impact on the condition of approval for line extensions.

The following is a narrative discussion based on the description of the review report for each drug in each Label.

Broad Label

Atezolizumab is an antibody medicine approved for the treatment of unresectable, advanced, or recurrent non-small cell lung cancer. Initially, it was defined as being prescribed in combination with carboplatin, paclitaxel, and bevacizumab; however, the restrictions on this combination were expanded after it was demonstrated to be effective in combination with multiple chemotherapies, including platinum anti-cancer drugs. Although it is a Broad Label as per the package insert, it can be considered a Same Label because the details of the regimen are specified in the Optimal Clinical Use Guidelines, which provide detailed information on various regimens to specify the most appropriate regimen from among the treatment options, as many combination therapies, including platinum anti-cancer agents, are recommended for the drug treatment of lung cancer [235].

Abemaciclib is approved for the treatment of unresectable or recurrent breast cancer that is hormone receptor-positive and HER2-negative. This is an example of a broader approval of endocrine therapy beyond the regimen investigated in a clinical trial. According to the review report, the review was conducted because the sponsor listed several drugs that were not concomitant with abemaciclib but were considered to be comparable with the regimens evaluated in the clinical trials and as other endocrine therapies may also be effective owing to abemaciclib's action mechanism. As a result, the PMDA reported that the only endocrine therapies that have shown clinical benefits in combination with abemaciclib were fulvestrant, letrozole, and anastrozole, and that no clinical trial results have been obtained showing clinical benefits when abemaciclib is administered in combination with other endocrine therapies. Therefore, when administering abemaciclib, it is important to understand the concomitant drug and to select the concomitant endocrine therapy in the package insert. Endocrine treatment is considered a standard choice for patients with estrogen-receptor positive cancers and several therapeutic regimens used in patients with breast cancer [236]. Given the accumulation of a significant amount of clinical data, a clinical trial to evaluate the combination with a typical regimen would likely establish a Broad Label for the combination with endocrine therapy. A similar discussion took place in the case of palbociclib, and a Broad Label was set in this drug as well.

Bevacizumab is approved for the treatment of unresectable advanced or recurrent colorectal cancer, unresectable advanced or recurrent non-small cell lung cancer excluding squamous cell carcinoma, ovarian cancer, and advanced or recurrent cervical cancer, all within the scope of the Broad Label. In the case of colorectal cancer, the PMDA has set a Broad Label in response to the sponsor's opinion that a regimen should be selected by comprehensively taking into account the safety profile of the regimen and the patient's condition as investigated in clinical trials. The mainstay of treatment for colorectal cancer is a combination of multiple anti-cancer drugs and molecularly targeted therapies; treatment is continued or changed based on the effects and general condition of the patient [237]. Based on these conditions, a Broad Label may have been set to allow investigator choice therapy for concomitant drugs. In the case of non-small cell lung cancer, the sponsor argues that the results can be extrapolated to other regimens that are comparable in efficacy to those reviewed in clinical trials. The PMDA set the Broad Label emphasizing that while there is no need to categorically restrict the use of combination chemotherapy with other platinum-based anti-cancer agents, careful attention should be paid to efficacy and safety profiles. This is similar to the atezolizumab case. For ovarian cancer, a Broad Label was set; it was emphasized, however, that this drug should be initiated in combination with carboplatin and paclitaxel, which is considered to be standard for ovarian cancer care [238] and only in a combination regimen evaluated in the clinical trial. Thus, this may not actually be a Broad label. In the case of cervical cancer, a Broad Label was set with the description that it should be initiated in combination with other anti-cancer agents, including Paclitaxel, because two regimens that include paclitaxel are considered to be the standard of care [239]. In this context, the current label allows physicians to select the optimal regimen.

Bortezomib is a drug approved for the treatment of multiple myeloma and mantle cell lymphoma. In the case of multiple myeloma, the PMDA has assigned a Broad Label to multiple myeloma, based on the opinion that a regimen should be selected based on the safety profile of the regimen studied in clinical trials and the patient's condition according to the clinical practice guidelines [240], [241]. In the case of mantle cell lymphoma, a Broad Label was also set in the same context. The same applies to daratumumab, as the drug is indicated for multiple myeloma.

Fulvestrant is a drug approved for the treatment of breast cancer. Clinical benefit is expected only when palbociclib and fulvestrant are administered concomitantly based on the clinical trial results. Therefore, the PMDA stressed that a cautionary warning should be provided in the package insert. Concomitant drugs are broadly defined as CDK4/6 inhibitors not limited to palbociclib. The details of

why such a decision was taken are not provided in the review report.

Mogamulizumab is approved for the treatment of CCR4-positive adult T-cell leukemia/lymphoma, and cancer chemotherapy, including mogamulizumab, has a wide range of concomitant chemotherapy options [242]. This includes a description of the choice given the patient's condition and history of chemotherapy based on familiarity with the clinical outcomes section and a reminder that concomitant chemotherapy should be selected based on clinical trial results.

Pertuzumab is an antibody drug approved for the treatment of unresectable or recurrent breast cancer. A Broad Label was set with the description that anti-cancer agents other than trastuzumab for concomitant use with pertuzumab are selected based on the description in the package insert.

Rituximab is approved for the treatment of CD20-positive chronic lymphocytic leukemia. The type of concomitant anti-cancer agent is described in the package insert, and a Broad Label was assigned to the concomitant anti-cancer agent along with a reminder that it should be selected after careful consideration of the description in the package insert and the latest treatment guidelines [243].

The inductive derivations from this series of case analyses are summarized below. In the case of endocrine therapy for breast cancer and platinum-based combination therapy for lung cancer, which were discussed in this case analysis, multiple regimens are equally effective and could be selected by physicians. If a clinical trial is conducted to evaluate the clinical benefit of adding new anti-cancer agents to one of the major regimens and an application is submitted for approval, there is a high probability of receiving a Broad Label. This conclusion is consistent with the lower number of regimens included in the applications for Broad Label approval compared to those for Narrow Label approval.

Narrow Label

Afribercept is indicated for use in combination with FOLFIRI (fluorouracil + levofolinate + irinotecan) as a second-line treatment for patients with advanced or recurrent colorectal cancer that progresses during or after oxaliplatin treatment. The application included two regimens, one in combination with S-1 and one in combination with FOLFIRI therapy. However, as the former was evaluated in a Phase I study and the latter in a Phase III study, it is reasonable to conclude that concomitant use with S-1 alone is not allowed. Therefore, this can essentially be considered Same Label.

Bevacizumab is approved for the treatment of unresectable or recurrent breast cancer. The application included four regimens: bevacizumab plus paclitaxel, bevacizumab plus taxane antineoplastic agents, chemotherapy including bevacizumab plus anthracycline antineoplastic agents, and bevacizumab plus

capecitabine. According to the review report, the PMDA determined that “the risk-benefit balance of bevacizumab was favorable and clinically meaningful only in combination with bevacizumab and paclitaxel.” Therefore, the dosage and administration of bevacizumab were defined as follows: “In combination with paclitaxel, bevacizumab is generally administered to adults at a dose of 10 mg/kg (body weight) by intravenous infusion. The dosing interval should be at least two weeks. In this case, it is appropriate to set it as follows.” In addition, the PMDA mentioned in the review report that the clinical efficacy results between the three studies submitted were inconsistent, that there were differences in the magnitudes of the benefit offered by this drug between studies with different combination anti-cancer agents, and that the short follow-up period did not provide sufficient data for evaluation. This case shows that, even for cancers for which multiple regimens are accepted as standards of care and even if the results of clinical trials on multiple regimens are included, regimens with immature data or those that have no clear clinical significance are not accepted for combination therapy.

Cabazitaxel is indicated for use in combination with prednisolone for the treatment of prostate cancer. The application included two regimens: concomitant use with prednisolone and concomitant use with capecitabine. However, as the former had been studied in Phase III studies and the latter in Phase I/II studies, it is reasonable that concomitant use with capecitabine was not permitted. Although abiraterone, enzalutamide, and cabazitaxel are secondary treatment options [244], none of them are used in combination with other anti-cancer agents, and the current label is considered reasonable.

Lapatinib is approved in combination with capecitabine for the treatment of unresectable or recurrent breast cancer with confirmed HER2 overexpression. The application included a multi-dose capecitabine combination regimen; however, the dosage and administration discussed in the Phase III study was defined. In addition, the review report stated that, given the limited clinical trial results in Japanese patients, the concomitant use of capecitabine must be indicated in the dosage and administration of lapatinib. However, if limited to concomitant use with capecitabine, the use of this combination in medical practice would be unlikely when new knowledge is gained about concomitant use with antineoplastic agents other than capecitabine. Physicians with sufficient knowledge and experience in cancer chemotherapy are not likely to administer concomitant chemotherapy with anti-cancer agents other than capecitabine at this time, but it is also important to provide appropriate information and reminders that concomitant use is recommended only with capecitabine. It is important to note that new information about concomitant use with antineoplastic agents other than capecitabine may make such concomitant therapy difficult to implement in medical practice.

Panobinostat is indicated in combination with bortezomib and dexamethasone for the treatment of relapsed or refractory multiple myeloma. When approval for this drug was applied for, concomitant regimens with multiple drugs, including bortezomib and dexamethasone, were included. However, only bortezomib and dexamethasone were evaluated in the pivotal study. Therefore, it is reasonable to limit the drugs that can be used in combination with panobinostat to bortezomib and dexamethasone.

Ramucirumab is indicated in combination with FOLFIRI for the treatment of advanced or recurrent colorectal cancer that is not curatively resectable. At the time of the application, concomitant therapy with FOLFIRI and FOLFOX (fluorouracil + folinic acid + oxaliplatin) was included. However, concomitant therapy with FOLFIRI was the regimen evaluated in the pivotal study. Therefore, it is reasonable to limit the number of drugs that can be used in combination with ramucirumab to FOLFIRI.

From the case analysis focusing on the Narrow Label, the study can gain insights via the inductively inferred information in the Broad Label case. First, even if more than one regimen is included, as in the case of bevacizumab, the combination regimen will be limited if it is not demonstrated to show clinical benefits in the Phase III study. The inclusion of multiple regimens in a clinical trial submitted with an application for approval, rather than narrowing it down to only a representative regimen, could lead to a Narrow Label. Conversely, this is scientifically and ethically reasonable in terms of finding the optimal combination regimen. Second, even if there are regimens that are considered clinically comparable, some combination regimens may be limited if the mechanisms of action of the drugs included in the regimen are completely different. In such cases, it is necessary to include all of the multiple regimens in the Phase III study. Third, as in the case of bevacizumab, the PMDA's position seems to be that, although the decision was made to grant a Narrow Label, the decision on the type of anti-cancer drug to be concomitantly treated should be based on the most up-to-date evidence at the time the treatment is actually provided and should be made available to the attending physician.

In both cases, it would be desirable to have early-phase Japanese data before initiating a Phase III trial of combination therapy. This was clearly described in the lapatinib review report, which showed that the clinical trial of iapatinib in Japanese patients in combination with capecitabine was initiated after the new drug application for iapatinib was filed, and that the new drug application was inappropriate under the circumstances, given that the application was filed without having addressed the points made by the PMDA. As can be seen from the case analysis, the case-by-case discussion is more important in the development of combination therapy than in the development of monotherapy. Japan has a mechanism for enabling access to innovative drugs like those in the US and Europe [245], and it is reported that the

PMDA consultation can shorten the review period [246]. It is important to seek advice from the PMDA at an early stage in the development process regarding the clinical position of any combination therapy under development as well as the description to be given in the package insert. This study's findings on the Broad and Narrow Labels, which are based on a small sample, should contribute to the discussions with the PMDA and to the planning of clinical development strategies.

The study has several limitations. First, the sample size is small. Therefore, continuous case analysis should be conducted to produce more reliable findings. Second, when considering the combination regimen, both the evaluation and reference documents described in the review report were analyzed in this study. However, the analysis should also consider cases in which only the evaluation documents were included, or only the pivotal study in the evaluation documents—in which overall survival or progression-free survival was set as the primary endpoint—was included. One important consideration in this regard are the predictive factors. It appears that there may be factors other than the ones discussed in this study that could contribute, and the findings of other studies need to be reviewed to identify these factors. Despite these limitations, this study is important in that it provides the first findings concerning descriptions in package inserts in the context of anti-cancer combination therapy, and thus builds the foundation for further research.

6.6 Conclusions

The study described the PMDA stance for reviewing the clinical data on anti-cancer combination therapies submitted by sponsors in their totality to allow physicians to provide patient-centric, evidence-based, optimized cancer care to patients (**Figure 6.4**).

- ✓ Approved combination therapies of anti-cancer drugs are classified into three label description groups: Broad Label, Same Label, and Narrow Label.
- ✓ There is a significant difference in the number of regimens included in the application for approval between the labels: There were, on average, 2.0, 1.1, and 3.7 regimens for the Broad, Same, and Narrow Labels, respectively.
- ✓ The factors that significantly contribute to labeling cannot be identified. However, key features of Broad Label approval have been identified that could maximize the prescription opportunities of anti-cancer drugs.
- ✓ If there are multiple clinically comparable regimens and a clinical trial is conducted to evaluate the clinical benefit of adding new anti-cancer agents to one of the major regimens, there is a high

probability of receiving a Broad Label such as in endocrine therapy for breast cancer, platinum-based combination therapy for lung cancer, and combination therapy for hematologic malignancy.

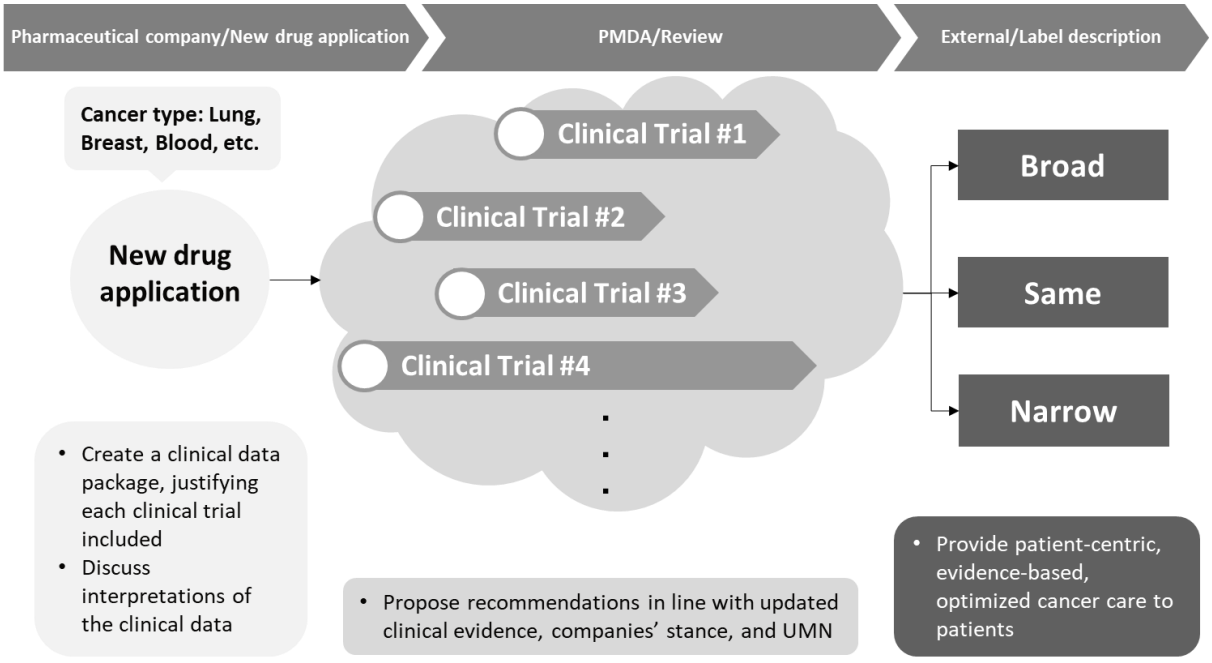


Figure 6.4. Visual abstract

Thus far, the principal point has been the characteristics of the Japanese pharmaceutical market, and discussion has been given to the possibility that anti-cancer drugs are related to "innovativeness", and direct implications for R&D strategies in anti-cancer drugs are provided.

In the following two sections, the drug pricing system is mainly discussed among pharmaceutical regulations in Japan. Since the drug pricing system is just one of the multiple pharmaceutical regulations, data is analyzed in the context of this thesis but may also be explored in aggregate with data from other reports. The availability of a larger dataset assists in identification and characterization of important aspects as part of the totality of evidence to increase the understanding of the drug pricing system and support future discussions. Therefore, this thesis includes evaluations of the drug pricing system, though preliminary.

7. Appraisal of the Japanese Drug Pricing System (1): Predictability of Sales and Drug Prices

7.1 Study Highlights

What is the current knowledge on the topic?

In Japan, there is an ongoing debate as to whether the unexpected pharmaceutical expenditures induced by drug-pricing methods that refer to predicted sales can be sufficiently suppressed by market expansion re-pricing. However, this topic remains under-researched.

What hypotheses did this study address?

5. The Japanese NHI price system underestimates the value of new drugs and must be restructured.

What does this study add to our knowledge?

This study showed that there was substantial upward deviation between actual and predicted drug sales in Japan. As long as drug sales predictions are used in drug price calculations, a flexible re-pricing system is needed to buffer unexpected pharmaceutical expenditures with ensuring adequate funding for innovation. A definite conclusion can hardly be drawn from the findings of this study to support or reject the above hypothesis, since there are other regulations besides the NHI drug pricing system, and the discussions have not been carried out in context of these regulations.

How might this change pharmaceutical companies' R&D strategy?

The findings from this study, although preliminary, should provide a basis for discussion of future revisions to the drug pricing system in the context of encouraging more innovations by the Japanese pharmaceutical industry.

7.2 Introduction

Drug pricing should aim at balancing patient access to drugs and ensuring adequate funding for innovation [102], [247]. Drug prices strongly determine the revenues of pharmaceutical companies, which need to recoup the significant investments they make for new drug development [248]-[251]. Furthermore, the success rates for investigational drugs are low [251], [252]. However, drug pricing is one of key measures for medical cost-cutting, because most developed countries are challenged by increasing pharmaceutical expenditures [253], [254]. Many of these countries directly cut drug prices or

impose reimbursement restrictions to reduce increasing pharmaceutical expenditures [147], [255]-[258]. Policies for drug pricing vary among counties. Drug prices in the US, the largest pharmaceutical market [259], are set without government restrictions [247]. European countries have used various pricing policies, such as price restrictions and reimbursement restrictions, to control pharmaceutical expenditure [247]. In Japan, although over 90% of NMEs are listed in NHI and targeted for NHI reimbursement [114], [260], only a certain proportion of the expenditure is covered by NHI. In this context, drug prices are determined by the Japanese government. One distinctive feature of the Japanese drug pricing system is that it guarantees corporate revenue to a certain extent by referring to the total cost of drug development. In detail, drug prices are calculated mainly by one of two methods: the CCM or CM. The pricing method to be applied is determined by the government depending on whether drugs similar to the targeted drug are already listed. The CCM is applied only when no similar drugs are listed. Drug prices of about one-third of NMEs are determined by the CCM [114]. In this method, the drug price is calculated based on the total cost: the drug development and manufacture cost, and plausible profit margin, divided by sales volume predicted by the pharmaceutical company. Therefore, the prediction of drug sales strongly and systematically influences drug prices when the CCM is applied. By contrast, the prediction of drug sales does not directly affect drug prices when determined based on the CM. However, the CM refers to the price of a similar drug priced by the CCM by following the original reference drug. Therefore, the prediction of sales volume indirectly affects drug prices even if the drug price is calculated by the CM. In addition, the prediction of drug sales is important for estimating future pharmaceutical expenditure. The management of pharmaceutical expenditure will become increasingly difficult with growing pressure on financial resources in Japan and most developed countries.

To control the hypertrophy of pharmaceutical expenditure and maintain proper drug prices, an NHI drug price revision is conducted in Japan every alternate year. The revision for on-patent drugs is conducted mainly using two methods: 1) the price divergence rate of the official price and delivery price [99], [100], [118], and 2) upward deviation of actual sales to predicted sales. The latter re-pricing system is called “market expansion re-pricing,” and it works as a counterplan against unexpected pharmaceutical expenditure caused by upward deviation of actual sales to predicted sales. When actual sales exceed predicted sales, after a certain level, market expansion re-pricing is applied every other year in Japan. This re-pricing policy has reduced drug prices depending on the degree of deviation of actual sales to predicted sales. Market expansion re-pricing aims not only to reduce unexpected pharmaceutical expenditure, but also to maintain fairness for pharmaceutical companies. If this re-pricing system does

not work, lower predicted sales contribute to higher prices based on the CCM, and this might give rise to disproportionate profits for pharmaceutical companies submitting inaccurate predictions.

In Japan, there is an ongoing debate as to whether the unexpected pharmaceutical expenditures induced by drug-pricing methods that refer to predicted sales can be sufficiently suppressed by market expansion re-pricing. Under market expansion re-pricing, the drug price is reduced by 50% at most. However, upward deviation remains for a maximum of 2 years because the price revision has only been conducted every other year thus far. The government determined that drug-price revision for market expansion would be conducted four times a year as a basic policy in 2016. A drastic re-construction of the drug-pricing and re-pricing system is planned, and the details have been discussed by the Japanese government.

In this context, it would be beneficial to quantitatively clarify the impact of an upward deviation of actual sales from predicted sales on pharmaceutical expenditure. In addition, revealing the factors associated with the upward deviation would be invaluable for enacting policies reflecting the market status quo. However, this topic remains under-researched. Therefore, this study aims to estimate the amount of upward deviation of actual sales from predicted sales, and explore the predictors of upward deviation in the Japanese pharmaceutical market.

7.3 Methods

Database

NMEs that were approved in Japan between January 2006 and December 2015, and the top 500 ethical drugs in the Japanese market in 2015, were included in the scope of this study; the data were obtained from the IQVIA Solutions Japan Pharmaceutical Market Database, which summarizes the sales amounts and prescription volumes for each drug of interest in an MS Excel file.

Additionally, the following two new datasets were created to examine the predicted value of upward deviation and the factors driving the deviation between the actual amount of sales and the predicted maximum amount of sales. The process for developing the two datasets is shown in **Figure 7.1**.

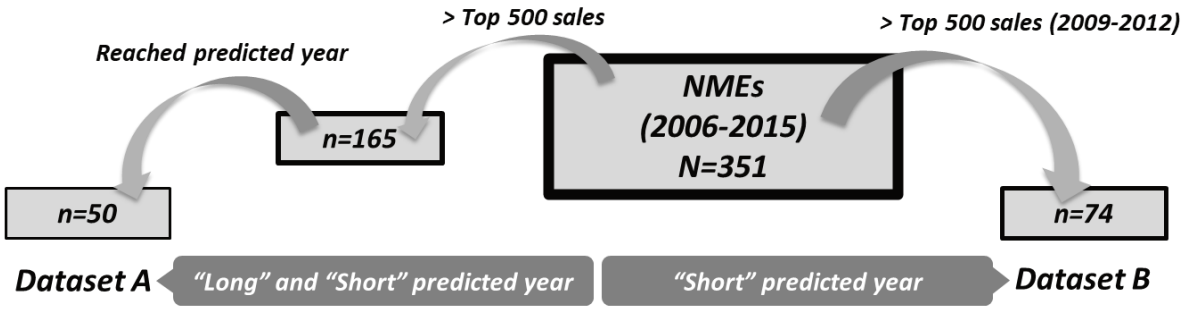


Figure 7.1. Development of dataset A and dataset B

A summary of the two datasets is shown in **Table 7-1**.

Therefore, this study used sample data, not population data.

Table 7-1. Summary of the dataset

Dataset	N	Summary
A	50	・ Of the 351 drugs listed as NMEs between 2005 and 2015, 165 drugs whose projected maximum sales amount exceeded the sales amount of the top 500 in 2015 (JPY 4.3 billion) were selected; among these 165 drugs, those who had already achieved the maximum sales amount by 2015, were finally selected. ・ The dataset includes not only drugs with longer durations to achieve the projected maximum sales amount, but also those with shorter durations.
B	74	・ Among the drugs NME drugs listed from 2009 to 2012, drugs whose projected maximum sales amount exceeded the sales amount of the top 500 in 2015 (JPY 4.3 billion) were selected. ・ Drugs with shorter durations to achieve the projected maximum sales amount were included.

Calculation based on the NHI price calculation method

The number of NMEs approved in Japan between January 2006 and December 2015 by ATC classification is shown in **Table 7-2**, according to the drug pricing method (CM or CCM).

Table 7-2. ATC classification system

Code	
A	Alimentary tract and metabolism
B	Blood and blood-forming organs
C	Cardiovascular system
D	Dermatological agents
G	Genitourinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Anti-infectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculoskeletal system
N	Nervous system
P	Anti-parasitic products, insecticides, and repellents
R	Respiratory system
S	Sensory organs
V	Various
N/A	Not applicable

Variables

In this study, sales amounts of all drugs with the same chemical composition, irrespective of manufacturer, were clustered, and the following two sales numbers were used.

$$\text{Actual sales amount (Actual sales)} = \text{Actual annual sales volume} \times \text{Revised price}$$

$$\text{Virtual sales amount (Virtual sales)} = \text{Actual annual sales volume} \times \text{First listed price}$$

For dataset B, maximum annual sales within three years of launch were used as actual sales to evaluate

drug profiles with relatively short projected maximum sales (3 years after launch). Drug prices have been revised every other year in Japan. Therefore, virtual sales were used to estimate the impact of drug-price revision on pharmaceutical expenditure. The presence or absence of additional indications was investigated until the targeted year after launch. In addition, the presence or absence of price reduction through market expansion re-pricing was investigated until the targeted year after launch.

Statistical analysis

Binary logistic regression analyses were conducted to reveal the factors associated with the upward deviation of actual sales from predicted peak sales.

This study set two outcomes to identify the factors associated with upward deviation of actual sales from predicted sales. The first outcome variable is a dichotomous indicator of whether actual sales exceed predicted peak sales. The second outcome variable is a dichotomous indicator of whether actual sales are more than 1.3 times predicted peak sales. This is one of the criteria for market expansion re-pricing.

One key research question is whether actual sales of drugs whose prices are calculated by the CCM tend to exceed predicted sales. As mentioned earlier, lower predictions of drug sales can lead to higher drug prices being set via the CCM. In this study, the pricing method is set as an explanatory variable. The presence of this additional indication is likely related to the upward deviation of actual sales from predicted sales, because a prediction submitted by a pharmaceutical company targets only the original indication when the drug is listed. Therefore, the presence of additional indications is also set as an explanatory variable. Furthermore, the predicted peak number of patients (one million) and predicted years in which peak sales are reached are set as explanatory variables.

Thus, the variable selection is justified because only those variables considered to be clearly related to drug pricing were selected from the relevant regulations.

7. 4 Results

Figure 7.2 shows the results of NMEs approved in Japan between January 2006 and December 2015 based on the drug price calculation method (CCM or CM). In both drug pricing methods, the most common indication is for "**L**."

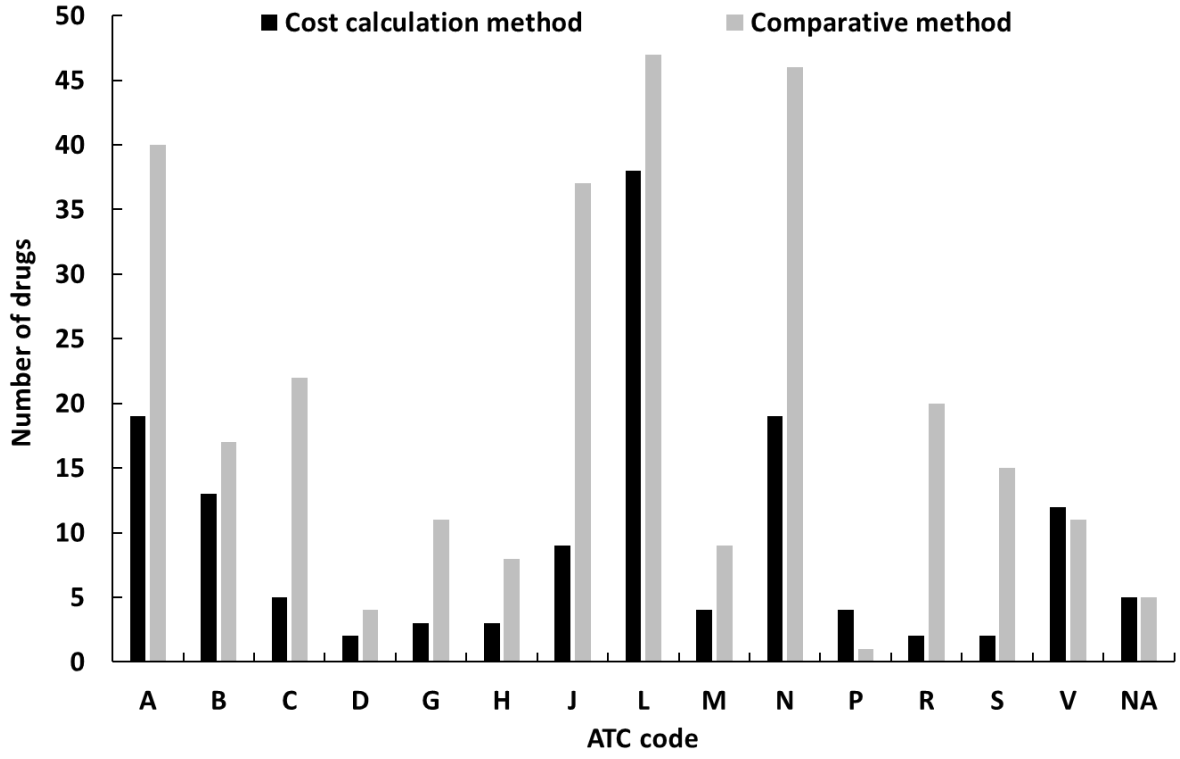


Figure 7.2. Number of drugs in each drug pricing system by the ATC code

Actual sales in 2015, virtual sales in 2015, and predicted peak sales of each targeted drug are shown in **Figure 7.3**. In all, 142 NMEs approved in 2006–2015 are ranked by top-500 sales in 2015. The total amount of upward deviation of virtual sales from predicted peak sales is JPY 1,350 billion. As the price revision is conducted every other year, the total amount is reduced to JPY 1,220 billion. Among the drugs whose prices are calculated by the CCM, the total amount of upward deviation of actual sales from predicted peak sales is JPY 430 billion. The total amount of upward deviation of actual sales from predicted peak sales based on whether drugs obtained additional indications or not was JPY 810 billion and JPY 410 billion, respectively. The actual sales of the 82 drugs exceeded predicted peak sales in the top-500 sales in 2015. There were 20 targeted drugs that underwent market expansion re-pricing after launch. The actual sales of nine drugs targeted for market expansion re-pricing did not exceed predicted

peak sales. One reason is that the market expansion re-pricing targets not only drugs whose sales exceed predicted sales at a certain level, but also drugs similar to these. Another reason is that one of the criteria when applying market expansion re-pricing is whether each year's sales exceed each year's predicted sales at a certain level, rather than the predicted peak sales in each year. Of the JPY 130 billion reduction in total pharmaceutical expenditure, JPY 110 billion could be attributed to drugs that underwent market expansion re-pricing at least once after launch. In this study, 71 drugs whose actual sales exceed predicted peak sales have not been targeted for market expansion re-pricing since their launch, as of 2015. Of these, 14 were subsequently targeted for market expansion re-pricing in the 2016 drug price revision.

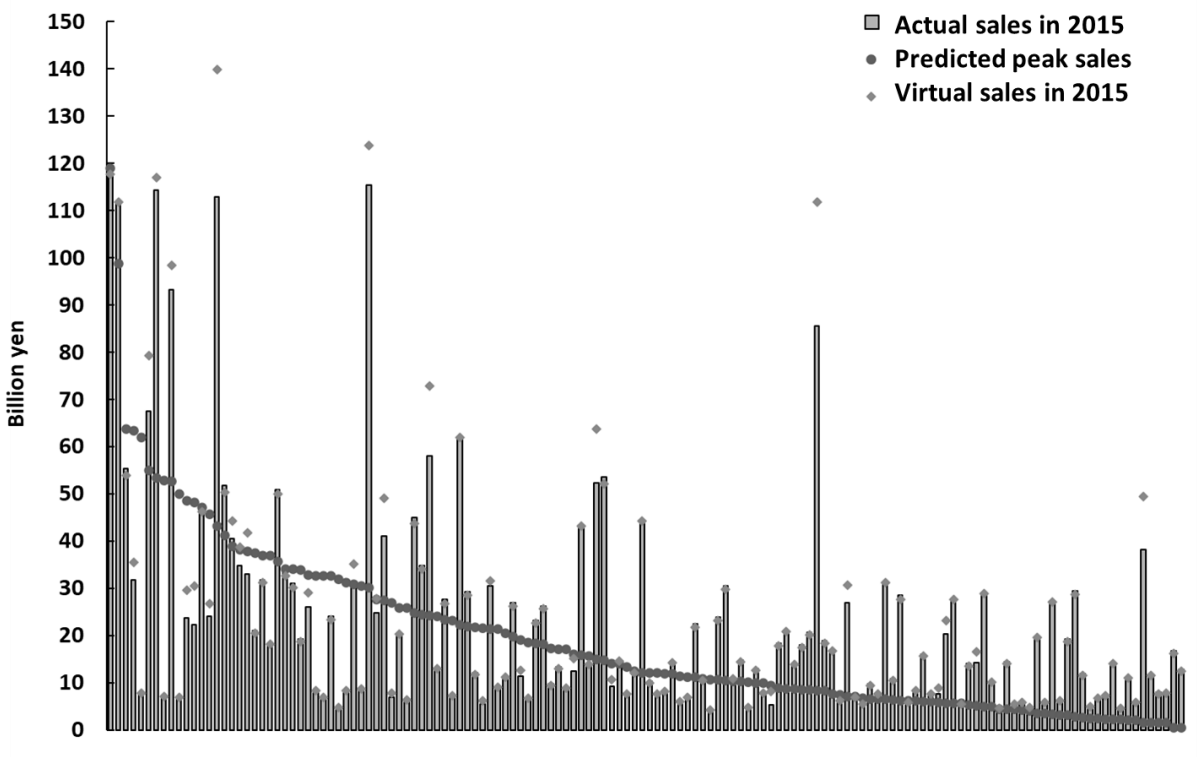


Figure 7.3. Actual sales, virtual sales, and predicted peak sales of each targeted drug

Table 7-3. Number of drugs and amount of upward deviation of actual sales, upward deviation of virtual sales, actual sales, virtual sales, and predicted peak sales

Category	Pricing method		Additional indications		Market expansion re-pricing		Total
	CCM	CM	Presence	Absence	Presence	Absence	
(JPY billion)							
Upward deviation (actual sales)	434	784	808	409	366	851	1,217
Upward deviation (virtual sales)	475	872	926	421	473	874	1,347
Actual sales	683	2,614	1,549	1,748	740	2,556	3,296
Virtual sales	725	2,736	1,685	1,776	874	2,587	3,460
Predicted peak sales	281	2,475	857	1,899	507	2,249	2,756
(Number of drugs)							
Upward deviation	24	58	35	47	11	71	82
Total	31	111	46	96	20	122	142

Next, the study focuses on the predictors of upward deviation of actual sales from predicted sales. The relationship between the year in which drugs are predicted to reach peak sales, and the ratio of upward deviation (actual sales–predicted peak sales) and predicted peak sales are shown in **Figure 7.4**. In dataset A, the maximum ratio of upward deviation and predicted peak sales is 2.5 for drugs that obtained additional indications and 2.3 for drugs with only original indications. In dataset B, the maximum ratio of upward deviation and predicted peak sales is 4.8 for drugs that obtained additional indications and 2.0 for drugs with only original indications. Over 40% of the targeted drugs exceed predicted peak sales in the year in which they were predicted to reach peak sales. More than one-fourth of the targeted drugs exceed the predicted peak sales within 3 years of launch, even though for most of these drugs, the year

in which they achieved this is different from the year in which they were predicted to reach peak sales.

The number of drugs whose actual sales exceed predicted peak sales is relatively higher under the CCM and in the presence of additional indications.

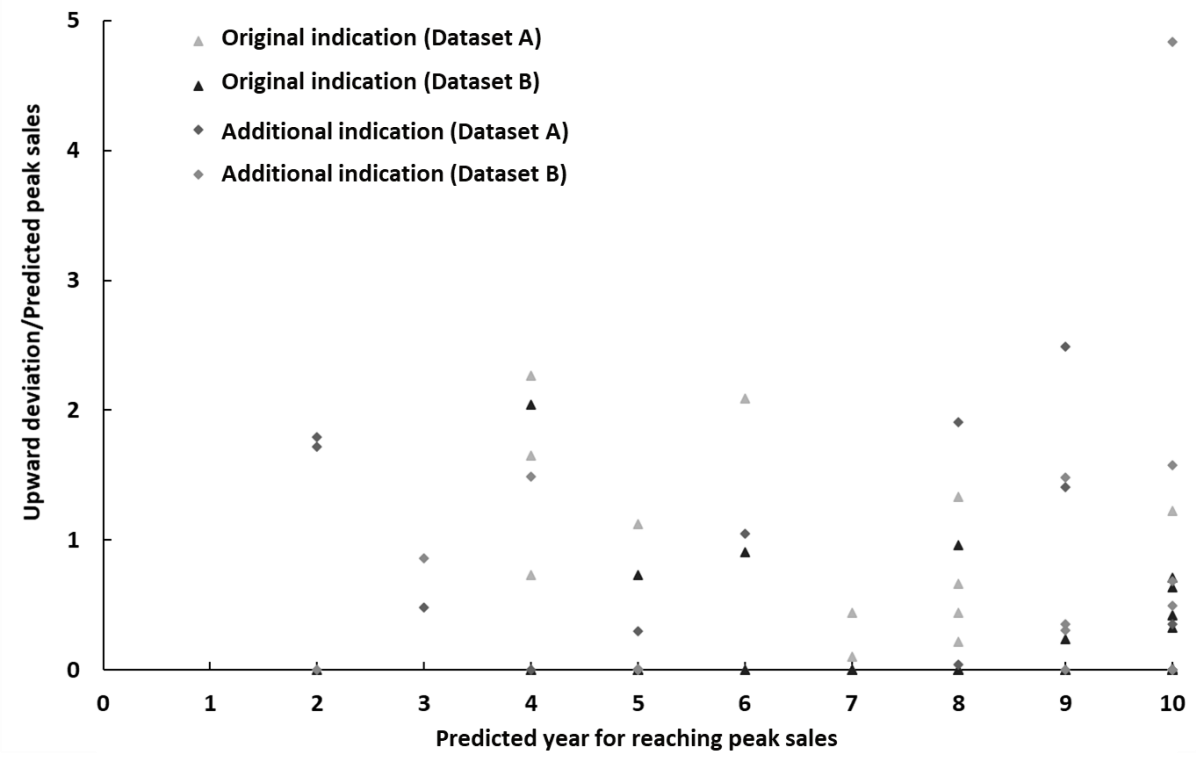


Figure 7.4. Relationship between predicted peak year and the ratio of upward deviation (actual sales–predicted peak sales) and predicted peak sales

Binary logistic analyses were conducted to reveal the factors associated with the upward deviation of actual sales from predicted peak sales. The analysis results are shown in **Table 7-4**. Drugs priced under the CCM are significantly more likely to record an upward deviation of actual sales from predicted peak sales. In addition, drugs that obtained additional indications are significantly more likely to induce upward deviation. There is a statistical relation between the prediction of the year in which peak sales would be reached and the peak numbers of patients, for the first outcome in dataset A. However, there is no statistically significant relationships in the other models.

Table 7-4. Binary logistic regression analyses for factors associated with upward deviation of actual sales from predicted peak sales

Value	Regression coefficient (Standard error)			
Dependent variable	First outcome		Second outcome	
Dataset	A	B	A	B
Pricing method				
CM (reference)	---	---	---	---
CCM	2.598 **	1.374 **	1.776 *	1.857 **
	(1.093)	(0.699)	(0.921)	(0.755)
Predicted year in which peak sales are reached	0.441 **	-0.039	0.215	-0.024
	(0.215)	(0.114)	(0.165)	(0.121)
Peak number of patients (one million)	-2.056 *	0.132	-1.153	0.196
	(1.099)	(0.287)	(0.833)	(0.302)
Additional indications	4.296 ***	1.748 ***	2.966 ***	2.001 ***
	(1.381)	(0.621)	(0.972)	(0.687)
(Constant)	-3.714 **	-0.163	-2.453 **	-2.276 *
	(1.687)	(1.087)	(1.302)	(1.177)
Number of samples	50	74	50	74
Cox-Snell R square	0.402	0.167	0.281	0.139
Nagelkerke R square	0.537	0.253	0.380	0.201

First outcome: a dichotomous indicator of whether actual sales exceed predicted peak sales
Second outcome: a dichotomous indicator of whether actual sales are more than 1.3 times predicted peak sales
Correlation analyses are conducted between all explanatory variables and show no significant correlation in any pairs. *** = $p < 0.01$, ** = $p < 0.05$, * = $p < 0.10$.

7. 5 Discussion

The drug-pricing system in Japan requires re-construction. One of the most controversial issues is how counterplans should be enacted to remedy the upward deviation of actual sales from predicted sales. Accordingly, it would be beneficial to quantitatively clarify the impact of an upward deviation of actual sales from predicted sales on pharmaceutical expenditure. In addition, revealing the factors associated with the upward deviation would be invaluable for enacting policies that reflect the market status quo.

The study aims to estimate the amount of upward deviation of actual sales from predicted sales. In addition, the amount of upward deviation is indicated for each category of drugs. Due to data limitations, drugs ranked in the top 500 in terms of sales in 2015 were targeted for the estimation. This limitation is acceptable, because the top-selling 500 drugs account for more than 75% of the total Japanese pharmaceutical market as of 2015 [128]. The total size of the Japanese pharmaceutical market in 2015 has been reported to be JPY 10.6 trillion [128], [129]. Even though the estimation targets only top-500 sales and NMEs approved in 2006–2015, the total amount of upward deviation of virtual sales from predicted peak sales was JPY 1,350 billion. Due to the price revision being conducted every other year, the total amount of upward deviation was reduced to JPY 1,220 billion.

The total amount of upward deviation does not directly reflect the curtailment of total pharmaceutical expenditure. Under the CCM, the predicted sales volume contributes to the systematic setting of drug prices. Therefore, upward deviation of actual sales from predicted sales induces disproportionate profits for pharmaceutical companies to some extent. By contrast, in the CM, predicted sales volumes do not directly impact the setting of drug prices. However, if the drugs obtain additional indications, the referred prices of similar drugs might become invalid. Moreover, the additional costs (e.g., manufacturing and operating costs) that accompany upward deviation cannot be curtailed. Furthermore, clinical trial costs are added to the drug development expenditure if the drug obtains additional indications. Even though additional costs should be considered during drug-price revision, the estimated amount of upward deviation of actual sales from predicted sales shown in this study provides a yardstick for political applications. The prediction of drug sales is applied for setting drug prices or reimbursement policies in various countries. The criteria for re-pricing or reimbursement restrictions are also different. To the best of the author’s knowledge, the price-volume agreement (PVA) program in South Korea is most similar to the Japanese re-pricing plan. Under the Korean PVA, a drug’s listing price is negotiated between the public payers and the pharmaceutical company based on the forecast sales volume, to consider the budgetary impact. Re-pricing is conducted every year if the actual sales volume is equal to

or exceeds 30% of the pre-agreed forecasted volume [261], [262]. Although there is substantial difference in the background of Korea and Japan, that is, their pricing methods for listed drug prices differ, the Korean PVA's requirements for re-pricing are stricter for upward deviation than is the case with Japan's market expansion re-pricing. Versions of the PVA have been implemented to stabilize pharmaceutical expenditure in many countries in Europe [263].

These re-pricing systems are categorized as a type of risk-sharing scheme between the government and pharmaceutical companies. In several European countries, the upper limit of reimbursement has worked to limit unexpected pharmaceutical expenditures [263]. The limitation of reimbursement is mainly based on cost-effectiveness. However, this also means that patient access is restricted to some extent. Although it might be beneficial to refer to the drug-pricing policies in various counties, the polices must be constructed by considering overall consistency.

The second aim of this study is to explore the predictors of upward deviation of actual sales from predicted sales in the Japanese pharmaceutical market. Clarifying the predictors of upward deviation could be helpful for enacting drug-pricing policies and estimating future pharmaceutical expenditure. Drugs that obtain additional indications are significantly more likely to induce an upward deviation of actual sales from predicted peak sales. Predicted peak sales are estimated for only original indications when the drug was listed. Therefore, logically, upward deviation is likely induced depending on the scale of patient expansion by obtaining additional indications. However, thus far, both the existence of this phenomenon as well as the extent of its impact, remains unclear. This study reveals that the phenomenon does really exist, showing ranges of upward deviation caused by obtaining additional indications in the Japanese pharmaceutical market. Even though the additional indications are added characteristics, the present study finds the original characteristics of drugs that induced upward deviation via the CCM. Drugs priced by the CCM are significantly more likely to induce an upward deviation of actual sales from predicted peak sales. Lower predicted sales contribute to higher prices under the CCM. By contrast, higher predicted sales reduce the likelihood of being targeted for market expansion re-pricing, even if the drug was priced by the CM. Therefore, there are incentives to set lower predictions for the CCM and higher predictions for the CM. The findings lead to potential concern that these incentives could drive the setting of predicted sales. Even though these incentives do not work and deviation of actual sales from predicted sales often out of control, reasonable re-pricing or a restriction on reimbursement systems is necessary to prevent disproportionate profits for pharmaceutical companies submitting inaccurate predictions. In addition, the fact that drugs priced by the CCM are significantly more likely to

induce upward deviation could be one of the predictors in managing financial adjustments to national health insurance, for predicting future pharmaceutical expenditure. This study indicates that these predictors are correlated with the upward deviation in the predicted year in which peak sales are reached and within 3 years of the launch. This suggests that these phenomena occur within 3 years and do not disappear in the predicted year in which peak sales are reached.

A drug-pricing method based on cost and predicted sales is reasonable for reducing the uncertainty involved in the development of new drugs. However, such a system includes the risk of further escalating pharmaceutical expenditure. The Japanese government has enacted new counterplan policies each time pharmaceutical expenditure has exceeded expectations. The price of nivolumab, for instance, whose actual sales dramatically outpaced predicted sales because the drug obtained additional indications, was cut outside of the drug-price revision scheme in 2016. Unscheduled price cuts adversely influence the corporate management of pharmaceutical companies. There is a strong need for established drug-pricing policies that balance patients' access to medication with ensuring adequate funding for innovation. One reasonable counterplan for unexpected pharmaceutical expenditure is re-pricing when a drug obtains additional indications. As demonstrated in this study, obtaining additional indications strongly causes upward deviation of actual sales from predicted sales. However, under the current Japanese system, no re-pricing policies are applied when a drug obtains additional indications. One possible policy is indication "value-based" pricing (IBP). IBP is used for setting drug prices depending on indication. IBP has been proposed in the US as a tool to capture the differential value of drugs across indications or patient groups, and is in the early phases of implementation [264], [265]. Introduction of the IBP based on cost-effectiveness is also being discussed in Japan [266]. However, indication "cost-based" pricing or indication "comparison-based" pricing could be applied without drastic changes in the current Japanese drug-pricing system.

This study has the following limitation: Only predicted peak sales are available, as the datasets used in this study could not adopt large samples. In future studies, predicted sales for each year should be investigated to clarify more specific predictors for upward deviation, such as therapeutic classifications.

Finally, the proposed new drug pricing system based on the findings of this study and future issues to be considered is discussed.

In the current drug pricing system for innovative drugs, especially the CCM, the evaluation of innovativeness is inadequate. However, there is no denying the impact that an improvement in drug pricing can have on the overall financial pressure facing the health care system in Japan. Therefore, for

the pricing of innovative drugs, it is necessary to set an upper limit to drug prices. A conceptual diagram of the proposed drug pricing system is shown in **Figure 7.5**. The following is the general framework of the proposal.

Utilizing international standards for innovative drugs

Utilizing drug prices in the European and US markets makes it possible to evaluate the prices of innovative new drugs based on the prices of internationally comparable drugs. This also allows Japanese pharmaceutical companies, which heavily depend on the Japanese market for their profits, to avoid disadvantages in terms of international competition.

Setting a maximum price and limiting the scope of coverage

By setting a ceiling price, unlimited increases in the drug prices can be prevented. Moreover, by limiting the scope of coverage only to innovative drugs, an unnecessary increase in drug prices can also be limited.

Corrections to the system of continuously falling drug prices

To promote the R&D of innovative new drugs, especially for innovative drugs, it is necessary to correct the system of continuously decreasing drug prices.

Several points need to be considered in this proposal. For example, the criteria for the “level” of drug prices in the European and US markets include: “What range of prices should be assumed?” “Will it be revised annually in response to changes in prevailing prices in overseas markets?” and “Will the drug pricing be conducted only at the time of launch?” The same consideration should be given to the upper limit price. To prevent the drug prices in the Japanese market from exceeding the highest price across all countries, an upper price limit should be set to the price of the highest priced country. Options should also be considered with regards to the “level,” such as “use of average drug prices in other countries” and “use of the price of the second highest country.”

The aforementioned discussions on “level” can include all stakeholders in the pharmaceutical industry. It should be noted that this scheme is proposed from the pharmaceutical industry’s perspective, in terms of what kind of drug pricing system is favorable to appropriately evaluate the prices for innovative new drugs.

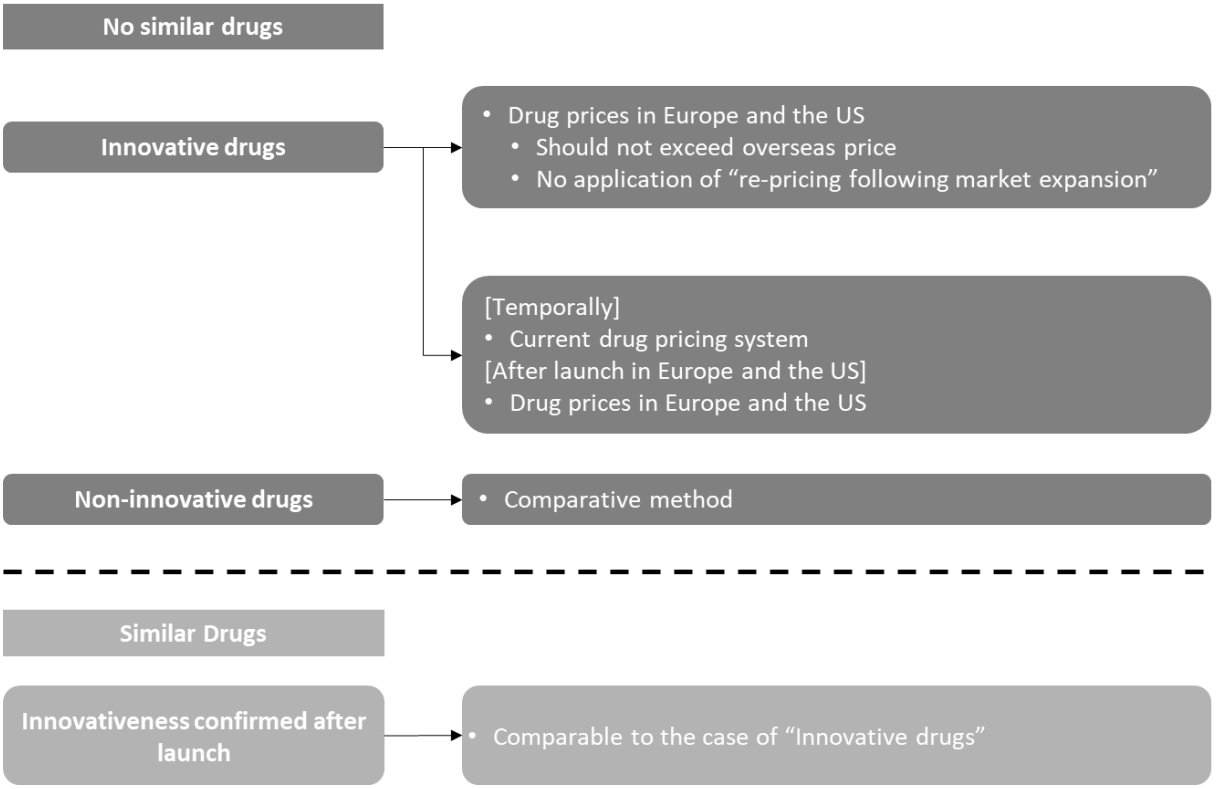


Figure 7.5. Proposed new drug pricing system

7. 6 Conclusions

The present study reveals that drugs that obtain additional indications or that are priced by the CCM are reasonable predictors of upward deviation, indicating that a flexible re-pricing system is needed to buffer unexpected pharmaceutical expenditure caused by upward deviation of actual sales from predicted sales (**Figure 7.6**).

- ✓ Estimated upward deviation was more than JPY 1,220 billion in 2015 for the targeted drugs.
- ✓ Drugs priced by the CCM or that obtain additional indications are significantly more likely to show an upward deviation in predicted peak sales.
- ✓ There is substantial upward deviation between actual and predicted drug sales in Japan. As long as drug sales predictions are used in drug price calculations, a flexible re-pricing system is needed to buffer unexpected pharmaceutical expenditures.
- ✓ A new drug pricing system is proposed based on the findings, setting an upper limit to drug prices and the scope of coverage.

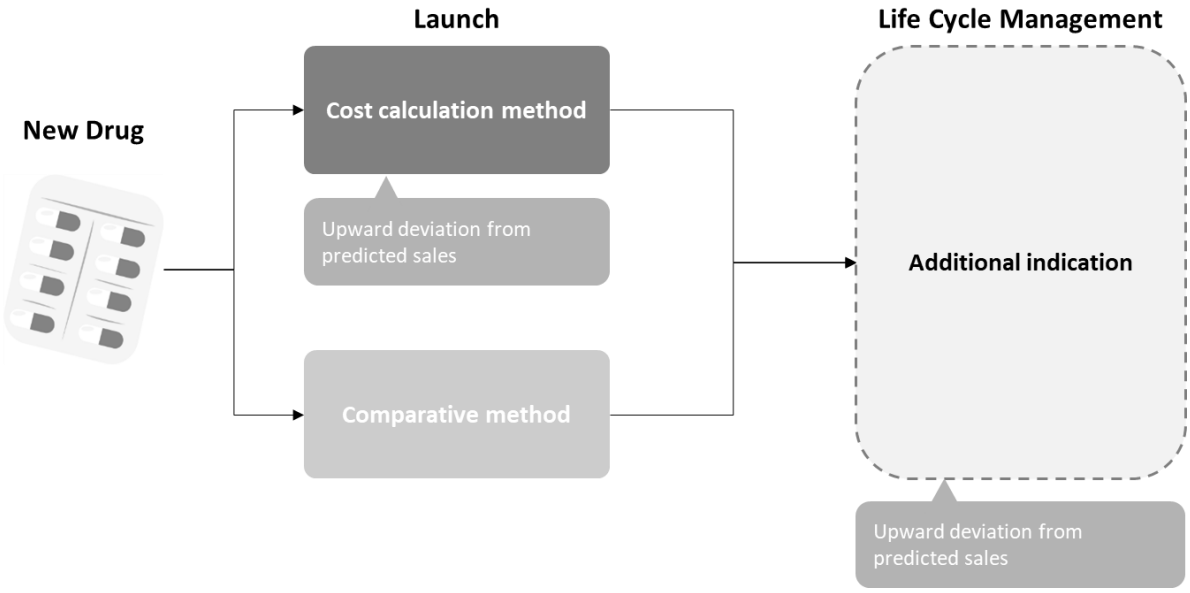


Figure 7.6. Visual abstract

The findings from this study, although preliminary, should provide a basis for discussion of future revisions to the drug pricing system in the context of encouraging more innovations by the Japanese pharmaceutical industry. In the next section, the preliminary appraisal of the drug pricing system from the perspective of the NMEs is presented.

8. Appraisal of the Japanese Drug Pricing System (2): New Molecular Entities

8.1 Study Highlights

What is the current knowledge on the topic?

There are various pharmaceutical regulations in Japan. The drug pricing system plays an important role as a part of incentive for innovations by pharmaceutical companies, however, there is limited evidence on the evaluation of the drug pricing system with attention to NMEs.

What hypotheses did this study address?

5. The Japanese NHI price system underestimates the value of new drugs and must be restructured.

What does this study add to our knowledge?

This study revealed that the number of NMEs and market size has increased and the number of drugs with significant clinical benefits has decreased, suggesting that NME innovation by Japanese companies has been decreasing. A definite conclusion can hardly be drawn from the findings of this study to support or reject the above hypothesis, since there are other regulations besides the NHI drug pricing system, and the discussions have not been carried out in context of these regulations.

How might this change pharmaceutical companies' R&D strategy?

The findings from this study, although preliminary, should provide a basis for discussion of future revisions to the drug pricing system in the context of encouraging more innovations by the Japanese pharmaceutical industry.

8.2 Introduction

Japan is one of the largest pharmaceutical markets worldwide, and as such, pharmaceutical companies are intensively conducting R&D for new drugs in Japan. In 2014, Japan's share in global sales was second largest, at approximately 10% [128], [129]. However, the current Japanese pharmaceutical market differs from those in Western countries. The share of "cardiovascular system" drugs is relatively high in the Japanese top 100 drugs market, while that of "antineoplastic and immunomodulating agents" is relatively low [267]. Since the Japanese drug pricing system has encouraged the R&D of new drugs in "antineoplastic and immunomodulating agents" and the "nervous system," which are likely to sell well in both Western and Japanese markets [99], [100], [118], the Japanese pharmaceutical market is rapidly

catching up to other Western countries' markets [129]. However, research focusing on NMEs in Japan is limited, although it is essential for offering a prognosis on the Japanese pharmaceutical industry.

Offering such a prognosis requires a detailed discussion on Japanese drug regulations. In Japan, health insurance coverage decisions and reimbursement prices are determined by the MHLW and not by health insurance bodies; however, the MHLW must consult with the Central Social Insurance Medical Council regarding these matters.

The new drug pricing process in Japan is described in **Figure 8.1** [268]. After marketing approval has been obtained, a price listing application is submitted by pharmaceutical companies (applicants), with the 1st Drug Pricing Organization deciding on an appropriate pricing plan. The applicants can express their opinions at this point, if needed. A notification of the pricing plan is then issued, and the drug price is fixed if there are no objections from the applicants. If applicants raise an objection, the price is re-evaluated at the 2nd Drug Pricing Organization. Subsequently, the pricing plan is reported and approved at the general meeting of the Central Social Insurance Medical Council, which will trigger the price listing (4 times/year).

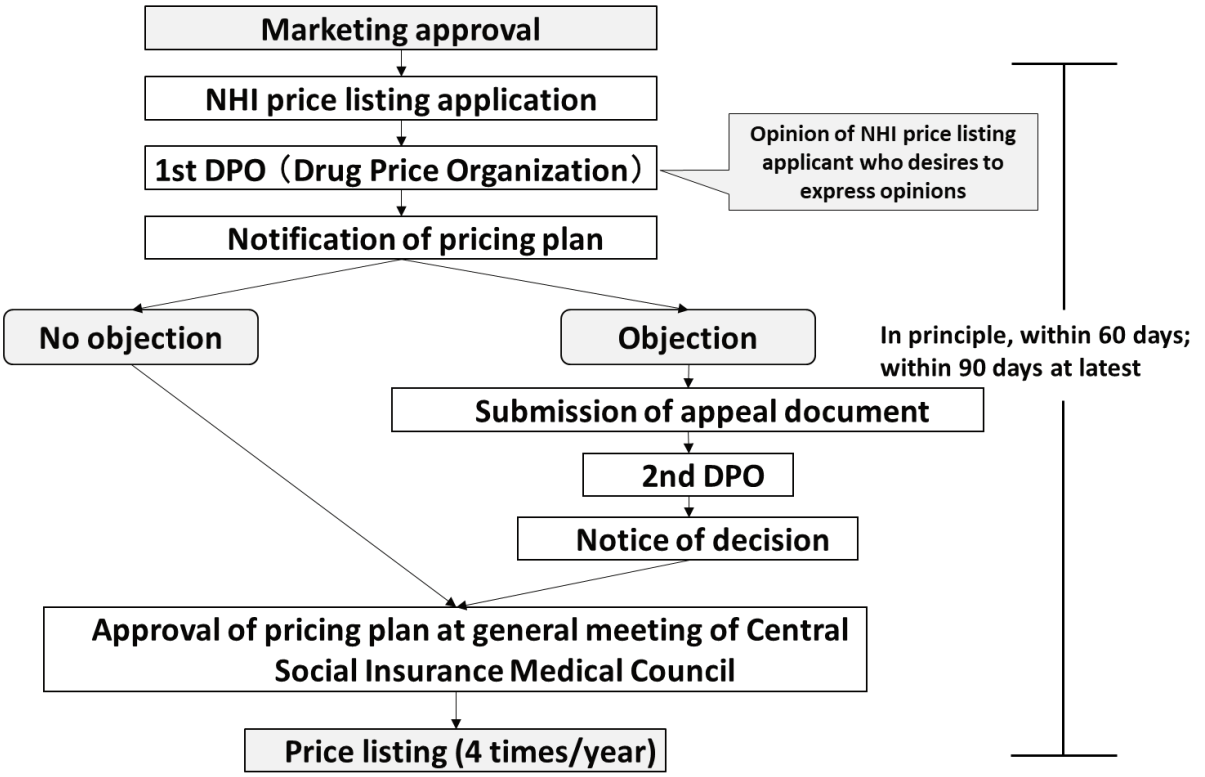


Figure 8.1. New drug pricing process in Japan (reshown, see Chapter 2, Section 2.1.2)

The price calculation method for new drugs in Japan is described in **Figure 8.2**. If there are comparable drugs with similar efficacy, the daily drug price of the NME is matched to the daily drug price of existing comparable drugs, to ensure fair competition in the market. If the relevant new drug has higher efficacy compared to other relevant drugs, the following corrective premiums are applied to the aforementioned amount: an innovativeness premium, usefulness premium, marketability premium, child premium, and SAKIGAKE review designation scheme premium. However, the premiums are not applied to drugs with less novelty. If there are no comparable drugs with similar efficacy, the CCM is applied, where costs (manufacturing, sales and general administration, operating profit, distribution and marketing, consumption tax, etc.) will be considered in setting the drug price.

This study quantitatively investigates whether the Japanese pharmaceutical industry has developed over the last 10 years, and also discusses if there is room for further development. Among the various indicators for the development of the pharmaceutical industry, this study used the three indicators of number of NMEs, market size forecasts, and the clinical innovativeness/usefulness of NMEs.

The number of NMEs is a typical indicators of pharmaceutical industry development [59]. In fixing drug prices, pharmaceutical companies have to submit the peak sales forecast based on the number of eligible patients for the new drugs. Several papers have used this forecast to investigate the Japanese pharmaceutical market [151], [269]. The use of clinical innovativeness/usefulness of NMEs is justified since these systems are applied to innovative drugs, as described above. In this context, the main purpose of this research is to quantitatively present the characteristics and trends, to grasp the current status of the Japanese pharmaceutical market, thereby creating a foundation for further research on this market.

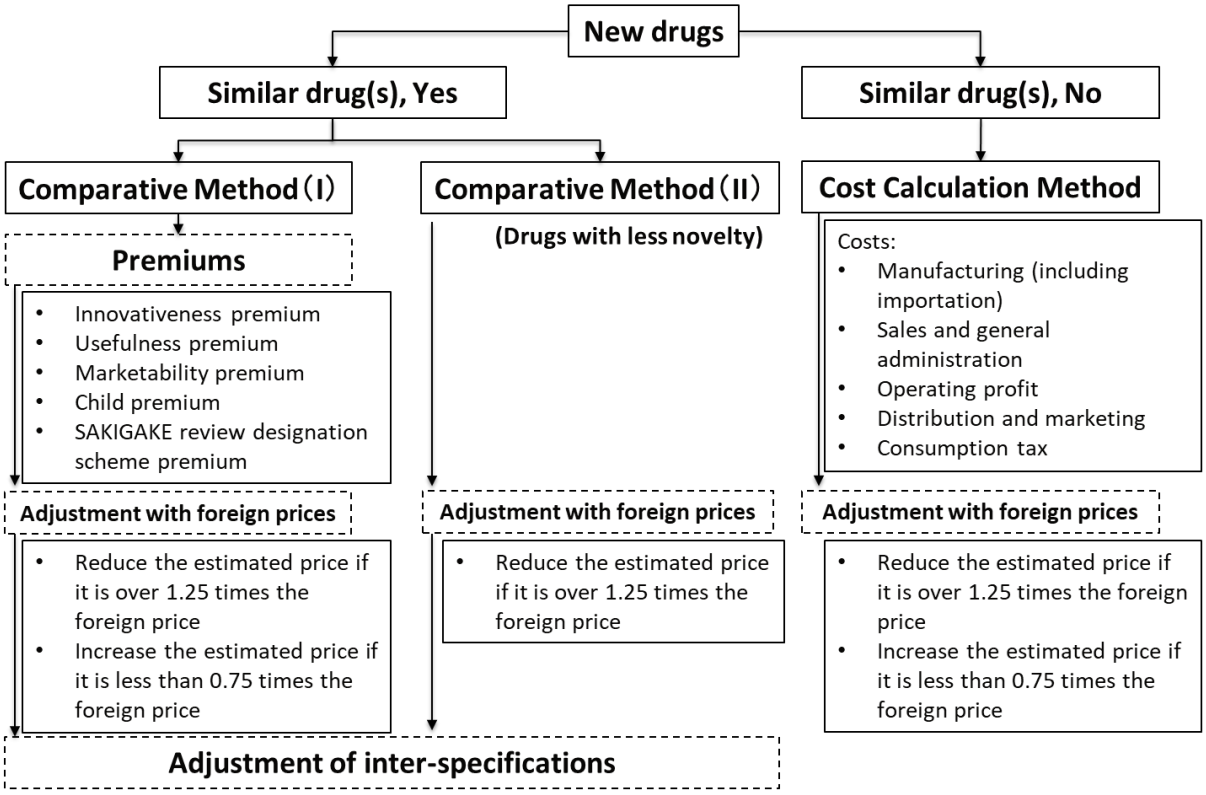


Figure 8.2. Price calculation methodologies for new drugs in Japan (reshown, see Chapter 2, Section 2.1)

8.3 Methods

Database

The dataset for this study comes from publicly available information on the PMDA website [270]. NMEs approved between 2006 and 2015 in Japan were selected as the drugs of interest. Data for predicted peak sales submitted by the pharmaceutical companies, the applied price calculation method, and the companies' profile (Japanese vs. Global) were obtained from the Japanese Central Social Insurance Medical Council [271].

Therefore, this study used population data, not sample data.

Drug classification and categories

The ATC classification system, a pharmaceutical coding system operated by the World Health Organization [13], was used to categorize the drugs included in the study (**Table 8-1**).

Table 8-1. ATC classification system

ATC codes	Therapeutic areas
A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Antiinfectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products, insecticides, and repellents
R	Respiratory system
S	Sensory organs
T	Diagnostic medicines
V	Various
N/A	Not applicable

Trend analysis

Trend analysis was conducted to calculate the number of drugs as well as its percentage change between 2006–2010 and 2011–2015. The changes in the number of NMEs approved in Japan between 2006–2015 and according to predicted peak sales/ATC codes were investigated. The percentage changes in NMEs approved in Japan according to drug pricing method/country that first obtained approval/ATC codes, categorized by the company types (Japanese vs. Global), and to which innovativeness/usefulness premiums were applied in the CM, were also investigated.

8. 4 Results

The number of NMEs approved in Japan between 2006–2015 is shown in **Figure 8.3**. The number of NMEs has continuously increased between 2006–2015.

To elucidate the relationship between the increase in the number of NMEs and in the Japanese market size, the number of NMEs was investigated for each expected peak sales amount.

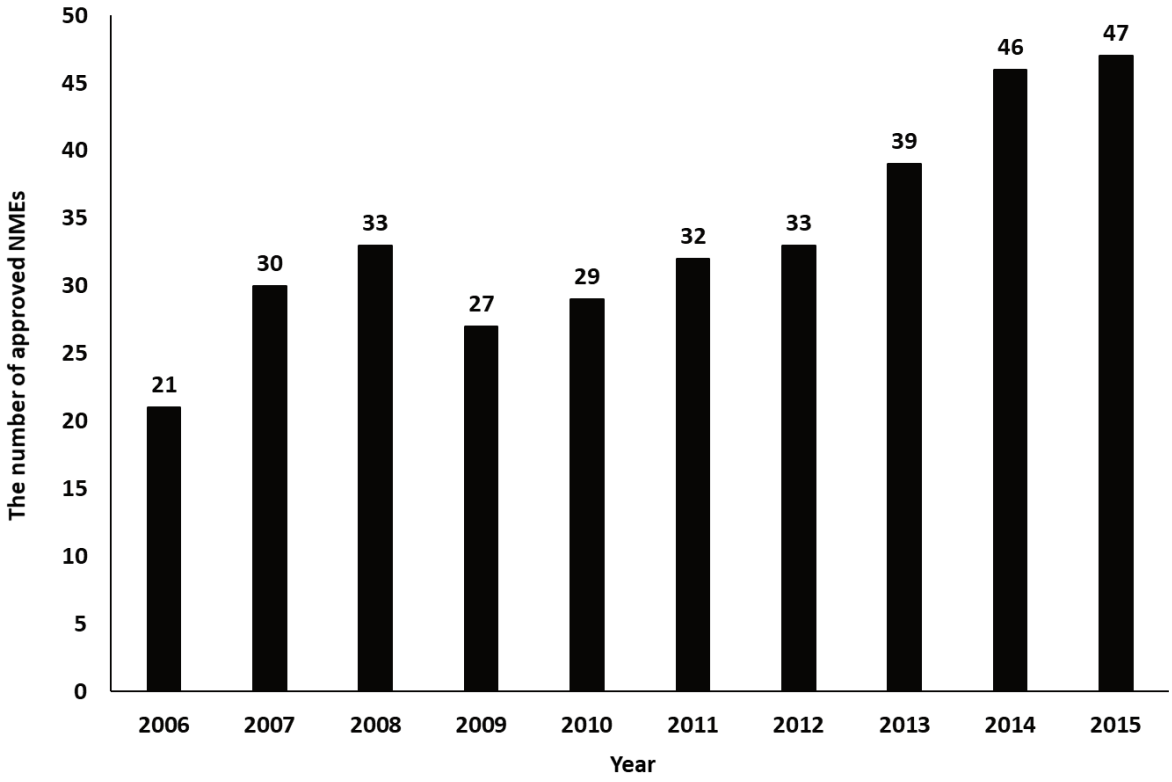


Figure 8.3. The number of NMEs approved in Japan between 2006–2015

The number of NMEs approved in Japan based on predicted peak sales is shown in **Figure 8.4**. Regardless of the market size, the number of NMEs is gradually increasing. The highest peak sales amount is in relation to a drug to treat hepatitis C, listed on the drug price list in 2015. The peak sales amount is approximately JPY 1190 hundred million. This was the only drug with sales over JPY 1000 hundred million.

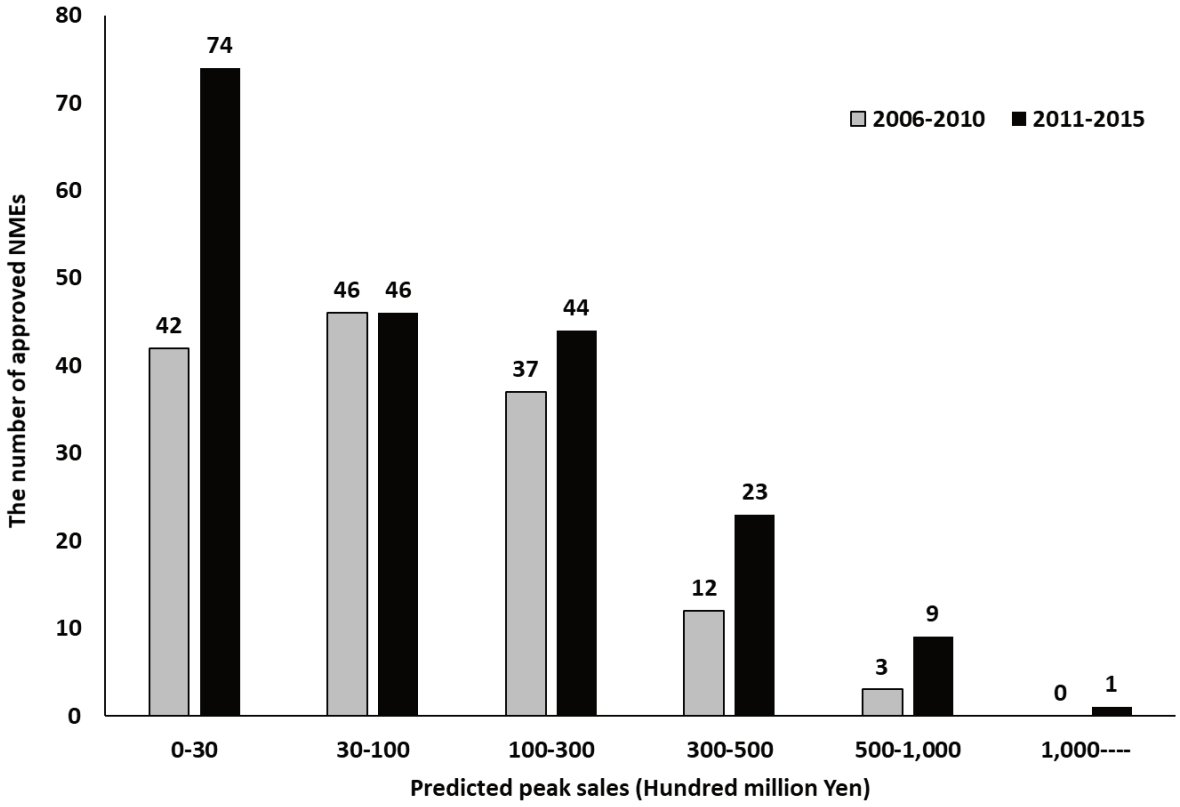


Figure 8.4. The number of NMEs approved in Japan based on predicted peak sales

The number of NMEs approved in Japan based on the ATC codes is shown in **Figure 8.5**. Compared to 2006–2010, the total number of NMEs increased in 2011–2015. However, each disease area exhibits a different trend. The number of drugs in **L**, **A**, and **B** increased remarkably (N=28 vs. N=52, N=16 vs. N=35, and N=9 vs. N=19, respectively). By contrast, although the number of samples is limited, the number of NMEs in **C** and **H** has decreased (N=9 vs. N=5 and N=5 vs. N=1, respectively).

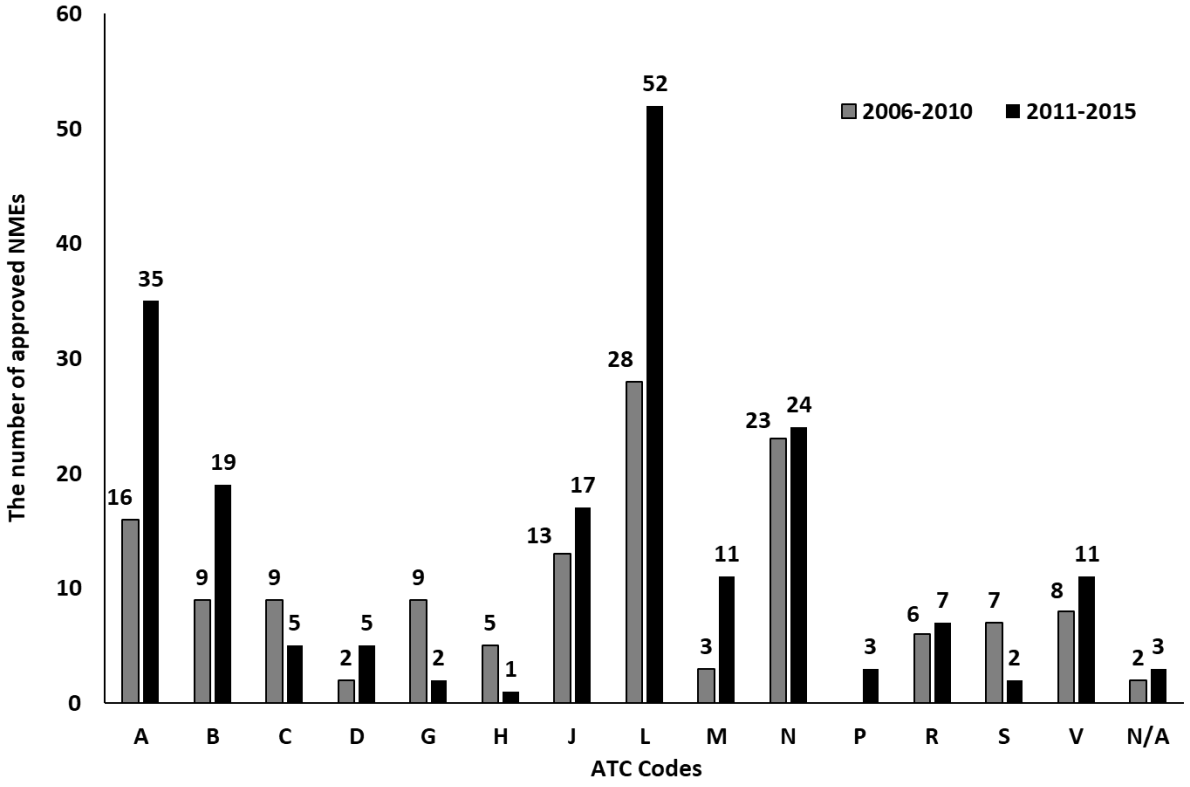


Figure 8.5. The number of NMEs approved in Japan based on ATC codes

The number of NMEs approved in Japan based on drug pricing method is presented in **Figure 8.6**. The percentage of drugs priced using the CCM is stagnant between 2006–2010 and 2011–2015 (34% in 2006–2010 and 34% in 2011–2015). The percentage under CM also did does not show any drastic change (66% in 2006–2010 and 65% in 2011–2015). Overall, no drastic differences can be found in relation to either drug pricing system between 2006–2010 and 2011–2015.

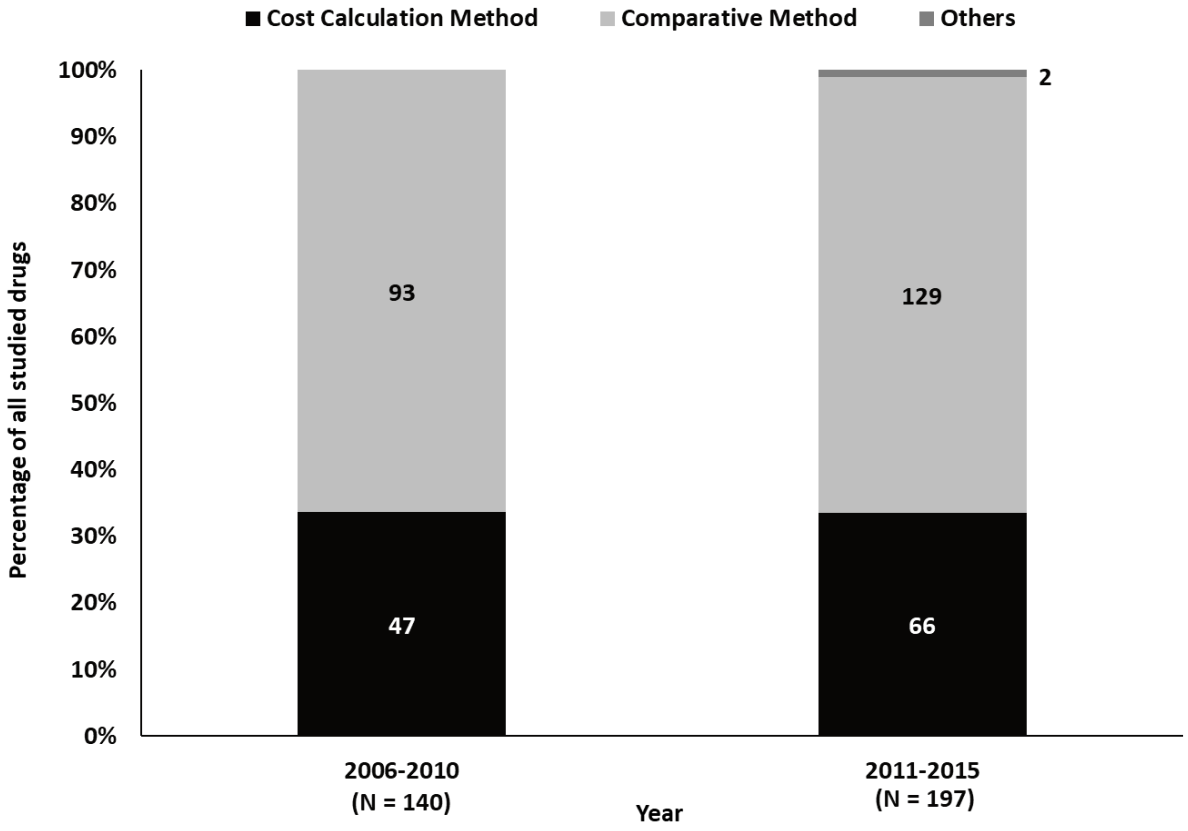


Figure 8.6. The number of NMEs approved in Japan based on drug pricing method

The number of NMEs approved in Japan, to which innovativeness/usefulness premiums were applied via the CM, is presented in **Figure 8.7**. Innovativeness/usefulness premiums are applied to products to which the CM has already been applied and which are expected to have a clinically significant effect. Therefore, the application rate of these premiums in the CM can be considered an index of the NMEs with novelty. The applicability rate of the innovativeness/usefulness premiums was 47% in 2006–2010 and 19% in 2011–2015. The difference is more than double.

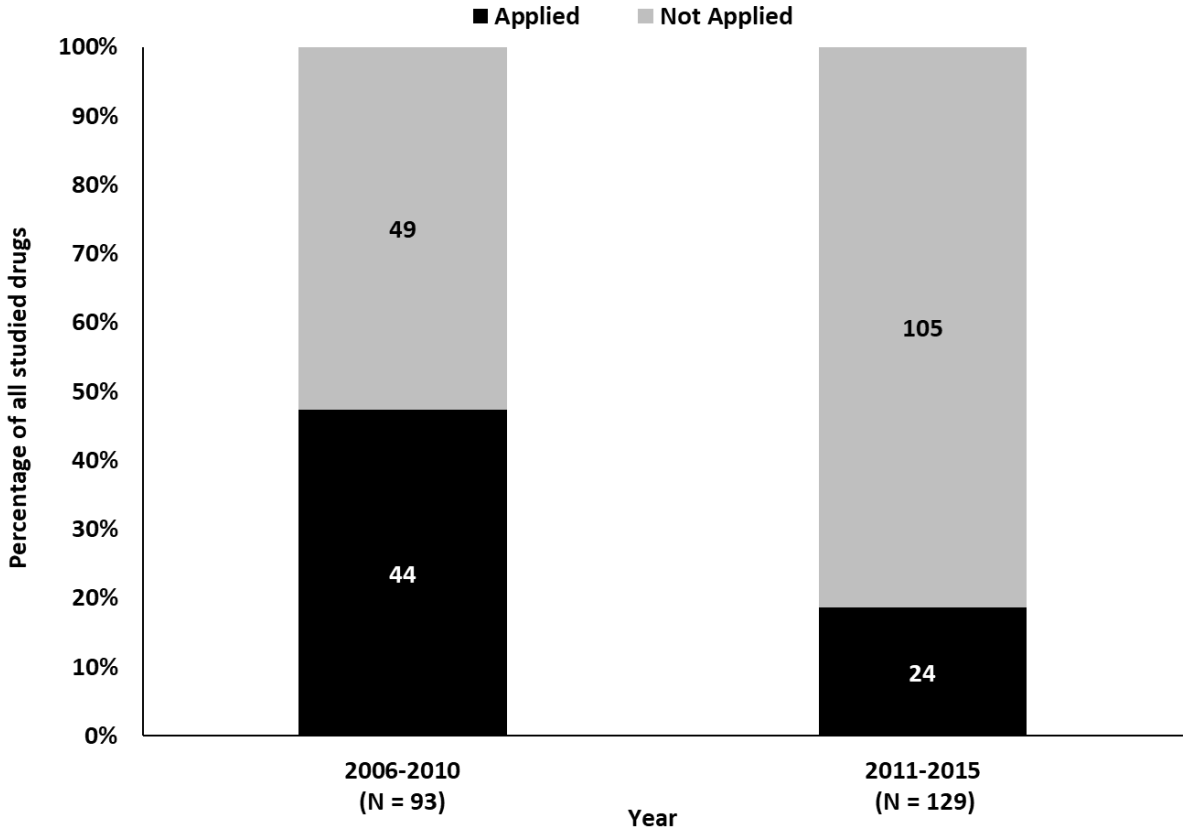


Figure 8.7. The number of NMEs approved in Japan, to which innovativeness/usefulness premiums were applied via the CM

The number of NMEs approved in Japan based on countries that first obtained approval is reported in **Figure 8.8**. The highest values are for: the number of **L** drugs first approved in the US (N=44), that of N drugs first approved in Europe (N=14), and that of **M** drugs first approved in Japan (N=6).

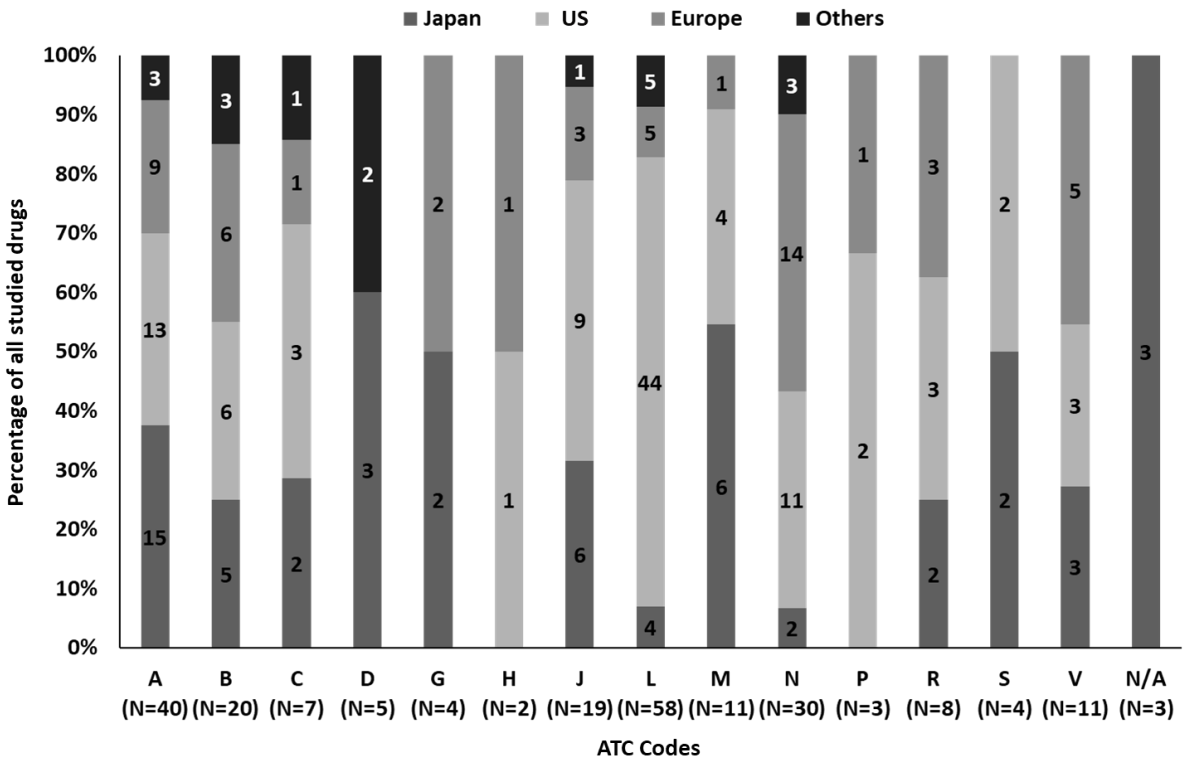


Figure 8.8. The number of NMEs approved in Japan based on the countries that first obtained approval

The number of NMEs approved in Japan based on ATC codes and categorized by the company type (Japanese vs. Global) is presented in **Figure 8.9**. The therapeutic areas of most drugs approved for the first time in Japan were **A** (N=15) and **M** (N=6). Most **M** drugs were developed by Japanese companies (N=10 out of 14) and **L** drugs by global companies (N=62 out of 70), consistent with the results in **Figure 8.8**.

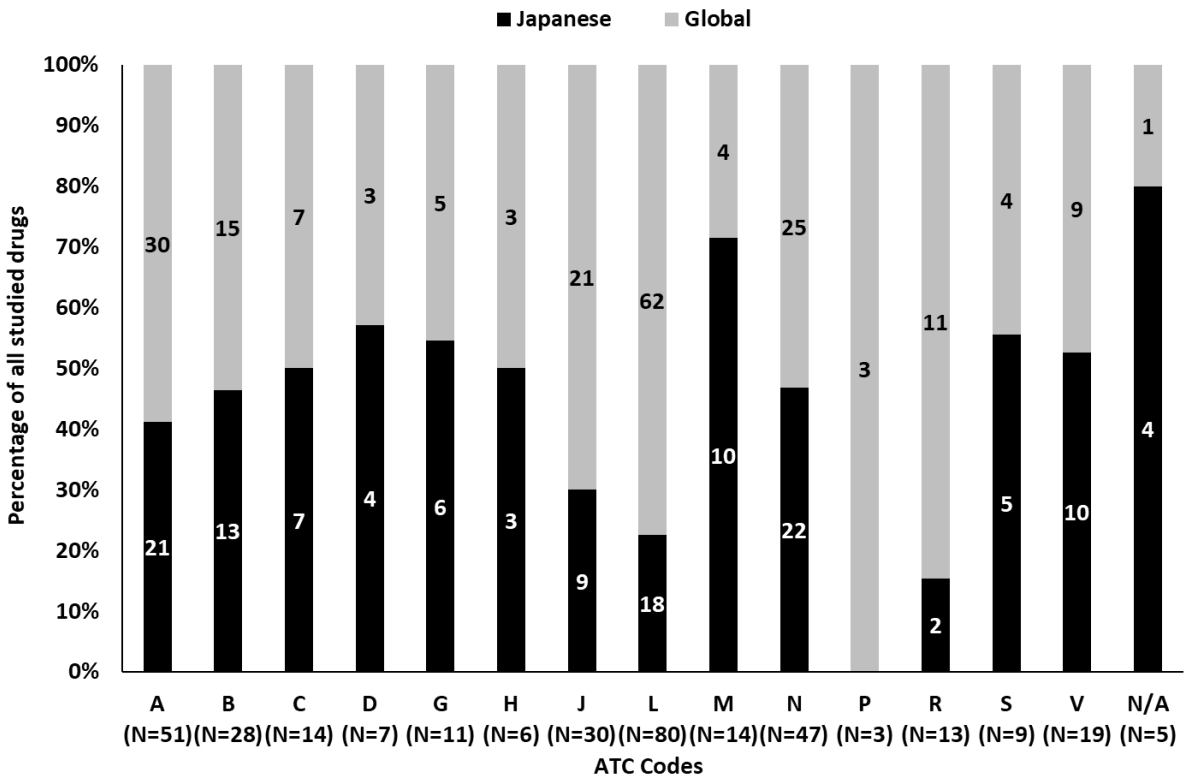


Figure 8.9. The number of NMEs approved in Japan based on ATC codes, categorized by company type (Japanese vs. Global)

8.5 Discussion

Japanese pharmaceutical profiles, focusing on NMEs approved in Japan between 2006–2015, were investigated. **Table 8-2** summarizes the evaluations of the Japanese pharmaceutical industry. The number of NMEs in the Japanese pharmaceutical industry has increased over the last decade, as has the market size. By contrast, the approval rate of highly innovative drugs may have decreased, considering that the number of the allocations of the CCM and innovativeness/usefulness premiums in the CM did not drastically increase. One reason may be that these pricing systems, including the submission of expected peak sales by pharmaceutical companies, do not seem to work well in Japan in relation to R&D on innovative drugs.

Table 8-2. Summary of an evaluation of the Japanese pharmaceutical market using the performance index defined in this research

Performance index	Number of NMEs	Market size forecasts	Number of drugs with significant clinical benefits
Results	Increased	Increased	Decreased
Notes	・ None	・ Accuracy of forecast by pharmaceutical companies	・ Discussions on appropriate systems that can encourage R&D in Japan ・ Cost calculation method ・ Comparative method 　・ Innovativeness premiums 　・ Usefulness premiums

The number of NMEs has increased between 2006 and 2015 (**Figure 8.3**), suggesting that the Japanese pharmaceutical industry has evolved over the last decade. However, it is necessary to evaluate the industry using multiple indicators, and it is difficult to confirm the growth of the Japanese pharmaceutical industry in recent years based only on this result.

The expected peak sales of each NME (**Figure 8.4**) were then investigated. Regardless of the market size, the number of NMEs has been increasing, suggesting an increasing trend in the Japanese drug market. In addition, the number of products whose expected peak sales amount is less than JPY 3 hundred million has increased significantly, while the number of NMEs with sales exceeding JPY 30 hundred million has also increased significantly. These results suggest a polarization in NME approvals, from drugs in the mass market to those in the niche market. For example, previous studies, specifically in relation to some **L** and **N** drugs, have reported this "from mass to niche market" trend in the Japanese market, which is harmonized with the global trend [131], [153].

The present study also investigates the NMEs based on their ATC classification (**Figure 8.5**). The increase in **L** drugs suggests that R&D on drugs with high UMN is encouraged in Japan, which reflects the global trend [272]. The number of **A** drugs has increased because the drugs for lysosomal diseases such as Gaucher's disease have been newly approved, and due to the launch of drugs for diabetes with new mechanisms of action, such as DPP-4 inhibitors and SGLT2 inhibitors. **A** is one of the therapeutic areas that include fatal and orphan/rare diseases [273]. The aforementioned "from mass to niche market" trend could also be confirmed in this disease area.

The CCM and innovativeness/usefulness premiums in the CM are applied to drugs that are expected to be clinically meaningful. Therefore, their application rate is also an index to evaluate the trend of innovative NME approvals. The rate of the application of the CCM has largely remained constant in 2011–2015 compared to 2006 and 2010 (**Figure 8.6**). The application rate of the innovativeness/usefulness premiums in the CM has decreased in 2011–2015 (**Figure 8.7**). The number of NMEs is certainly increasing. However, taken together, few of them can be considered "innovative," suggesting that the number of the innovative NMEs has been decreasing in Japan.

The first-approval countries and originator companies for NMEs were also investigated (**Figure 8.8** and **Figure 8.9**). The main reason why first-approval countries differ by therapeutic area is the development strategy of the company, which is reported to be affected partly by the location of the headquarters [68]. In 2015, the MHLW formed the "SAKIGAKE Designation System" to lead the world in the practical application of innovative medical products in Japan [274]. This new regulatory scheme encourages the conduct of R&D of new therapeutic products in Japan, especially in areas that global pharmaceutical companies have been focusing on [63], [275]-[278]. When regulatory approvals are obtained in Japan ahead of other countries, a SAKIGAKE review designation scheme premium is also be applied [274], encouraging more R&D by Japanese pharmaceutical companies in therapeutic areas

mainly dominated by global pharmaceutical companies, and thereby, ensuring that Japanese pharmaceutical market are comparable to their global counterparts. Several reports show an upward trend especially in oncologic drugs in Japan [47], [130], [132], [133], [279], [280], which will be accelerated through these schemes.

There are a few limitations to this research. The rationale of the performance indexes introduced in this research is limited, especially in terms of justifying the application rate of the CCM and innovativeness/usefulness premiums in the CM, since the drug pricing system in Japan has been reformed and the environment has changed drastically. It has not been concluded the cause of the decrease in innovation of new drugs can be attributed to the drug pricing system or to the lack of innovation by pharmaceutical companies. It is difficult to draw a clear conclusion on whether innovative drugs are decreasing because there is room for improvement in the drug pricing system, or whether new drugs applicable to premiums are decreasing simply because there is no problem with the drug pricing system and innovative drugs are decreasing. As mentioned above, the present discussion warrants further investigation to clarify the causality, particularly because the discussion needs to be addressed as a whole of the pharmaceutical regulations. However, although primitive, this is the first report revealing the 10-year trend for the NMEs approved in Japan based on the total numbers and the numbers categorized by ATC codes, expected peak sales, applied pricing systems, first-approval countries, and originator company profiles (Japanese vs. Global), warranting the further robust research.

8. 6 Conclusions

The number of NMEs in the Japanese pharmaceutical industry has increased over the last decade and the market size has also increased. By contrast, the approval rate of highly innovative drugs may have decreased, considering that the number of allocations of the CCM and innovativeness/usefulness premiums in the CM has decreased (**Figure 8.10**).

- ✓ The use of various performance indexes, such as market forecasts and significance of clinical benefits, reveals that the number of NMEs and market size has increased and the number of drugs with significant clinical benefits has decreased.
- ✓ These results suggest that NME innovation by Japanese companies has been decreasing, and the government's CM for pricing does not work well in Japan.

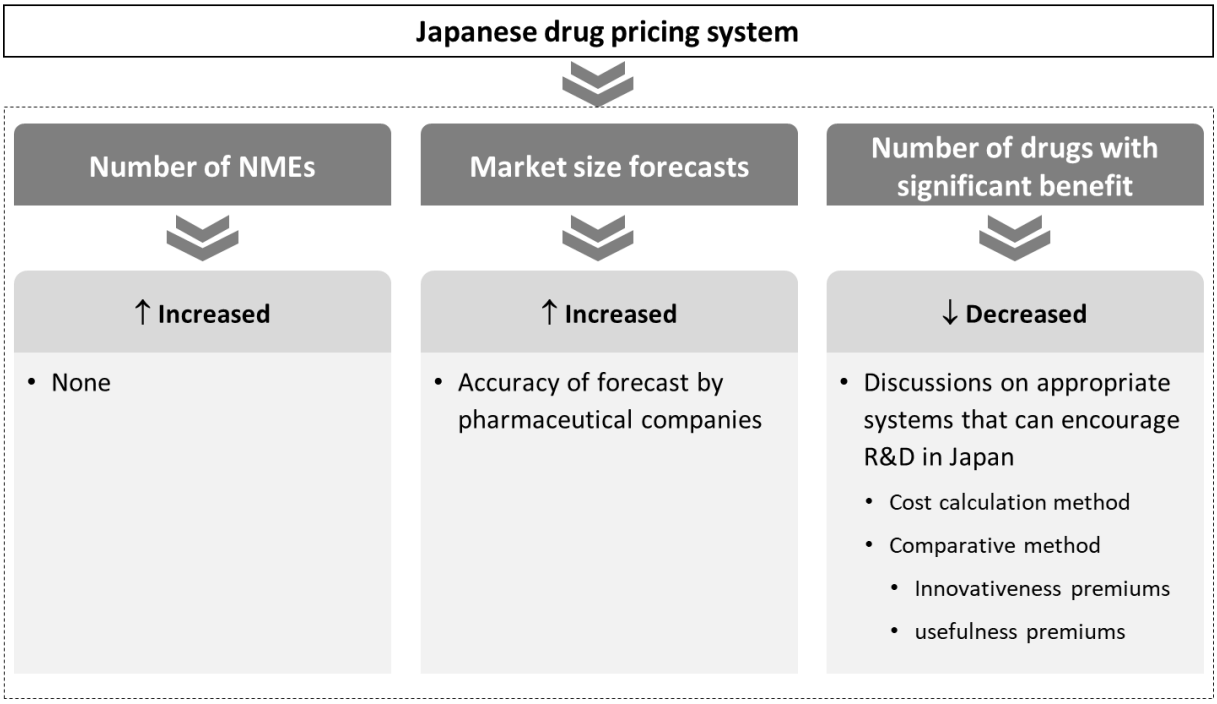


Figure 8.10. Visual abstract

A preliminary evaluation focusing on NMEs was conducted to appraise the current NHI pricing system in terms of incentives for innovation. The findings suggest that the drug pricing system may act as a potential disincentive, although there are various limitations, such as no causal relationship identified. This study supports the previous findings. The findings indicate further discussion on the NHI drug price system reform should be addressed to promote R&D of "innovative" new drugs such as anti-cancer drugs going forward, and these findings should provide a foundation for future discussion.

9. Discussion and Conclusions

9.1 Summary of Results

9.1.1 Primary Analyses of the Japanese Pharmaceutical Market

The following fit-for-purpose assessments of the Japanese pharmaceutical market was conducted with the database including the sales amount and prescription volume to better characterize the Japanese market profile, define therapeutic areas of "innovativeness", and establish the direction of R&D strategies in such therapeutic areas; Characteristics of the Japanese Pharmaceutical Market Compared to the US and European markets, Overview of Anti-cancer Drug Market in Japan, Implications for the Direction of R&D Strategy of Anti-cancer Drugs (1): Rare Cancers, and Implications for the Direction of R&D Strategy of Anti-cancer Drugs (2): Combination Therapies.

The Japanese market is dominated by cardiovascular drugs, unlike the global market where drugs for the treatment of central nervous system diseases and anti-cancer drugs dominate. If the current market trend continues, the Japanese market is expected to shift to a market structure similar to that of overseas markets in the future, suggesting that the Japanese market is currently in a transitional period. The anti-cancer drug market has grown annually from 2010 to 2016 and its market size was over 1 trillion in 2015. The market for molecularly targeted therapeutics has more than doubled in size compared to 2010. Although there are some limitations, analyzing the sales amounts and prescription volumes of rare cancer drugs and the details of approved combination therapies of anti-cancer drugs produces a quantitative determination of whether such drugs can produce high sales for pharmaceutical companies.

Given the above-mentioned, part of the direction of the R&D strategies has been proposed; however, given that all factors relevant here have not been comprehensively investigated, these conclusions will remain limited.

9.1.2 Exploratory Analyses of the Japanese Drug Pricing System

The following preliminary assessments on the drug pricing system was performed in an effort to evaluate factors that may have been responsible for the R&D strategies, understand the association of the current regulation scheme with response to the development of innovative drugs, and increase the understanding of the drug pricing system as part of the whole pharmaceutical regulations in Japan; Appraisal of the Japanese Drug Pricing System (1): Predictability of Sales and Drug Prices and Appraisal of the Japanese Drug Pricing System (2): New Molecular Entities.

As long as drug sales predictions are used in drug price calculations, a flexible re-pricing system is

needed to buffer unexpected pharmaceutical expenditures. The use of various performance indexes, such as market forecasts and significance of clinical benefits, reveals that the number of NMEs and market size has increased and the number of drugs with significant clinical benefits has decreased.

These limited scope analyses are short of an assessment of whether the drug pricing system goes far enough in stimulating the R&D. Interpretation of the findings of these analyses should be performed in the context of the total pharmaceutical regulatory system, hence any definitive conclusions on the appraisal of the drug pricing system are not readily drawn. The following sections describe the details of these limitations. However, although preliminary, this is the first appraisal in the context of the R&D of innovative drugs, primarily focusing on the drug pricing system, thereby making a key contribution to the advancement of further research.

9.1.3 Research Hypotheses and Discussions

This thesis tested the following research hypotheses, to determine the optimal R&D strategy for Japanese pharmaceutical companies, by focusing on the characteristics of the Japanese pharmaceutical market and, appraising the drug pricing system as a preliminary investigation among pharmaceutical regulations in Japan:

1. “Innovativeness” is applied to a therapeutic area as unique in the Japanese pharmaceutical market compared to the market structure of other countries around the world.
2. The structure of the Japanese market differs from that of global markets, and different drugs are often used to treat the same disease in different countries. This discrepancy is particularly pronounced in high UMN areas such as cancer and central nervous system diseases.
3. One therapeutic area that is likely to witness innovative new drugs is oncology.
4. Utilizing pharmaceutical regulations and considering the characteristics of anti-cancer drugs with the potential for high sales will enable the development of new drugs with high sales potential in Japan.
5. The Japanese NHI price system underestimates the value of new drugs and must be restructured.

Chapter 3 elucidated the characteristics of the Japanese pharmaceutical market and the results supported the hypotheses 1 and 2.

Chapter 4 investigated the current status and prospects of the Japanese anti-cancer drug market. Chapters 5 and 6, focusing on the increased revenues that rare cancer drugs will bring to pharmaceutical companies as well as the contents of the labeling of anti-cancer drug combination therapy, proposed new

types of new drug development that Japanese pharmaceutical companies should pursue to achieve high sales. The results supported the hypotheses 3 and 4.

Chapters 7 and 8 evaluated Japan's NHI pricing system among pharmaceutical regulations in Japan through two preliminary studies, and investigated whether the current system can promote the Japanese pharmaceutical industry. A definite conclusion can hardly be drawn from the findings of the present study to support or reject hypothesis 5, because there are other regulations besides the NHI drug pricing system, and the discussions have not been carried out in context of these regulations.

The summary is that hypotheses 1-4 were supported while no firm conclusions could be drawn on hypothesis 5 because of a lack of robust discussion of pharmaceutical regulations on the whole.

9.2 Interpretation of Results

As previously stated, the key context in this thesis is the characteristics of the Japanese pharmaceutical market. This thesis includes the exploratory assessment of the drug pricing system as potential contributing factors related to the R&D strategies. This research allows for the preliminary evaluations of the drug pricing system among pharmaceutical regulations in Japan, as well as the primary analyses of characteristics of the Japanese pharmaceutical market. Therefore, this thesis allows the interpretation of the findings derived from this perspective together with the data from the preliminary analyses of the drug pricing system among pharmaceutical regulations in Japan.

The study's interpretation of the data is summarized in **Figure 9.1**.

Figure 9.1. Summary of data interpretation

This thesis clearly discussed "innovativeness" in relation to new drugs (Chapter 2); the unique characteristics of the Japanese pharmaceutical market in relation to international pharmaceutical markets (Chapter 3); the current status and future directions of the anti-cancer drug market in Japan (Chapter 4); novel perspectives on how pharmaceutical companies in Japan could conduct R&D in the field of oncology while utilizing the current drug pricing system, by focusing on rare cancers and anti-cancer drug combination therapies (Chapters 5 and 6); the regulatory framework, focusing on the drug pricing system among pharmaceutical regulations in Japan, and whether it has been able to promote R&D on new drugs in Japan in the context of predictability of sales/drug prices (Chapter 7); and the underestimation of the value of new drugs (Chapter 8).

It should be noted that the pharmaceutical companies can not simultaneously execute all the presented insights in this thesis. Therefore, considerations should be given about the timing of strategy implementation given the findings. First, the findings should be refined through further studies, given the limitations of the preliminary discussions in this thesis in terms of possible reforms to the drug pricing system. The findings should be presented to the government scientifically to promote the reform

of the pricing system. This requires a long-term outlook, hence these strategies should not be implemented immediately. Second, with regard to R&D of anti-cancer drugs that can be classified as "innovative" new drugs, pharmaceutical companies with R&D capabilities in oncology should promote R&D activities in this field and aim to achieve FIC. One strategy to achieve this should be strategies focused on rare cancers and combination therapies as identified in this thesis. Finally, pharmaceutical companies with limited capabilities should establish a portfolio focused on anti-cancer drugs as a mid-term strategy. As such, one strategy should be to create R&D strategies in areas with UMN such as rare cancers rather than in highly competitive areas. In summary, in the long term, the findings of the NHI pricing system should be proposed to the government based on the entire framework of the health care system to foster a supportive environment for future R&D strategies of "innovative" new drugs in the Japanese pharmaceutical industry, and in the short term, R&D in rare cancers and combination therapies should be accelerated, and in the mid-term, a portfolio of potential drugs specifically targeting anti-cancer drugs should be prepared. Importantly, no single pharmaceutical company should be responsible for all of these strategies so that each should choose the optimal strategy based on the characteristics of each pharmaceutical company.

Based on these findings, there are three strategies that pharmaceutical companies can adopt: "wait and gate," "strategic diversification," and "go broad and fast" (**Figure 9.2**).

Approach	Advantages	Disadvantages
Wait and Gate Focus on utilizing the current drug pricing system; feedback on the current system	• Potential to encourage more R&D projects • Policies that are beneficial to all stakeholders	• May strain organizational resources, requiring re-prioritization of existing activities • Large investment required
Strategic Diversification Selective portfolios focusing on oncology and neuroscience	• Chance to be competitive in multiple diseases, meeting high unmet medical needs in oncology and neuroscience • Leapfrog competition into high unmet medical needs area	• Moderate risk due to the low probability of technical success caused by limited scientific rationale for some companies • May strain organizational resources, requiring re-prioritization of existing activities
Go Broad and Fast Move quickly into oncology portfolio across multiple cancer types	• Possibility of securing first-to-market anti-cancer drugs in more indications • If truly "innovative" new drug can be delivered, it will bring benefits to more patients faster	• Large investment required, with high risk • May strain organizational resources, requiring re-prioritization of existing activities

Figure 9.2. Proposed approach

"Wait and gate" is a new approach to the drug pricing system. In this approach, pharmaceutical companies put forth recommendations for a better drug pricing system, while conducting R&D, to ensure maximum profits within the scope of the current drug pricing system. This is expected to maximize the opportunities for R&D activities; furthermore, it will enable the establishment of a beneficial regulatory system for the government, patients, and health care professionals. Second, "strategic diversification" is an approach to the companies' product pipelines. The innovative drugs identified in the present research are all related to oncology. However, if drugs in other therapeutic areas are also identified, pharmaceutical companies can push forward the development of drugs in those areas. This will not only improve the presence of pharmaceutical companies by introducing new drugs into areas with significant medical needs, but also enable companies to achieve a leadership position in those markets. Finally, "go broad and fast" is related to effective R&D on innovative drugs. This approach focuses on rare cancers and anti-cancer drug combination therapies, especially in the field of oncology. This will allow the development of FIC drugs to meet high medical needs.

There are disadvantages to each approach. One common issue relates to resource constraints. While each company has its own R&D strategy for new drugs, navigating in the aforementioned specific direction will involve greater risk. Of note, the discussion thus far has addressed the approaches that can be taken by pharmaceutical companies engaged in the R&D of anti-cancer drugs; however, this discussion may not necessarily apply to companies that do not have expertise in the R&D of those drugs.

The aforementioned three approaches have further been translated into measures that can be taken by pharmaceutical companies (**Figure 9.3**).

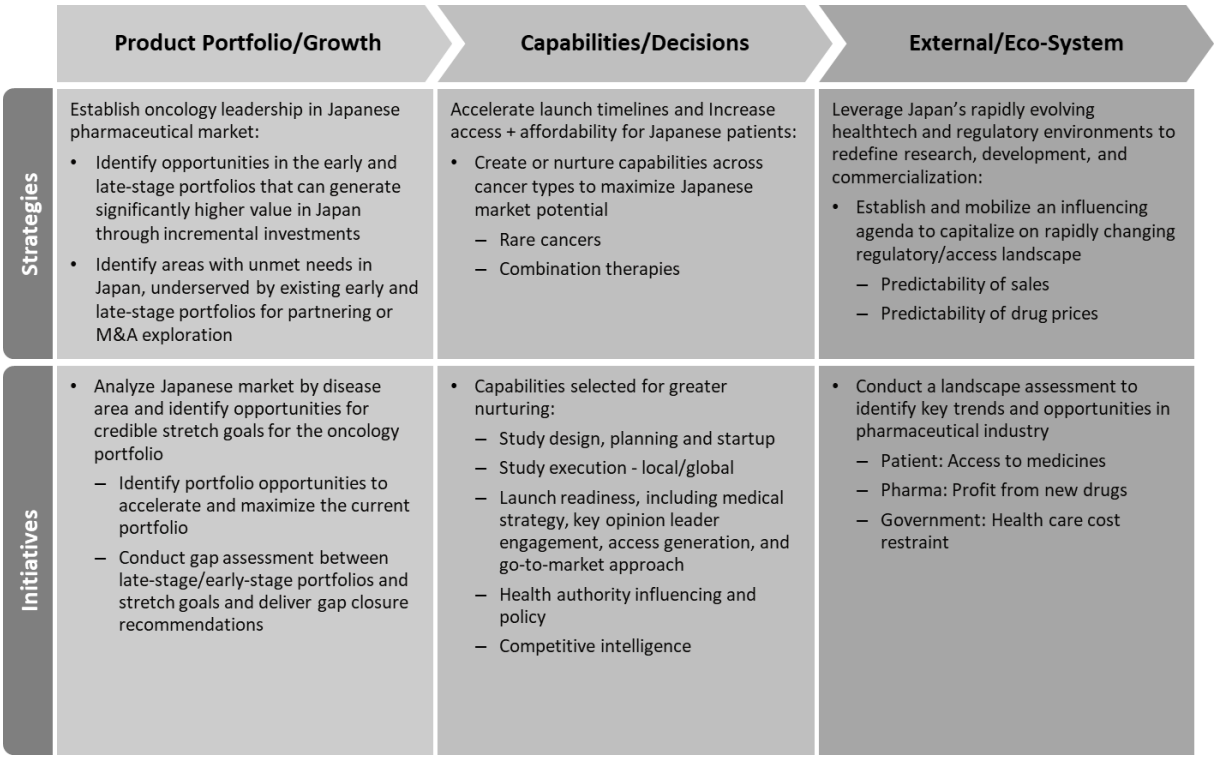


Figure 9.3. Proposed oncology-focused strategic plan for Japanese pharmaceutical companies

In the R&D of innovative new drugs in the field of oncology, a market analysis should be conducted not only from the perspective of which segment of the patient population has medical needs but also from the perspective of expected profitability in establishing an anti-cancer drug-related R&D strategy. This research provides basic findings regarding possible directions: rare cancers and anti-cancer drug combination therapies. However, R&D should be carried out according to the capability and portfolio of each pharmaceutical company. Since this strategy is oriented to pharmaceutical companies, policy predictability is a key approach to the external environment. As has been discussed, pharmaceutical companies tend to emphasize predictability of drug prices. By contrast, since the government must consider the impact on health insurance finances, sales—rather than drug prices—are likely to be an important perspective. In this context, pharmaceutical companies should take the lead and partner with the government to ensure predictability of sales as well as drug prices, the two sides should also deepen their understandings of regulatory frameworks, which will help create an integrated ecosystem characterized by deeper collaboration among stakeholders. Embracing this type of ecosystem will address pressing problem areas in the Japanese pharmaceutical industry and allow pharmaceutical companies to proactively shape the future of the industry. As a preliminary analysis, it represents a

faithful assessment of where the current drug pricing system stands at the moment, warranting additional validation of the data as a potential contributing factor to the R&D strategies considering the other pharmaceutical regulations in Japan.

The findings of this thesis are discussed below, based on the perspectives of the six players (**Figure 9.4**)

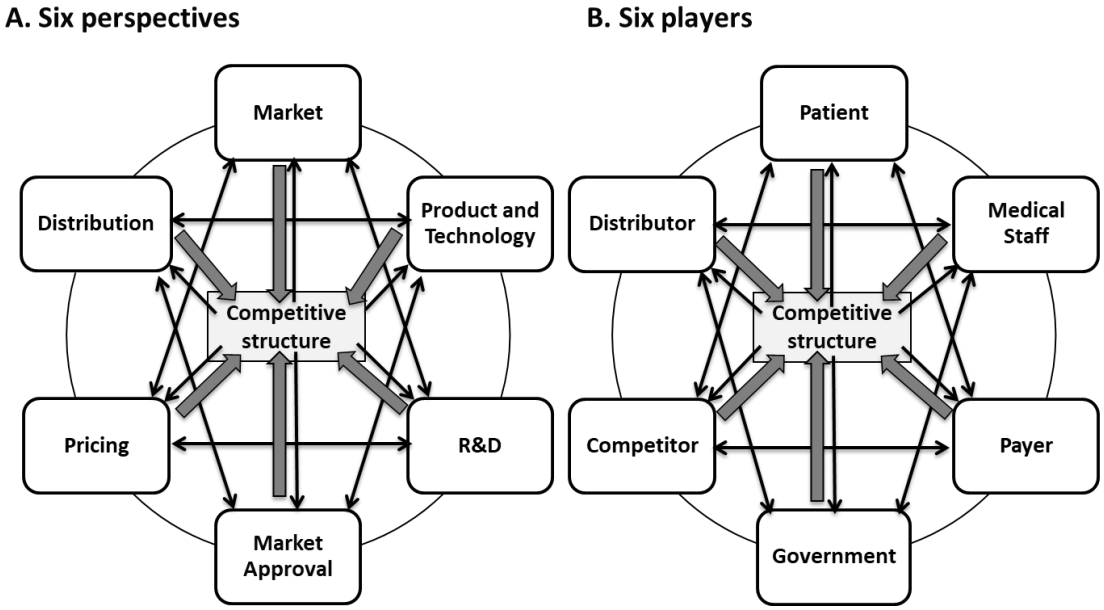


Figure 9.4. "Six perspectives" and "Six players" (reshown, see Chapter 1, Section 1.1)

Payer

The impact of the findings on payers is considered to be limited. In other words, there are likely to be no positive or negative effects.

Since Japanese insurers are forbidden by law to impose different co-payment ratios based on whether the medication includes generics or brand-name drugs, and because no insurer utilizes "a prescription drug list," which severely restricts the use of brand-name drugs for which generic alternatives exist, the findings are expected to have minimal impact. Thus, these proposals are considered to be reasonable for the payer.

Government

The series of findings suggested in this study are likely to have a positive impact.

Japan is one of the few countries in the world that can create new drugs, and the pharmaceutical

industry, a knowledge-intensive industry, is expected to be an important engine for economic growth. In particular, promoting innovation and continuously creating innovative new drugs is important. However, there is no clear agreement as to what constitutes “innovative.”

The discrepancy between the structure of the Japanese market and the global market as suggested in this study, means that a potential solution is the development of drugs in the field of oncology. The direction R&D should take in this area has been discussed in detail, by distinguishing the case of generic drugs and brand-name products. In conclusion, this thesis will help the government properly evaluate the innovation in the pharmaceutical industry because it shows the direction of the R&D of pharmaceutical companies. Moreover, it will be possible for the government to identify bottlenecks to development in terms of corporate behavior and to quickly formulate and implement policies based on the findings. Overall, the findings are positive for the government in terms of the promotion of the Japanese pharmaceutical industry.

Competitor

The findings are likely to have a positive impact.

Japanese pharmaceutical companies should research and develop innovative drugs that are competitive not only in Japan but also overseas, by concentrating their R&D in oncology, where treatment satisfaction is drastically low and new drugs are strongly desired. In particular, the optimal R&D direction for each generic drug manufacturers and new drug manufacturer in the pharmaceutical industry is clearly provided, and an NHI price system that aims at the appropriate evaluation of innovation, which will in turn contribute to the further development of the Japanese pharmaceutical industry, is also proposed. Competitors can utilize these findings to promote the industry in Japan by delivering innovative drugs.

Distributor

Although the findings may have limited value for distributors, the following points should be considered if the penetration of generic anti-cancer drugs in the Japanese market increases.

As an incentive for the penetration of generic drugs in Japan, a new point was made available to insurance pharmacies as a fee for providing information on drug quality and an additional point was provided for dispensing generic drugs, in the revision of medical fees in 2002. However, since the price of generic drugs is low to begin with, it is difficult to generate a profit based on the difference in drug

prices, compared to the potential profit in selling the original product. This is because even if the insurance pharmacy reduces the purchase price by a proportion equal to the drug price, the difference between the drug price and the higher-priced brand-name product will be greater. Therefore, even with the addition to the drug price by the regulations described above, the incentives for insurance pharmacies to handle generic drugs are small.

For wholesalers, who are responsible for drug distribution, it is more advantageous to handle brand-name drugs with higher drug prices than generic drugs. This is because even if the same profit margin is obtained, the profit itself is greater for the higher-priced brand-name drug. In addition, generic drug manufacturers, who do not have the financial resources, do not provide sufficient support to wholesalers compared to brand-name drug manufacturers. Therefore, some wholesalers are not proactive in dealing with generic drugs. To summarize, the findings of this thesis are not expected to affect distributors significantly; however, it may be necessary to reconceptualize the ideal model for Japan's pharmaceutical industry.

Patient

Overall, the findings of this study have a generally positive impact on patients. Focusing pharmaceutical R&D on oncology, where therapeutic satisfaction is considered to be poor and new drugs are strongly required, is a promising trend from the perspective of patients' QoL.

Increased penetration of the Japanese market by generic anti-cancer drugs, as discussed from the distributor's perspective, can lead to questions regarding generic drugs.

Patients' preference for generic drugs are likely to be more directly influenced by their out-of-pocket costs than by the drugs' prices. In Japan, the out-of-pocket costs can be reduced. In addition, since most medical staff as well as patients tend to be skeptical about the quality of generic drugs, the number of patients who prefer to receive these drugs is limited. If patients have concerns about generic drugs, they may experience a negative placebo effect, which can affect their medical condition; therefore, even if the generic drugs are therapeutically equivalent, the psychological effects of the generic drugs may diminish the effectiveness of the drugs, lowering the drug's reputation. Accordingly, the factors that hinder the penetration of generic drugs in the Japanese market should be addressed.

Medical staff

The findings of this thesis are considered to have a positive impact. However, the increased

penetration of generics poses potential problems. Health care providers, especially doctors and pharmacists, are not always aware that there is a difference between original drugs and generic drugs. In particular, many medical staff may have doubts about the therapeutic equivalence of generic and brand-name due to differences in the additives. In other words, the information currently available, such as approval information, is not sufficient to eliminate the information asymmetry. In such an environment, medical staff, such as doctors and pharmacists, may exhibit strong resistance to the use of generic drugs. The issue of information asymmetry should be fully considered.

9.3 Concluding Remarks

In the context of the progress of the Japanese pharmaceutical industry, there have been several discussions based on the underlying policies and characteristics of the Japanese pharmaceutical market and the Japanese NHI drug pricing system. This thesis has listed the key issues, policies, and management reforms required to maintain and improve R&D incentives for innovative new drugs and control rising health care costs, and summarized the major points. However, the present data especially on the drug pricing system should be observed as a preliminary analysis requiring further research and discussions as the whole body of the pharmaceutical regulations and evaluation of the drug pricing system, although preliminary, may provide evidence for directions of revision points and may allow for the development of new regulation schemes to help establish which R&D strategies may be beneficial for the pharmaceutical industry.

The Japanese pharmaceutical industry has been on a growth trajectory and has developed higher R&D capabilities. To create innovative new drugs in Japan that enjoy a strong competitive advantage in the global market, the Japanese pharmaceutical industry must develop awareness of global pharmaceutical companies' portfolio, and the government should appropriately evaluate the innovation of pharmaceutical companies through various pharmaceutical regulations such as the NHI drug pricing system.

Therefore, the following perspectives are important when considering the future direction of the Japanese pharmaceutical market:

- ✓ The current structure of the Japanese and global pharmaceutical markets has been diverging. However, the Japanese market is expected to have a market structure comparable to the global market, and drugs in the area of oncology will become very important.

- ✓ Pharmaceutical companies should have comprehensive strategies for the overall product portfolio in terms of lifecycle management; this is expected to generate profits not only in the Japanese market but also in international markets.
- ✓ The government and regulatory authorities need to design a system that will encourage the R&D of new drugs and allow Japan to create innovative new drugs that have a competitive advantage in the global market.

This thesis concludes with the hope that the new drugs developed in Japan, with appropriate incentives for innovation, will contribute to the health of people suffering from cancer all over the world and eliminate death from cancer entirely.

9. 4 Thesis's Contribution to the Current State of Knowledge

A summary of this thesis's contribution is presented in **Figure 9.5**.

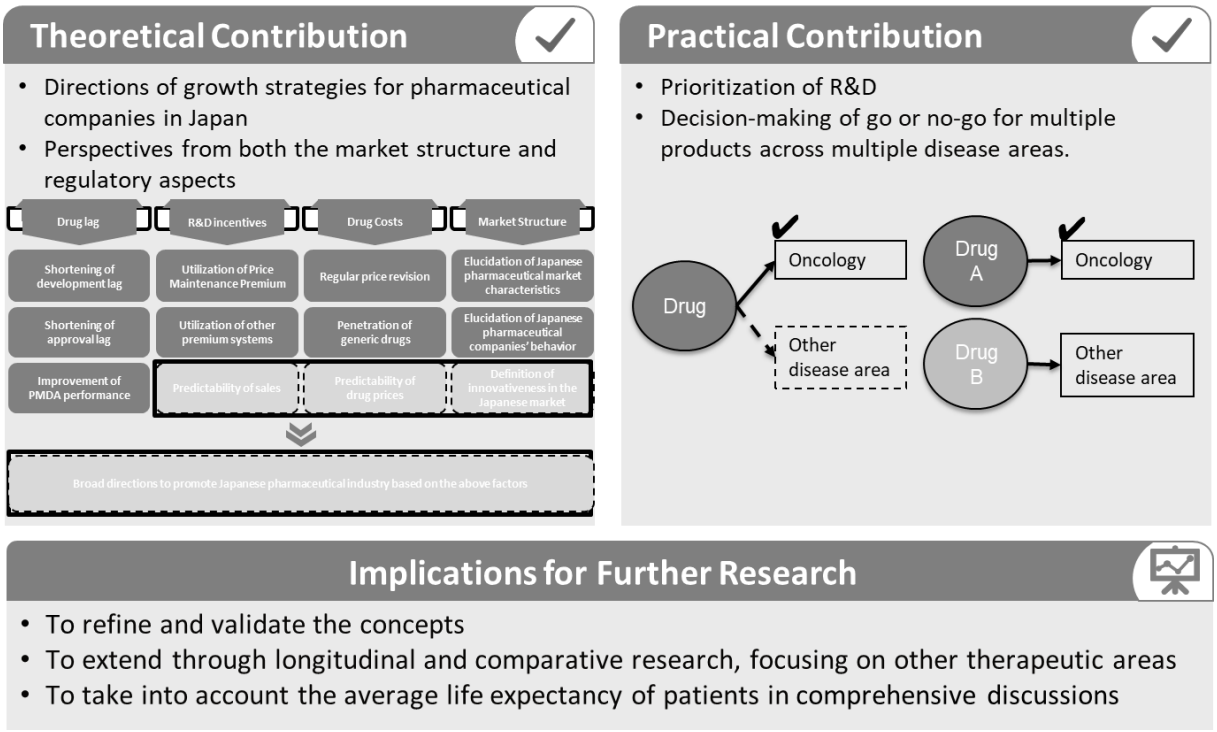


Figure 9.5. Thesis's contribution to the current state of knowledge

9. 4. 1 Theoretical Contribution

This thesis discusses growth strategies for the Japanese pharmaceutical market and pharmaceutical companies from the market structure and regulatory aspects, after considering the complexity of the pharmaceutical industry.

The evidence it presents on each country's market will be of great academic significance, as each country has different regulatory or insurance systems. In this context, the perspectives shared by this thesis on the Japanese pharmaceutical market can be considered a significant academic contribution.

9. 4. 2 Practical Contribution

The probability of technical success in the R&D of a new drug is extremely low. Nevertheless, pharmaceutical companies work day and night on the R&D of new drugs, undertaking R&D projects for multiple candidate compounds simultaneously. Moreover, companies often work on candidate compounds in more than one therapeutic area. Therefore, companies must consider the lifecycle of the

products and the profitability over the medium to long term. This thesis finds the oncology area to be apt for further study.

Thus far, there has been a vague perception that R&D should focus on oncology, because of the existence of high levels of UMN. This thesis provides data on the strategies Japanese pharmaceutical companies should adopt to create internationally competitive new drugs from Japan, and may provide an impetus for a shift in the management strategies of Japanese pharmaceutical companies. Specifically, when confronted with multiple candidate compounds, firms should prioritize R&D based on the evidence provided in this thesis. The findings also offer guidance on what type of capabilities pharmaceutical companies without an R&D portfolio of anti-cancer drugs should acquire, and which cancer drug categories they should pursue when initiating anti-cancer drug R&D.

9.5 Implications for Further Research

This thesis has raised several opportunities for future research in terms of theory development and concept validation. Further research is necessary to refine and further elaborate the findings.

First, even though the thesis presents new findings and useful conceptual guidelines for pharmaceutical companies, it does not address feasibility, warranting further empirical research on this issue. The applicability of the R&D strategies elicited in this thesis is limited given the lack of analysis after proper classification of the companies in interest through a comprehensive consideration of all contributing factors to the R&D strategies. The results obtained in this thesis are also limited by the lack of consideration of relevant pharmaceutical regulations such as the health care system and reimbursement system in the discussions on the drug pricing system. Therefore, more detailed discussions are required to specify the companies applicable to the R&D strategies proposed in this thesis, and the evaluation of the Japanese drug pricing system is necessary to be implemented in the context of entire Japanese pharmaceutical regulation. Nevertheless, this research will provide a cornerstone for such an advanced research.

Second, there are limitations resulting from the database used in this thesis (**Table 9-1**). A major limitation of the study is that the data in Chapter 3 were mainly from 2014, indicating that further empirical investigations are needed to determine whether the trend found in this study holds true today. Chapters 4, 5, 7, and 8 have the same limitations as Chapter 3, and although the data are relatively recent, they are not the latest. For Chapter 6, statistical estimation was performed on the sample data, though it was exploratory, with intensive narrative analysis focusing on Broad and Narrow Labels. Although there

are no significant differences in the results, additional research is needed to conduct appropriate estimation using appropriate sample data.

Table 9-1. Limitations related to the database

Chapter	Database Characteristics		
	Population data vs. Sample data	Statistical Analysis	Period
3	Population	Chi-square test Descriptive	2014
4	Population	Descriptive	2010–2016
5	Population	Descriptive	2010–2016
6	Sample	Descriptive Multinomial logistic regression	2006–2020
7	Sample	Binary logistic regression	2006–2015
8	Population	Descriptive	2006–2015

Limitations

Low Middle High

Third, this thesis provides an opportunity to refine and validate the concepts and constructs that emerged from our inductive analysis. For example, considerations of anti-cancer drug development strategies will need to be further refined and elaborated, in terms of both the relationship between anti-cancer drugs and innovation and their viability.

Fourth, this research could also be extended in a longitudinal, comparative way. For example, the primary hypothesis is that pharmaceutical companies should drive anti-cancer drug development by relating innovative drugs to anti-cancer drugs. Further research could provide valuable information to pharmaceutical companies and governments by focusing on drugs in other therapeutic areas, such as neuroscience, through similar investigations.

Finally, as to the appropriateness of oncology as a priority area for R&D, the discussion in this thesis is largely from the perspective of facilitating the Japanese pharmaceutical industry's growth; it does not account for the average life expectancy of patients. According to an international comparison of life expectancy, the average life expectancy of Japanese men is second-highest and that of women is highest,

compared to the world. In other words, Japan's present market structure is ideal, and the argument that the Japanese market should aim for a market structure similar to that of the global market could be wrong. However, whether the global market should aim for a structure similar to the Japanese market, is a subject that has not been addressed in this thesis. Therefore, this thesis could also be extended to existing and new supporting structures in order to offer a more informed prognosis on the Japanese pharmaceutical industry. Although this perspective needs to be verified by further research, it has a sound scientific rationale based on past findings.

As mentioned above, Japan has the longest life expectancy in the world, suggesting that its medical environment is more favorable than that in other countries, as life expectancy can be an indicator of the efficacy of the health care system [281]-[284]. However, the incidence of cancer has been increasing all over the world, including in Japan [285]. Previous studies show that cancer is the leading cause of death in Japan, with gastric, liver, and lung cancers being the leading cause of death in men and women [286]. A major reason for this could be lifestyle diseases and the aging population. The first is hypertension. Although high levels of UMN exist in developing countries, this is not the case in major Western countries, including Japan. More importantly, there is no significant difference in the incidence and mortality of hypertension in developed countries [287]-[289]. In Japan, the medical infrastructure is well-developed and medical needs are met, especially in terms of lifestyle diseases [290]. With regard to the aging of the population, the accumulation of damage to the genes triggers carcinogenesis [291], and as such, many pharmaceutical companies have been conducting R&D targeting this mode of action [292], [293]. As Japan has one of the most aged populations in the world [294], cancer therapy as well as prevention of cancer is critical.

Focusing on life expectancy among the elderly in the US, Sweden, France, the UK, and Japan, one report showed that the US ranks first [295]. Surprisingly, several reports from Japan have indicated that overall mortality rates among the elderly are different for men and women [296], and that the mortality rates for some cancers has been increasing each year [297]. This suggests that although the overall life expectancy in Japan is the longest globally, this is not the case specifically with the elderly.

Among various previous studies evaluating "satisfaction" with the health care system [298], [299], a report focusing on the Japanese health care system found that "satisfaction" is higher in the elderly than in young people [300]. This result shows that the medical infrastructure for the elderly in Japan is adequate. There are probably no major challenges to the Japanese health care system. However, there are a variety of problems associated with age-related diseases such as cancer. Care levels for these diseases

may be lower than in Western countries. One possible approach is encouraging R&D on anti-cancer drugs in Japan.

The R&D of anti-cancer drugs in Japan is expected to play an important role, considering that the progress of cancer treatments will be a key factor in the future of Japanese society. In other words, it might be reasonable to expect that the Japanese pharmaceutical market will become similar to the global market, though more in-depth empirical research is warranted.

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11. Appendix

11. 1 List of Abbreviations and Definitions of Terms

The following abbreviations and special terms are used in this thesis in **Table 11-1**.

Table 11-1. Glossary of abbreviations

Abbreviation	Definition
ATC	Anatomical Therapeutic Chemical
CCM	Cost Calculation Method
CM	Comparative Method
CML	Chronic Myelogenous Leukemia
CRC	Colorectal Cancer
DPO	Drug Price Organization
FIC	First-In-Class
FOLFIRI	Fluorouracil + Levofolinate + Irinotecan
FOLFOX	Fluorouracil + Folinic acid + Oxaliplatin
HER2	Human Epidermal Growth Factor Receptor 2
HHI	Herfindahl-Hirschman Index
HTA	Health Technology Assessment
IBP	Indication Value-based Pricing
IO	Immune-oncology
M&A	Mergers and Acquisitions
MASTER KEY	Marker Assisted Selective ThErapy in Rare cancers: Knowledge database Establishing registrY
MHLW	Ministry of Health, Labour and Welfare
MSI-H	High Microsatellite Instability
NET	Neuroendocrine Tumor
NHI	National Health Insurance
NME	New Molecular Entity
PMDA	Pharmaceutical and Medical Devices Agency
PVA	Price-Volume Agreement
QoL	Quality of Life
R&D	Research and Development
SCRUM-Japan	Cancer Genome Screening Project for Individualized Medicine in Japan
UK	United Kingdom
UMN	Unmet Medical Needs
US	United States

11. 2 Publication List

This thesis is composed of papers I wrote with my co-authors, noted in the Acknowledgements, over the past three years, first, as an MBA candidate (2018–2020) and then, as a DBA candidate (2020–2021) at the University of Tsukuba.

[1] **Shibata S**, Ozaki K, Suzuki T. (2020). Japanese Pharmaceutical Industry: Recent Perspectives and Areas for Further Research. *Journal of Regulatory Science,* 8(1), 1–13.

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