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Japanese Pharmaceutical Industry: Recent Perspectives and Areas for Further Research

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Abstract

The Japanese pharmaceutical market is one of the largest in the world. The Japanese government has increasingly been trying to control rising health care costs, and as a result, pharmaceutical companies are expecting that fewer opportunities will be available to command a higher price based on higher levels of innovation; this will likely lead to decreased interest in research and development (R&D) activities. With this background, the purpose of this article is to review current perspectives for R&D by the Japanese pharmaceutical industry, and to discuss the limitations and challenges for further research from the regulatory science and management perspectives. Given the substantial amount of evidence of regulatory science and management perspectives from the pharmaceutical industry outside of Japan and the limited amount of evidence from inside of Japan, it is important to review perspectives focusing on the Japanese pharmaceutical industry in comparison with those from other countries to understand the complexities of the Japanese pharmaceutical market, as well as the limitations and challenges associated with increasing productivity.

Keywords: Japan, pharmaceutical industry, drug pricing, regulatory science, clinical development, marketing strategy

1. Background

1.1. Japanese Pharmaceutical Industry

Despite being one of the largest in the world, between 2014 and 2018, the pharmaceutical market in Japan had the smallest average annual market growth rate, at approximately 1.0 percent, among all developed countries [3]. A complex regulatory process and a strict price control policy, including regular price cuts, have made it difficult for pharmaceutical companies to conduct research and development (R&D) of innovative drugs. Another reason for the stagnant market is the promotion of generic drugs adopted by the government since 2007 to reduce increasing health care expenditures, since generic competition may reduce market share of the branded drug [61]. Furthermore, in 2013, a 5-year plan was announced to expand the prescription of generic medicines to over 60 percent by 2018 [63], which has accelerated generic drug penetration in Japan. As drug patents eventually expire, Japanese companies are forced to adapt to a changing market environment, leading to the prompt formation of other business models or strategic alliances and acquisitions. In this context, expectations for a pharmaceutical industry that supports Japan's growth in the pharmaceutical industry and contributes to the creation of innovation have been increasing since 2000. The Ministry of Health, Labor and Welfare (MHLW) formulated visions for the pharmaceutical industry in 2002, 2007, and 2013 [60, 62, 64] (Table 1).

In the 2002 vision, in the context of an intensifying competitive environment as a result of industry reorganizations mainly in Europe and the United States, it was expected that at least two or three Japanese companies should have a large number of globally accepted portfolios (Global Mega Pharma).

In the 2007 vision, the following two points were noted: a) the competitive landscape regarding the R&D of antibody drugs and molecular-targeted drugs, as opposed to small molecule drugs, which have been the centerpiece of the blockbuster of drugs that generate annual sales of ≥ $1 billion, increased, and b) changes that had occurred in the global market environment. It was also envisioned that at least one or two companies should become the new type of Global Mega Pharma, which would allow them to adapt to changes in the new drug development environment; that even small companies should grow based on the results of innovative R&D activities (Global Niche Pharma); and that some companies should strengthen their international competitiveness by focusing R&D specifically on their specialties (Global Category Pharma).

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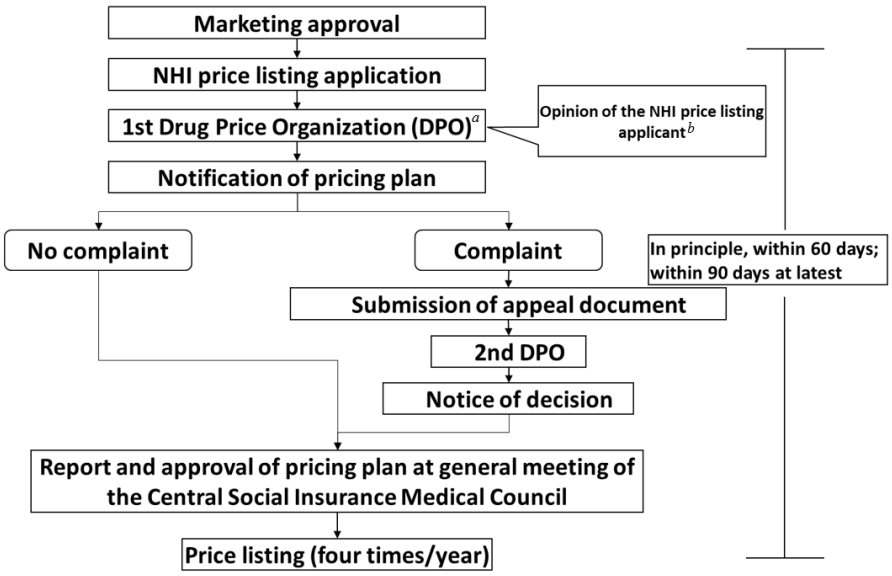
Table 1: Visions for the Pharmaceutical Industry in Japan

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



[a]DPO = the Drug Pricing Organization
[b]NHI =National Health Insurance

Figure 1: Drug Pricing Process in Japan

The 2013 vision pointed out an environmental change where medical needs expanded from lifestyle-related diseases to therapeutic areas with high unmet medical needs, such as oncology or neuroscience, and that the focus of R&D on antibody drugs was rapidly increasing. It stressed that the pharmaceutical industry should go beyond the categories shown in the past two visions to create a completely new business model. Additionally, the Japanese pharmaceutical industry was requested to deliver innovation in the area of life sciences.

The 2013 vision also mentioned industrial promotion actions, such as expanding tax support for R&D expenses and evaluating the drug pricing system. The relationship between drug pricing policy and industry promotion is described in the next section.

1.2. Japanese Drug Pricing System

In Japan, the government sets the initial price for drugs. To control increasing health care costs, the government revises drug prices biennially. The latest pricing reform was carried out in April 2018.

The pricing process for new drugs in Japan is shown in Figure 1 [67]. When a new drug is set to launch, a price listing application is submitted by the pharmaceutical company. A 1st Drug Pricing Organization is then established to discuss the appropriate pricing plan. The company can express its opinions at this point, regardless of whether or not it agrees with the outcome of the discussion. The pricing plan is then announced and the drug price is fixed if no objections are made. If an objection is made, the price is discussed in a 2nd Drug Pricing Organization. Based on the outcome of the second discussion, the pricing plan is approved at a general meeting of the Central Social Insurance Medical Council, which leads to the price listing (four times/year: February, May, August, and November).

The government sets the initial price according to two primary methodologies: the comparative method and the cost calculation method, as described in Figure 2 [67]. If similar drugs to the new drugs already exist on the market, then the comparative method is applied and some premiums will be given, if appropriate, also outlined in Figure 2. If similar drugs to

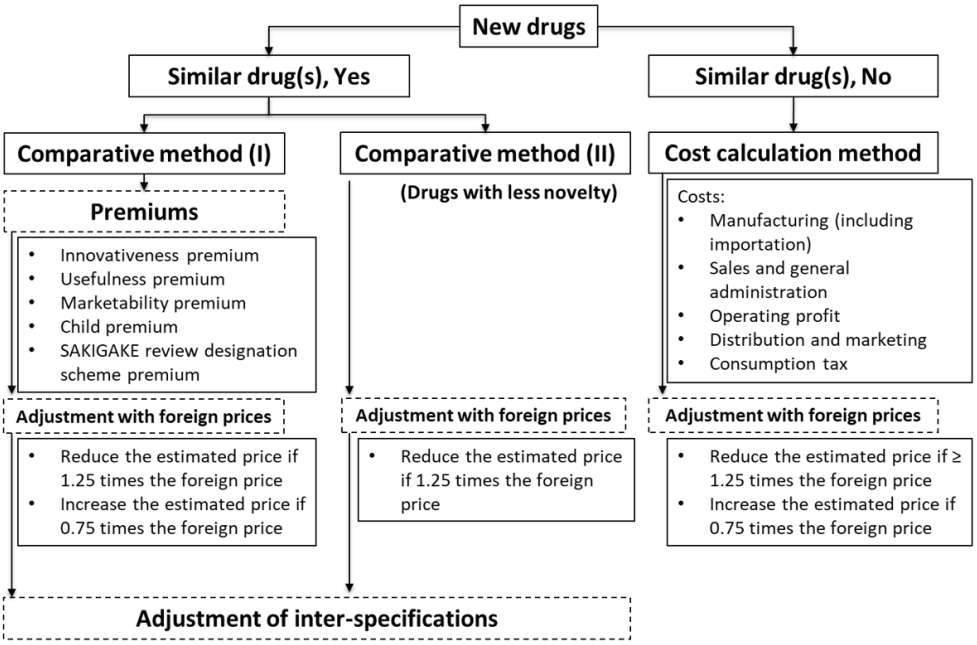


Figure 2: Price Calculation Methodologies for New Drugs in Japan

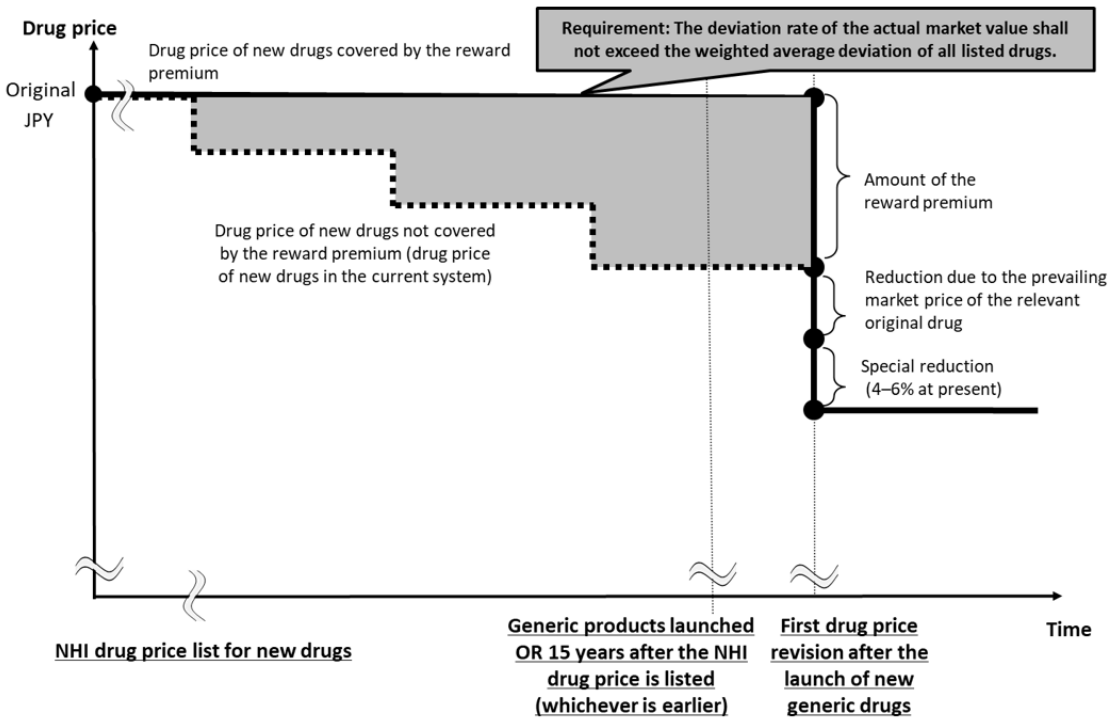


Figure 3: The Price Maintenance Premium

the new drugs do not exist on the market, then the cost calculation method is used to set the price, considering some costs (e.g., manufacturing, sales and general administration, operating profit, distribution and marketing, consumption tax).

Notably, there are two other drug price systems in Japan: the price maintenance premium (Figure 3) and re-pricing following market expansion (Figure 4) [67].

The price maintenance premium is a scheme that adds price premium rewards to innovative drugs and protects their prices for the duration of the period of exclusivity or patent. This system is considered to encourage pharmaceutical companies to develop new drugs for Japan early because a mechanism is in

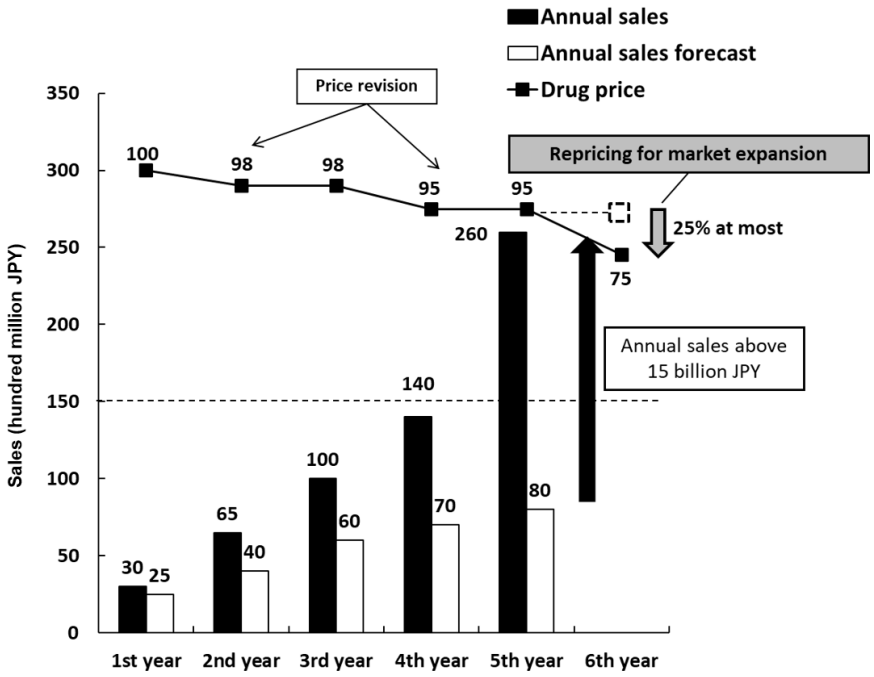


Figure 4: Re-pricing Following Market Expansion

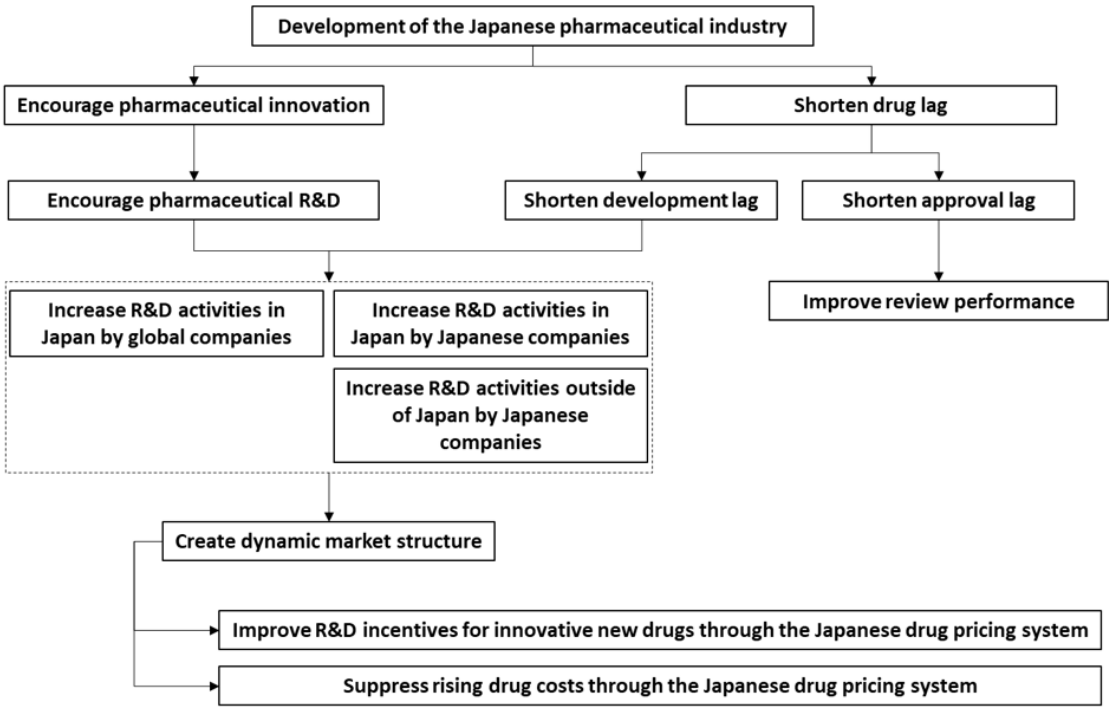


Figure 5: Issues Involved in Improving Access to New Drugs in Japan

place to obtain a reimbursed price that would reduce towering R&D costs.

Re-pricing following market expansion is a scheme in which drug prices are reduced (up to 25 percent) when annual sales of a drug exceed the estimated figure. Furthermore, some drugs with massive annual sales are treated as exceptions to the current rule, and their prices can be reduced up to 50 percent. This exceptional re-pricing (a 50 percent reduction from its first indication for melanoma) was applied to nivolumab on February 1, 2017 after it obtained a new indication for non-small-cell lung cancer, a disease with a relatively large patient population [66].

Table 2: Drug Lag of New Molecular Entities in Japan

	2014	2015	2016	2017	2018
Development lag [a] (years)	1.1	1.7	1.0	0.2	0.7
Approval lag [b] (years)	0	0	0	0.2	0.2
Drug lag [c] (development lag + approval lag) (years)	1.1	1.7	1.0	0.4	0.9

[a]Median new drug application submission time difference for new molecular entities between Japan and the U.S.
[b]Median regulatory review time difference for new molecular entities between Japan and the U.S.
[c]Sum of development lag and approval lag.

In summary, these pricing systems in Japan are considered to contribute to the maintenance and improvement of not only R&D incentives for innovation by pharmaceutical companies, but also sound health insurance financing.

2. Literature Review

2.1. Scope and Justification of the Review

In recent years, the promotion of the pharmaceutical industry in Japan has been taken up as a major policy issue. Factors associated with limited access to new drugs in Japan are considered to include problems in the Japanese clinical trial environment, such as high costs, a lack of clinical trial staff at clinical trial sites, and regulatory problems [60, 62, 64]. In this context, substantial efforts have been made to improve both the clinical trial environment and regulatory process in Japan to shorten the drug lag (the delay in bringing a drug to market, which can have serious consequences for patients). However, a wide variety of factors can result in limited access to new drugs. Therefore, it is necessary to solve issues comprehensively and view them from a holistic perspective.

Figure 5 shows the issues involved in improving access to new drugs in Japan. The challenges for improving access to new drugs can be broadly divided into two categories: "Encourage pharmaceutical innovation" and "Shorten drug lag".

To solve the drug lag problem - any delay in making a pharmaceutical medicine available in a particular market for the patient - it is necessary to initiate clinical trials in Japan without delay in the rest of the world and to improve the approval review process in two ways: "Shorten development lag" and "Shorten approval lag". Regarding the former, the timing of the start of clinical trials seems to be strongly related to the characteristics and structure of the Japanese pharmaceutical market. Regarding the latter, measures such as promoting global clinical trials and improving both the clinical trial environment and the performance of the review system have been intensively implemented in Japan.

If R&D activities have economic rationality, meaning that the resources required will be sufficiently recovered by the launch of new drugs on the Japanese market, then these should be prioritized by pharmaceutical companies. In other words, improving the clinical trial environment and shortening the drug lag should motivate pharmaceutical companies to develop new drugs in Japan.

Furthermore, the characteristics and structure of the Japanese pharmaceutical market are associated with the expected profits that pharmaceutical companies can obtain from launching new drugs in Japan. If the expected profits sufficiently exceed the cost of new drug development, then R&D may be a priority in Japan. In addition, the characteristics and structure of the Japanese pharmaceutical market are considered to be a factor in determining the number of new drug launches. To increase the number of new Japanese drugs being launched in the Japanese market, the number of products developed in Japan needs to be increased. One effective method to accomplish this is the development of new Japan-origin drugs by Japanese and global pharmaceutical companies. In this context, "Encourage pharmaceutical innovation" is divided into the following three categories: "Increase R&D activities in Japan by global companies"; "Increase R&D activities in Japan by Japanese companies"; and "Increase R&D activities outside of Japan by Japanese companies". To solve these issues, it is important to have an attractive market for the launch of new drugs in Japan to recover R&D investments. Therefore, the three categories mentioned above are combined into "Create a dynamic market structure".

A typical characteristic of the Japanese market is the suppression of growth in the new drug market due to a constant decline through regular drug price revisions. The current pricing system may make it more difficult for pharmaceutical companies to recover their R&D investments in a timely manner. Therefore, a market structure that enables the early recovery of R&D investments is needed; to achieve this, steps such as "Improve R&D incentives for innovative drugs through the Japanese drug pricing system" and "Suppress rising drug costs through the Japanese drug pricing system" must be taken.

This article, therefore, focuses on the relationship between new drug access and market factors to gain a better understanding of the current status of new drug access and the characteristics and structure of the Japanese pharmaceutical market by reviewing and comparing the perspectives of the Japanese pharmaceutical industry and those of other countries. To improve

the productivity of the pharmaceutical industry in Japan, the complexities of the Japanese pharmaceutical market, including the associated limitations and challenges, need to be clarified.

3. Results

3.1. Drug Lag

Drug lag consists of two types of lag. The first is development lag, which is the time required for clinical development, and the second is approval lag, the time required from submission of a new drug application to approval by each country. Table 2 shows a summary of drug lag for new molecular entities (NMEs) in Japan [80]. Overall, drug lag has been shortened, and now stands at less than one year.

However, the probability remains extremely low in regard to the technical success of clinical development of experimental drugs being investigated, being reported as 15.3 percent for the use of drugs for treating a particular disease in all therapeutic areas from Phase 1 to approval [32]; for oncologic agents, a lower success rate has been reported compared with other therapeutic areas from Phase 1 to approval (3.4 percent [119] and 13.4 percent, respectively [17]). Indeed, the rate of failure of clinical development in oncology has been reported as 32 percent, which is the highest among all therapeutic areas [28]. The Japanese health authorities, the MHLW and the Pharmaceuticals and Medical Devices Agency (PMDA) have implemented countermeasures to reduce the drug lag in Japan. Detailed discussions on each lag are presented in the next sections.

3.1.1. Development Lag

Development lag has been minimized by the PMDA and the pharmaceutical industry. The PMDA has issued various types of guidance to promote global clinical development in Japan, including guidance related to global clinical trials [77, 78] and first-in-human clinical trials [79]. As a result, the number of global clinical trials being conducted increased between 2008 and 2017 [49].

From the industrial perspective, pharmaceutical companies have been implementing effective clinical development strategies globally by utilizing the above guidance issued by the PMDA. Pharmaceutical companies are strategically utilizing Asian global clinical trials [7, 103] and bridging strategies [47], aided by Japan's participation in global clinical trials [85, 115, 104]. As a result, several reports have indicated that the drug lag for anticancer drugs has decreased in Japan, given that the clinical development of oncologic agents, including those for cancer immunotherapy, has been expanded [96, 55, 121].

To summarize, the development lag in Japan has been reduced because the delay in the initiation of clinical development, which is considered a cause of the delay in the drug lag in Japan, has been mitigated by the PMDA and pharmaceutical companies. However, not all of the drug lag-related problems have been resolved. Indeed, a drug lag still exists in Japan, specifically for rare cancers [122]. Moreover, the R&D efficiency of the Japanese pharmaceutical industry has not improved, despite increases in R&D expenditures [31], and efficient pharmaceutical behaviors to maximize profits worldwide have resulted in delays in the launching of new drugs in Japan [34], suggesting that Japanese pharmaceutical companies should review their management of R&D activities not only to diminish drug lag, but also to promote the Japanese pharmaceutical industry itself with the purpose of developing innovative drugs that can win in the global market.

3.1.2. Approval Lag

Approval lag has been tackled solely by the PMDA. To minimize approval lag, the PMDA has reinforced resources so that reviewers can review new drugs quickly [36], and this countermeasure has been reported to be effective in shortening the approval lag [35]. The review time for oncologic agents, which have been shown to have the lowest success rate, has been diminishing [56]. For other therapeutic areas, a downward trend in review time has also been reported [90, 91].

All in all, the countermeasures taken by the PMDA have been effective. Furthermore, the international vision and strategy for the simultaneous development of new drugs issued by the PMDA has increased the number of internationally-minded reviewers [114].

Although this topic still has some debatable points, numerous studies have investigated this matter intensively. In the next sections, the results of a literature review are discussed from the perspective of "Encouragement of Pharmaceutical Innovation" to seek out areas for investigation in future studies.

3.2. Encouragement of Pharmaceutical Innovation

An earlier review of the literature defined "Innovativeness" in drug development [43]. In that article, "counts of new products" was used to define pharmaceutical innovation. A survey of physicians led to the description of "highly efficacious new drug classes that address clinical needs" [42], and another article reported a similar definition using the term "radical innovation" [4]. In the present review, the following definition encompassing all of the above definitions is used for the discussion of "Pharmaceutical Innovation": the number of NMEs that address unmet medical needs.

Japan is known as one of the leading countries for the development of new drugs; it is also known to have an effective clinical information network and to have most new drugs delivered by pharmaceutical companies [45, 58], which suggests that the pharmaceutical industry has a crucial responsibility for delivering innovative drugs in Japan. Recently, 54 percent of biologic NMEs and 24 percent of small-molecule NMEs approved were first-in-class drugs [59], indicating that the biologic NME market has been evolving.

How to increase the number of NMEs that address unmet medical needs in Japan by utilizing the characteristics of the Japanese R&D environment is worth discussing.

3.2.1. R&D Activities by Pharmaceutical Companies

Sustaining a competitive advantage is critical to R&D strategies. Numerous studies have elucidated the characteristics

that confer a competitive advantage for pharmaceutical companies to promote R&D activities, including technological capabilities [1]. Discussions to improve technological capabilities are categorized mainly into two topics: strategic alliances and mergers and acquisitions (M&A).

Strategic alliances are an essential tool for gaining a competitive advantage through resource concentration [2]. In building strategic alliances, partners are likely to be novel ones that focus on new portfolio resources as organizational slack (defined as the excess capacity maintained by an organization), increases [41], partner selections are conducted together with rival pharmaceutical companies [87], and asset accumulation is strengthened as a result of rapid technological changes in the industry [112, 54, 11]. Therefore, strategic alliances are a key behavior for the pharmaceutical industry to stimulate their R&D activities.

The past decades have seen a lot of M&A cases in the pharmaceutical industry; for instance, Takeda's recent acquisition of Shire. In addition, many small M&A cases have occurred because M&A is known to be an effective method to increase R&D activities in pharmaceutical companies [84, 21]. M&A may also lead companies to become multinational. The relationship between multinationalism and performance has been shown to fit an S-shaped curve in a sample of Japanese companies [53], which is not the case with companies in the United States [81]. Although the relationship between multinationalism and performance has regional differences, M&A advantages such as an increase in R&D performance have been confirmed in Japanese pharmaceutical companies [76], suggesting that M&A is central to encourage R&D activities.

To summarize, numerous articles discuss the "system" and "its modes of action", such as strategic alliances, M&A, and the effects they will have on companies or an industry in terms of how to promote R&D activities. These are considered to be effective measures to increase R&D activities, given characteristics of the pharmaceutical industry such as the importance of nonmarket strategies with regulatory bodies [8] and the informal collaboration structure within the industry [27], drastic changes in the drug discovery approach, from "Target-based (Target selectivity)" to "Functional-based (Biological effect)" [88], and the emergence of the biotech sector [113]. However, detailed discussions are critically lacking. To the best of our knowledge, no comprehensive, empirical, or concrete discussions have been reported on the optimal therapeutic areas for the pharmaceutical industry to promote. Also, discussions in the context of the pharmaceutical industry, an industry that includes different environments in other countries, such as strict drug pricing policies, have also been limited in Japan. Therefore, research to clarify the best direction specifically for the Japanese pharmaceutical industry remains warranted.

3.2.2. Effects of Price Control Strategies on Pharmaceutical R&D

This section reviews the issue of drug pricing policy in Japan and emphasizes the need to reconstruct its drug pricing system. Factors that influence drug pricing, policies and methods to reduce the rising costs of drugs while maintaining the sustainability of universal health insurance, and the promotion of innovation, which are the basic principles of drug pricing policy in Japan, are reviewed [65].To ensure the soundness of health insurance financing, it is important to balance unnecessary financial burdens on patients and increase drug pricing incentives to promote R&D among pharmaceutical companies. Several articles have discussed reforms needed in the Japanese drug pricing system [71, 6, 74, 5].

A multitude of factors are known to drive Japan to spend more on pharmaceuticals. Major influencers of increased spending include pricing for brand name medications [38] and the low penetration rates of generic medications [72]. As described earlier, price cuts have been conducted regularly in Japan. This price cut policy has been reported as an effective measure to control the rapid growth of medication expenditures. For instance, two reports clarified the effectiveness of this policy in the Chinese market, focusing on oncologic agents available in China [26] through a comparison with other countries in the Asia-Pacific region [13]. The regulation of drug prices in the Taiwanese market has also been reported to have a positive impact on medication expenditures [51]. Recently, a critical review reported finding little evidence of positive effects of government drug price control policies in promoting R&D [75]. Indeed, government drug price control policies delay generic drug adoption in the market [14], and this launch delay has also been shown to occur for new drugs [23, 22, 50], which decreases investment in the pharmaceutical industry [46] by affecting profitability [120]. In summary, under the drug pricing system, there are points to be considered regarding R&D policies for both new and generic drugs. Higher drug prices for innovative products are known to have positive effects on R&D activities [86]. A nonlinear relationship between sales and R&D intensity was reported based on an analysis of European companies [18]. In this context, the price maintenance premium in Japan was reported to be an effective way to promote R&D, with the premium rates of this system being approximately 10 percent of those under a comparative method [116], as described in Section 1.2, and accelerating the development of new drugs that can meet high medical needs, such as oncologic and neurological agents [116, 94, 95, 117].

Another policy that helps control drug costs is reference pricing. Many countries have adopted it as a reimbursement system for pharmaceuticals. This policy consists of clustering drugs and defining a reference price for each cluster. Drugs can be clustered according to 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 a certain drug at a price that is lower or equal to the reference price of that cluster, then they are reimbursed up to the reference price value. If the purchased drug is priced higher than the reference price, the patients pay the difference between the reference price value and the actual drug price. This system has two known challenges [25]. First, if there is no reference drug on the market, other costly procedures will be adopted, which will have negative effects in terms of increased health care expenditures. Second, if there is no innovation in the pharmaceutical and the existing drugs are old, the drug price will be calculated as an

inexpensive, fixed price, which will reduce the profits of pharmaceutical companies. Looking at the evidence from the first perspective, an article focusing on the French market reported that the magnitude of the decrease in healthcare expenditures might depend heavily on the degree of cost-reducing innovations [9]. Reference pricing policies have been reported to lead to increases in healthcare expenditures [68]. Looking at the evidence from the second perspective, due to fixed prices, modeling and simulations have shown that the reference price system has the potential to discourage R&D activities [12]. The reference price was reported to be a function of R&D incentives depending on the competitive situation in the market, suggesting that the reference price does not always produce competitive situations where R&D activities are stimulated [20]. Similar discussions in reference to the Germany reference pricing system have focused on the effects of the reference price on the Japanese market [105]; the reference price system does not always lower pharmaceutical companies' profits, which suggests that it does not always lower R&D incentives. Pharmaceutical companies would be able to focus their R&D in order to obtain higher prices. Recently, a literature review reported that uncertainties remain in the association between reference pricing policies and R&D investments based on the evidence obtained so far, indicating the strong need for further evidence [118].

Altogether, drug prices and pharmaceutical company profits are known to have positive impacts on the R&D of new drugs, and the drug pricing policy plays a central role. The setting of high drug prices, such as the price maintenance premium in Japan, is considered to encourage R&D (Figure 3). However, further research regarding the reference pricing system is warranted.

Previous studies have reported that the market prices of medical products in Japan are higher than those in other developed countries such as the United States [37, 15, 10, 83], suggesting that the competitive environment is well organized in Japan, and thus likely to stimulate new drug R&D in the Japanese market [82]. In addition, the hurdle to new drugs in Japan was reported to be low compared with European countries, with an average of 66 days between marketing authorization and reimbursement, which is automatically deducted from the price charged at the pharmacy [108]. Notably, transparency in the Japanese drug pricing system has been ensured through an investigation of the mechanisms for granting premium rewards under the comparative method [109]. Regarding the cost calculation method, a previous report clarified that this would be applied mostly to oncologic agents when setting higher drug prices, which could be expected to lead to higher sales for pharmaceutical companies [40, 70]. However, not only high-priced, but also reasonably-priced drugs are widely prescribed by Japanese physicians, and this is expected to mitigate the increasing health care expenditures in Japan [69]. If the current regulatory environment continues, the promotion of the Japanese pharmaceutical industry can be easily achieved.

However, some remaining topics must be discussed. One such topic is re-pricing following market expansion (Figure 4). This system contradicts the price maintenance premium (Figure 3), as it denies pharmaceutical companies the recovery of R&D costs by reducing the prices of drugs of interest, including similar drugs [93]. Another topic is predictability. Previous research has stressed that a lack of predictability in drug pricing policy makes it difficult for pharmaceutical companies to devise R&D strategies, resulting in a drug lag [73, 98]. In other words, if predictability in drug pricing policy exists, R&D incentives can be achieved without raising drug prices. There are three types of predictability in drug pricing policy in Japan: predictability for rules (transparency), predictability for drug prices, and predictability for sales. The latter two are topics for discussion, since the transparency of rules is well assured in Japan, as described earlier. Pharmaceutical companies tend to value price predictability, since this affects their profits. However, considering the overall impact on the health insurance system, the government considers that not only drug prices, but also sales, are important. As a result, drug prices are reduced if sales increase significantly higher than expected, for instance, because of the expansion of indications. In the future, if sales deviate significantly from forecasts, and some cases exist where the current rules cannot be followed, the government may set new rules to deal with the situation. Therefore, it is important that the government and the pharmaceutical industry share the predictability of sales, rather than the predictability of drug prices. In this context, it is critically important to generate evidence that forms the basis of the discussion from the perspectives of both sales and drug prices. Indeed, two quantitative reports have focused on the predictability of drug prices by evaluating premium rates in Japan, investigating the contributing factors that affect the gap between the actual market price and reimbursement price, and stressing the importance of the predictability of the drug pricing system [106, 107]. These two papers provided another important insight into the drug pricing policy in Japan, in that it is increasingly important to have a drug pricing system that properly reflects increases in a drug's clinical value. One of the methodologies to be considered for this is health technology assessment (HTA). The process of HTA has been intensively discussed to establish an optimal process in Japan [29, 30, 52, 19, 44, 48]. In the future, in addition to HTA, it will be important to analyze the process of negotiations between pharmaceutical companies and the government to consider appropriate systems that can manage incentives for pharmaceutical companies.

3.2.3. Japanese Pharmaceutical Market

Although the perspectives are limited, some articles have focused on the Japanese pharmaceutical market. In this section we discuss selected articles related to the promotion of the Japanese pharmaceutical industry.

Several reports have assessed the Japanese pharmaceutical market with a sample of the top-selling 100 drugs [92, 89, 111]. These studies discussed the unique Japanese topline market, where drugs for lifestyle-related diseases such as hypertension ranked in the top class on the market, whereas drugs that meet urgent medical needs, such as those for cancers or neurological diseases, did not, which has been a continuous trend since 1995 [97]. Despite some recent reports clarifying the upward trend of prescription volumes and R&D of drugs for cancers or

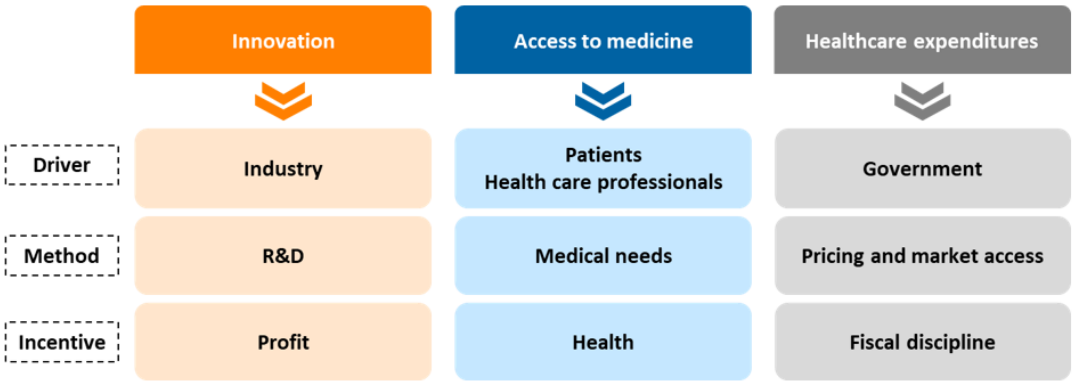


Figure 6: Three aspects determining the direction of the Japanese pharmaceutical industry

neurological diseases [102, 99, 100, 101], in the context of "innovativeness" and the pharmaceutical industry vision issued by the MHLW (Table 1), the Japanese market has not been following the right path. However, as expected returns are one of the most important decision factors in R&D investments [24, 57], and R&D strategies strongly depend on a company's business strategy, which can delay new drug applications, especially in Japan, from the entire optimization perspective, not prioritizing the Japanese market [33, 110], the international harmonization of the Japanese pharmaceutical market with trends in the global market is not a preferable strategy for the Japanese pharmaceutical industry. Nevertheless, innovation and global engagement are known to be key factors for the sustainable growth of the industry [39]; this is still the case with the Japanese pharmaceutical industry. Therefore, future studies are strongly warranted to clarify the overall business strategies from the variety of perspectives discussed in this review, so that Japanese pharmaceutical companies can make decisions regarding business strategies, including R&D strategies, that fulfill their social responsibilities for what patients need most.

4. Discussion and Conclusion

4.1. Summary of Current Perspectives

Regarding drug lag, although this topic still has some debatable points, several studies intensively addressed this matter and found that the measures taken by the PMDA and pharmaceutical companies have been contributing to more efficient clinical development in Japan.

Regarding R&D activities by pharmaceutical companies, many articles discussed the "system" and "its modes of actions", such as strategic alliances, M&A, and their effects on companies or industry regarding how to promote R&D activities. These are considered to be effective measures to increase R&D activities in view of the characteristics of the pharmaceutical industry. However, more detailed discussions are lacking. To the best of our knowledge, no comprehensive, empirical, or concrete discussions on the optimal therapeutic area to be promoted by the pharmaceutical industry have been presented. In addition, discussions have also been limited in the context of the Japanese pharmaceutical industry, including different environments in other countries and strict drug pricing policies.

Regarding the effects of price control strategies on pharmaceutical R&D, various studies reported a positive correlation between drug prices and R&D activities. For the Japanese market in particular, three types of predictability in terms of drug pricing policy must be considered: predictability for rules (transparency), predictability for drug prices, and predictability for profits. Since transparency of rules is well assured in Japan, the latter two are the main discussion points. Pharmaceutical companies tend to value price predictability, since this affects their profits. However, considering the overall impact on the health insurance system, the government considers not only drug prices but also sales. Therefore, it is important that the government and the pharmaceutical industry share information on the predictability of sales, rather than the predictability of drug prices.

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

Issues regarding the promotion of the Japanese pharmaceutical industry are complex. Finding solutions to these issues requires that all parties, including the pharmaceutical industry, the government, patients, and health care professionals, play key roles in each category and interact with each other (Figure 6).

The Japanese health care system needs to have a pricing scheme that balances medication accessibility with the cost of developing new medications. The pharmaceutical industry, government, patients, and health care professionals can use a variety of strategies to combat negative views surrounding drug pricing, and work with policy makers and others to fix some of the current issues. In this context, the following three topics that lack sufficient attention need to be studied: the predictability of sales, the predictability of drug prices, and the definition of innovativeness in the Japanese market (Figure 7). Additionally, directions to promote the Japanese pharmaceutical industry have to be discussed based on the multitude of factors covered in this review.

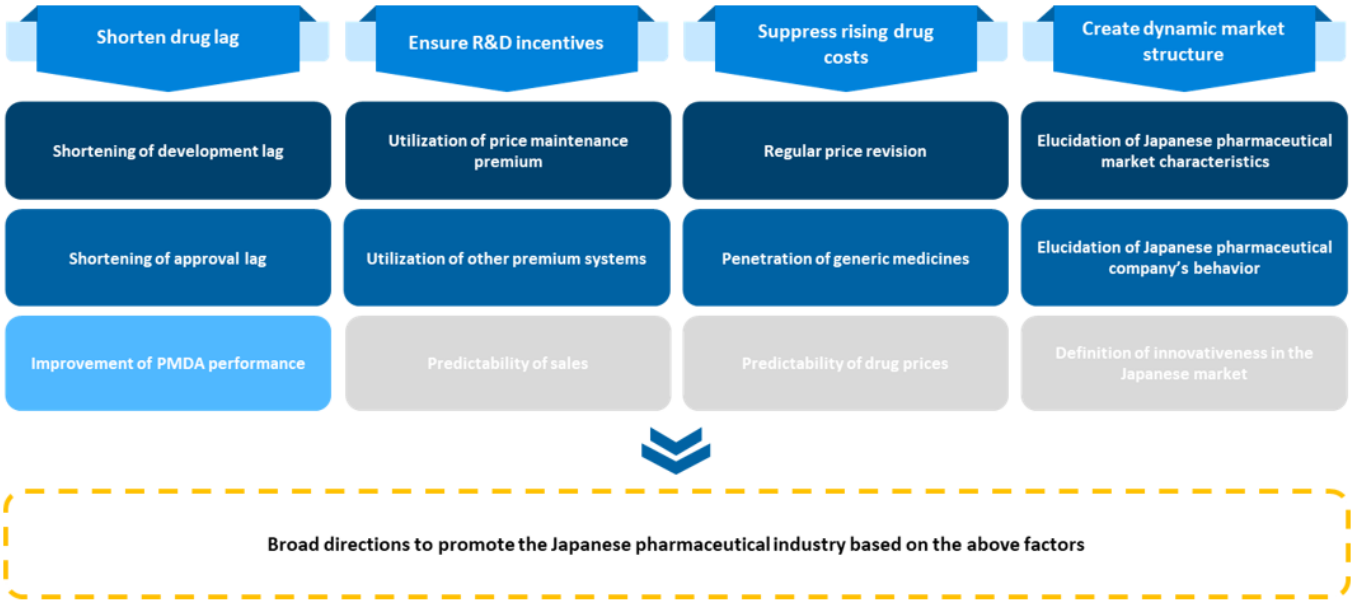


Figure 7: Directions for future studies

5. Declaration of Conflicting Interest

Shoyo Shibata is an employee of Chugai Pharmaceutical Co., Ltd. However, his affiliation with the company did not influence the results or discussion in this paper. This work was supported in part by Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science and Keio Gakuji Academic Development Funds (TS).

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7. References

[1] Afuah, A. (2002). Mapping technological capabilities into product markets and competitive advantage: the case of cholesterol drugs. *Strategic Management Journal, 23*(2), 171-179. doi: 10.1002/smj.221

[2] Aggarwal, V. A. (2019). Resource congestion in alliance networks: How a firm's partners' partners influence the benefits of collaboration. *Strategic Management Journal, 41*(4), 627-655. doi: 10.1002/smj.3109

[3] Aitken, M., Kleinrock, M., Simorellis, A., & Nass, D. (2019). *The Global Use of Medicine in 2019 and Outlook to 2023: Forecasts and Areas to Watch*. IQVIA Institute.

[4] Alt, S., & Helmstädter, A. (2018). Market entry, power, pharmacokinetics: what makes a successful drug innovation? *Drug Discovery Today, 23*(2), 208-212. doi: 10.1016/j.drudis.2017.09.009

[5] Aoi, M., & Nakamura, H. (2003). Changes in external environments in the U.S. drug market and the impacts on R&D oriented pharmaceutical companies: implications for the Japanese system and R&D oriented pharmaceutical companies (in Japanese). *Iryo To Shakai, 13*(2), 85-111.

[6] Asakawa, K., & Nakamura, H. (2005). Co-evolution of innovation systems in Japan's pharmaceutical and biotechnology industries (in Japanese). *Iryo To Shakai, 15*(1), 1-15.

[7] Asano, K., Uyama, Y., & Tohkin, M. (2018). Factors Affecting Drug-Development Strategies in Asian Global Clinical Trials for Drug Approval in Japan. *Clinical and Translational Science, 11*(2), 182-188. doi: 10.1111/cts.12520

[8] Barber, B., IV., & Diestre, L. (2019). Pushing for speed or scope? Pharmaceutical lobbying and Food and Drug Administration drug review. *Strategic Management Journal, 40*(8), 1194-1218. doi: 10.1002/smj.3021

[9] Bardey, D., Bommier, A., & Jullien, B. (2010). Retail price regulation and innovation: Reference pricing in the pharmaceutical industry. *Journal of Health Economics, 29*(2), 303-316. doi: 10.1016/j.jhealeco.2009.11.015

[10] Berndt, E. R. (2000). International comparisons of pharmaceutical prices: what do we know, and what does it mean? *Journal of Health Economics, 19*(2), 283-287. doi: 10.1016/s0167-6296(99)00043-0

[11] Bierly, P., & Chakrabarti, A. (1996). Generic knowledge strategies in the U.S. pharmaceutical industry. *Strategic Management Journal, 17*(S2), 123-135. doi: 10.1002/smj.4250171111

[12] Brekke, K. R., Königbauer, I., & Straume, O. R. (2007). Reference pricing of pharmaceuticals. *Journal of Health Economics, 26*(3), 613-642. doi: 10.1016/j.jhealeco.2006.11.003

[13] Chen, Y., & Schweitzer, S. O. (2008). Issues in drug pricing, reimbursement, and access in China with references to other Asia-Pacific region. *Value in Health, 11*(Suppl 1), S124-S129. doi: 10.1111/j.1524-4733.2008.00376.x

[14] Costa-Font, J., McGuire, A., & Varol, N. (2014). Price regulation and relative delays in generic drug adoption. *Journal of Health Economics, 38*, 1-9. doi: 10.1016/j.jhealeco.2014.04.004

[15] Danzon, P. M., & Chao, L. W. (2000). Cross-national price differences for pharmaceuticals: how large, and why? *Journal of Health Economics, 19*(2), 159-195. doi: 10.1016/s0167-6296(99)00039-9

[16] Danzon, P. M., Wang, Y. R., & Wang, L. (2005). The impact of price regulation on the launch delay of new drugs – evidence from twenty-five major markets in the 1990s. *Health Economics, 14*(3), 269-292. doi: 10.1002/hec.931

[17] DiMasi, J. A., Reichert, J. M., Feldman, L., & Malins, A. (2013). Clinical approval success rates for investigational cancer drugs. *Clinical Pharmacology & Therapeutics, 94*(3), 329-335. doi: 10.1038/clpt.2013.117

[18] Eger, S., & Mahlich, J. C. (2014). Pharmaceutical regulation in Europe and its impact on corporate R&D. *Health Economics Review, 4*(1), 23. doi: 10.1186/s13561-014-0023-5

[19] Fukuda, T., & Shiroiwa, T. (2019). Application of economic evaluation of pharmaceuticals and medical devices in Japan. *Journal of the National Institute of Public Health, 68*(1), 27-33.

[20] Ghislandi, S. (2011). Competition and the reference pricing scheme for pharmaceuticals. *Journal of Health Economics, 30*(6), 1137-1149. doi: 10.1016/j.jhealeco.2011.08.010

[21] Goldsmith, A. D., & Varela, F. E. (2017). Fragmentation in the bio-

pharmaceutical industry. *Drug Discovery Today, 22*(2), 433-439. doi: 10.1016/j.drudis.2016.10.013

[22] Golec, J., & Vernon, J. A. (2010). Financial effects of pharmaceutical price regulation on R&D spending by EU versus US firms. *Pharmacoeconomics, 28*(8), 615-628. doi: 10.2165/11535580-000000000-00000

[23] Golec, J., Hegde, S., & Vernon, J. A. (2010). Pharmaceutical R&D Spending and Threats of Price Regulation. *Journal of Financial and Quantitative Analysis, 45*(1), 239-264. doi: 10.1017/S0022109009990512

[24] Grabowski, H., & Vernon, J. (2000). The determinants of pharmaceutical research and development expenditures. *Journal of Evolutionary Economics, 10*(1), 201-215.

[25] Gregson, N., Sparrowhawk, K., Mauskopf, J., & Paul, J. (2005). Pricing medicines: theory and practice, challenges and opportunities. *Nature Reviews Drug Discovery, 4*(2), 121-130. doi: 10.1038/nrd1633

[26] Guan, X., Wushouer, H., Yang, M., Han, S., Shi, L., Ross-Degnan, D., & Wagner, A. K. (2019). Influence of government price regulation and deregulation on the price of antineoplastic medications in China: a controlled interrupted time series study. *BMJ Open, 9*(11), e031658. doi: 10.1136/bmjopen-2019-031658

[27] Guler, I., & Nerkar, A. (2012). The impact of global and local cohesion on innovation in the pharmaceutical industry. *Strategic Management Journal, 33*(5), 535-549. doi: 10.1002/smj.957

[28] Harrison, R. K. (2016). Phase II and phase III failures: 2013-2015. *Nature Reviews Drug Discovery, 15*, 817-818. doi: 10.1038/nrd.2016.184

[29] Hasegawa, M. (2020). HTA system implemented in Japan. *PharmacoEconomics & Outcomes News, 846*, 15. doi: 10.1007/s40274-020-6554-6

[30] Hasegawa, M., Komoto, S., Shiroiwa, T., & Fukuda, T. (2020). Formal Implementation of Cost-Effectiveness Evaluations in Japan: A Unique Health Technology Assessment System. *Value in Health, 23*(1), 43-51. doi: 10.1016/j.jval.2019.10.005

[31] Hashimoto, A., & Haneda, S. (2008). Measuring the change in R&D efficiency of the Japanese pharmaceutical industry. *Research Policy, 37*(10), 1829-1836. doi: 10.1016/j.respol.2008.08.004

[32] Hay, M., Thomas, D. W., Craighead, J. L., Economides, C., & Rosenthal, J. (2014). Clinical development success rates for investigational drugs. *Nature Biotechnology, 32*(1), 40-51. doi: 10.1038/nbt.2786

[33] Hirai, Y., Kinoshita, H., Kusama, M., Yasuda, K., Sugiyama, Y., & Ono, S. (2010). Delays in New Drug Applications in Japan and Industrial R&D Strategies. *Clinical Pharmacology & Therapeutics, 87*(2), 212-218. doi: 10.1038/clpt.2009.215

[34] Hirai, Y., Yamanaka, Y., Kusama, M., Ishibashi, T., Sugiyama, Y., & Ono, S. (2012). Analysis of the success rates of new drug development in Japan and the lag behind the U.S. *Health Policy, 104*(3), 241-246. doi: 10.1016/j.healthpol.2011.11.008

[35] Honig, P. K. (2014). Recent trends and success factors in reducing the lag time to approval of new drugs in Japan. *Clinical Pharmacology & Therapeutics, 95*(5), 467-469. doi: 10.1038/clpt.2013.256

[36] Ichimaru, K., Toyoshima, S., & Uyama, Y. (2010). PMDA's Challenge to Accelerate Clinical Development and Review of New Drugs in Japan. *Clinical Pharmacology & Therapeutics, 88*(4), 454-457. doi: 10.1038/clpt.2010.190

[37] Ide, H., Yasunaga, H., Imamura, T., & Ohe, K. (2007). Price differences between Japan and the U.S. for medical materials and how to reduce them. *Health Policy, 82*(1), 71-77. doi: 10.1016/j.healthpol.2006.08.003

[38] Ikegami, N., Ikeda, S., & Kawai, H. (1998). Why Medical Care Costs in Japan Have Increased Despite Declining Prices for Pharmaceuticals. *PharmacoEconomics, 14*(Suppl 1), 97-105. doi: 10.2165/00019053-199814001-00012

[39] Ito, K., & Lechevalier, S. (2010). Why some firms persistently outperform others: investigating the interactions between innovation and exporting strategies. *Industrial and Corporate Change, 19*(6), 1997-2039. doi: 10.1093/icc/dtq056

[40] Kato, Y., Matsui, T., Hane, Y., Abe, J., Ueda, N., Sasaoka, S., Motooka, Y., Hatahira, H., Umetsu, R., & Nakamura, M. (2016). *Analysis of new drug price calculation according to National Health Insurance (NHI) drug price list in Japan* (in Japanese). *Regulatory Science of Medical Products, 6*(2), 171-183.

[41] Kavusan, K., & Frankort, H. T. W. (2019). A behavioral theory of alliance portfolio reconfiguration: Evidence from pharmaceutical biotechnology. *Strategic Management Journal, 40*(10), 1668-1702. doi: 10.1002/smj.3041

[42] Kesselheim, A. S., & Avorn, J. (2013). The most transformative drugs of the past 25 years: a survey of physicians. *Nature Reviews Drug Discovery, 12*(6), 425-431. doi: 10.1038/nrd3977

[43] Kesselheim, A. S., Wang, B., & Avorn, J. (2013). Defining "Innovativeness" in Drug Development: A Systematic Review. *Clinical Pharmacology & Therapeutics, 94*(3), 336-348. doi: 10.1038/clpt.2013.115

[44] Kido, K., Matsumaru, N., & Tsukamoto, K. (2019). Health Technology Assessment in Japan: A Pharmaceutical Industry Perspective. *Therapeutic Innovation & Regulatory Science, 53*(4), 472-480. doi: 10.1177/2168479018791136

[45] Kneller, R. (2010). The importance of new companies for drug discovery: origins of a decade of new drugs. *Nature Reviews Drug Discovery, 9*(11), 867-882. doi: 10.1038/nrd3251

[46] Koenig, P., & MacGarvie, M. (2011). Regulatory policy and the location of bio-pharmaceutical foreign direct investment in Europe. *Journal of Health Economics, 30*(5), 950-965. doi: 10.1016/j.jhealeco.2011.07.005

[47] Kogure, S., Koyama, N., & Hidaka, S. (2017). Utilization of the Bridging Strategy for the Development of New Drugs in Oncology to Avoid Drug Lag. *Journal of Clinical Pharmacology, 57*(11), 1479-1490. doi: 10.1002/jcph.951

[48] Kogushi, K., Ogawa, T., & Ikeda, S. (2019). An impact analysis of the implementation of health technology assessment for new treatment of orphan diseases in Japan. *Expert Review of Pharmacoeconomics & Outcomes Research*. doi: 10.1080/14737167.2019.1665513

[49] Kondo, H., Shimada, Y., & Ozawa, T. (2019). Promotion of Japan's participation in global clinical trials. *Drug Discovery Today, 24*(4), 939-942. doi: 10.1016/j.drudis.2019.01.016

[50] Kyle, M. K. (2007). Pharmaceutical Price Controls and Entry Strategies. *The Review of Economics and Statistics, 89*(1), 88-99.

[51] Liu, Y-M., Yang, Y-H. K., & Hsieh, C-R. (2012). Regulation and competition in the Taiwanese pharmaceutical market under national health insurance. *Journal of Health Economics, 31*(3), 471-483. doi: 10.1016/j.jhealeco.2012.03.003

[52] Liu, G., Wu, E. Q., Ahn, J., Kamae, I., Xie, J., & Yang, H. (2020). The Development of Health Technology Assessment in Asia: Current Status and Future Trends. *Value in Health Regional Issues, 21*, 39-44. doi: 10.1016/j.vhri.2019.08.472

[53] Lu, J. W., & Beamish, P. W. (2004). International Diversification and Firm Performance: The S-curve Hypothesis. *Academy of Management Journal, 47*(4), 598-609. doi: 10.5465/20159604

[54] Macher, J. T., & Boerner, C. (2012). Technological development at the boundaries of the firm: a knowledge-based examination in drug development. *Strategic Management Journal, 33*(9), 1016-1036. doi: 10.1002/smj.1956

[55] Maeda, H., & Kurokawa, T. (2015a). Recent trends for drug lag in clinical development of oncology drugs in Japan: does the oncology drug lag still exist in Japan? *International Journal of Clinical Oncology, 20*(6), 1072-1080. doi: 10.1007/s10147-015-0825-4

[56] Maeda, H., & Kurokawa, T. (2015b). Regulatory review time for approval of oncology drugs in Japan between 2001 and 2014. Considerations of changes, factors that affect review time, and difference with the United States. *The Journal of Clinical Pharmacology, 55*(5), 481-489. doi: 10.1002/jcph.458

[57] Mahlich, J. C., & Roediger-Schluga, T. (2006). The Determinants of Pharmaceutical R&D Expenditures: Evidence from Japan. *Review of Industrial Organization, 28*(2), 145-164. doi: 10.1007/s11151-006-0010-z

[58] Matsushita, S., Tachibana, K., & Kondoh, M. (2019). The Clinical Innovation Network: a policy for promoting development of drugs and medical devices in Japan. *Drug Discovery Today, 24*(1), 4-8. doi: 10.1016/j.drudis.2018.05.026

[59] Miller, K., L., & Lanthier, M. (2015). Regulatory watch: Innovation in biologic new molecular entities: 1986–2014. *Nature Reviews Drug Discovery, 14*(2), 83. doi: 10.1038/nrd4535

[60] Ministry of Health, Labour and Welfare. (2002). *Pharmaceutical Industry Vision* (in Japanese). Retrieved from https://www.mhlw.go.jp/shingi/2002/08/dl/s0830-1c.pdf

[61] Ministry of Health, Labour and Welfare. (2007a). *Action Program for Promotion of the Safe Use of Generic Drugs* (in Japanese). Retrieved from https://www.mhlw.go.jp/houdou/2007/10/dl/h1015-1a.pdf

[62] Ministry of Health, Labour and Welfare. (2007b). *New Phar-*

maceutical Industry Vision (in Japanese). Retrieved from https://www.mhlw.go.jp/houdou/2007/08/dl/h0830-1b.pdf

[63] Ministry of Health, Labour and Welfare. (2012). *Promotion of the Use of Generic Drugs* (in Japanese). Retrieved from https://www.mhlw.go.jp/english/policy_report/

[64] Ministry of Health, Labour and Welfare. (2013). *Pharmaceutical Industry Vision 2013* (in Japanese). Retrieved from https://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/iryou/shinkou/dl/vision_2013a.pdf

[65] Ministry of Health, Labour and Welfare. (2016a). *Basic Policy for Fundamental Reform of the Drug Pricing System* (in Japanese). Retrieved from https://www.mhlw.go.jp/file/05-Shingikai-12404000-Hokenkyoku-Iryouka/0000146567.pdf

[66] Ministry of Health, Labour and Welfare. (2016b). *Central Social Insurance Medical Council* (in Japanese). Retrieved from https://www.mhlw.go.jp/stf/shingi2/0000142573.html

[67] Ministry of Health, Labour and Welfare. (2018). *Update of Drug Pricing System in Japan* [Presentation]. Retrieved from https://www.mhlw.go.jp/content/11123000/000335166.pdf

[68] Miraldo, M. (2009). Reference pricing and firms' pricing strategies. *Journal of Health Economics, 28*(1), 176-197.

[69] Morioka, K., Takayama, A., & Narukawa, M. (2017). Investigation of Characteristics of Long-Selling Drugs in Japan. *Regulatory Science of Medical Products, 7*(3), 151-162. doi: 10.14982/rsmp.7.151

[70] Nakajima, R., & Aruga, A. (2017). Analysis of New Drug Pricing and Reimbursement for Antibody Agents for Cancer Treatment in Japan. *Regulatory Science of Medical Products, 7*(3), 173-184. doi: 10.14982/RSMP.7.173

[71] Nakamura, H. (2005). Toward construction of Japan's new drug pricing system: aiming at financially improving Japan's national health insurance system and at stimulating R&D activities of innovative drugs in Japan (in Japanese). *Iryo To Shakai, 15*(1), 97-109.

[72] Nakamura, H. (2007). Perspectives on structural changes in the pharmaceutical industry and new types of M&A and alliance: from the viewpoint of consistency between structural changes and the existing business model (in Japanese). *Iryo To Shakai, 17*(1), 39-53.

[73] Nakamura, H., & Wakutsu N. (2019). Reducing pharmaceutical reimbursement price risk to lower national health expenditures without lowering R&D incentives. *International Journal of Economic Policy Studies, 13*(1), 75-88. doi: 10.1007/s42495-018-0002-7

[74] Nambu, T. (1997). The industrial organization of pharmaceuticals: the consequences of price regulation in Japan (in Japanese). *Iryo To Shakai, 7*(1), 3-15.

[75] Patterson, J. A., & Carroll, N. V. (2020). Should the United States government regulate prescription prices? A critical review. *Research in Social and Administrative Pharmacy, 16*(5), 717-723. doi: 10.1016/j.sapharm.2019.06.010

[76] Penner-Hahn, J., & Shaver, J. M. (2005). Does international research and development increase patent output? An analysis of Japanese pharmaceutical firms. *Strategic Management Journal, 26*(2), 121-140. doi: 10.1002/smj.436

[77] Pharmaceuticals and Medical Devices Agency. (2007). *Basic Principles on Global Clinical Trials*. Retrieved from https://www.pmda.go.jp/files/000153265.pdf

[78] Pharmaceuticals and Medical Devices Agency. (2014a). *Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials*. Retrieved from https://www.pmda.go.jp/files/000157777.pdf

[79] Pharmaceuticals and Medical Devices Agency. (2014b). *Guidance for Establishing Safety in First-in-Human Studies during Drug Development* (in Japanese). Retrieved from https://www.pmda.go.jp/files/000208201.pdf

[80] Pharmaceuticals and Medical Devices Agency. (2018). *Drug Lag Estimation* (in Japanese). Retrieved from https://www.pmda.go.jp/files/000233084.pdf

[81] Pisani, N., Garcia-Bernardo, J., & Heemskerk, E. (2020). Does it pay to be a multinational? A large-sample, cross-national replication assessing the multinationality-performance relationship. *Strategic Management Journal, 41*(1), 152-172. doi: 10.1002/smj.3087

[82] Porter, M. E., & van der Linde, C. (1995). Toward a New Conception of the Environment-Competitiveness Relationship. *Journal of Economic Perspectives, 9*(4), 97-118. doi: 10.1257/jep.9.4.97

[83] Ridley, D. B. (2007). International Price Comparisons for Novel and Follow-on Drugs. *Value in Health, 10*(6), 510-511. doi: 10.1111/j.1524-4733.2007.00238.x

[84] Ringel, M. S., & Choy, M. K. (2017). Do large mergers increase or decrease the productivity of pharmaceutical R&D? *Drug Discovery Today, 22*(12), 1749-1753. doi: 10.1016/j.drudis.2017.06.002

[85] Rokuda, M., Matsumaru, N., & Tsukamoto, K. (2018). Identification of Drug Characteristics for Implementing Multiregional Clinical Trials Including Japan. *Clinical Therapeutics, 40*(2), 284-295. doi: 10.1016/j.clinthera.2017.12.010

[86] Roughead, E. E., Lopert, R., & Sansom, L. N. (2007). Prices for innovative pharmaceutical products that provide health gain: a comparison between Australia and the United States. *Value in Health, 10*(6), 514-520. doi: 10.1111/j.1524-4733.2007.00206.x

[87] Ryu, W., Reuer, J. J., & Brush, T. H. (2020). The effects of multimarket contact on partner selection for technology cooperation. *Strategic Management Journal, 41*(2), 267-289. doi: 10.1002/smj.3106

[88] Sams-Dodd, F. (2007). Research & market strategy: how choice of drug discovery approach can affect market position. *Drug Discovery Today, 12*(7-8), 314-318. doi: 10.1016/j.drudis.2007.02.014

[89] Shibata, S., & Suzuki, T. (2018) The pharmaceutical market and drug development prognosis in Japan: Current and future perspectives according to pharmacological classes. *Journal of Generic Medicines, 14*(2), 70-80. doi: 10.1177/1741134317737344

[90] Shibata, S., Chiba, K., & Suzuki, T. (2017a). Downward trend in review time in Pharmaceuticals and Medical Devices Agency in Japan under the unique premium rewards system of the Japanese pharmaceutical market. *American Journal of Pharmacy and Health Research, 5*(7), 25-36.

[91] Shibata, S., Chiba, K., & Suzuki, T. (2017b). Downward trend in review time in Pharmaceuticals and Medical Devices Agency in Japan under the unique premium rewards system of the Japanese pharmaceutical market: 2nd report. *American Journal of Pharmacy and Health Research, 5*(7), 37-52.

[92] Shibata, S., Uemura, R., & Suzuki T. (2016a). Comparative analysis between the top-selling drugs in the Japanese pharmaceutical market and those in the United States, the United Kingdom, France, and Germany. *Therapeutic Innovation & Regulatory Science, 50*(2), 221-227. doi: 10.1177/2168479015604182

[93] Shibata, S., Uemura, R., & Suzuki, T. (2016b). Evaluating the effectiveness of repricing for market expansion in the Japanese drug pricing system. *Therapeutic Innovation & Regulatory Science, 50*(6), 751-758. doi: 10.1177/2168479016652927

[94] Shibata, S., Uemura, R., & Suzuki, T. (2016c). Factors that affect the acquisition of reward premiums for promotion of innovative drug discovery in Japan. *Therapeutic Innovation & Regulatory Science, 50*(1), 56-65. doi: 10.1177/2168479015596007

[95] Shibata, S., Uemura, R., & Suzuki, T. (2016d). Impact of premium rewards for the promotion of innovative drug discovery on the Japanese pharmaceutical market: An analysis by therapeutic area. *Therapeutic Innovation & Regulatory Science, 50*(1), 49-55. doi: 10.1177/2168479015600205

[96] Shibata, S., Uemura, R., Chiba, K., & Suzuki, T. (2016). A comprehensive analysis of factors that contribute to conditional approval and all-case surveillance designations that subsequently lead to shortening of review times in Japan. *Journal of Regulatory Science, 4*(1), 1-9. doi: 10.21423/jrs-v04n01p001

[97] Shibata, S., Fukumoto, D., Suzuki, T., & Ozaki, K. (2020a). A Comparative Study of the Market Configuration of the Japanese Pharmaceutical Market Using the Gini Coefficient and Herfindahl–Hirschman Index. *Therapeutic Innovation & Regulatory Science, 54*(5), 1047-1055. doi: 10.1007/s43441-020-00122-6

[98] Shibata, S., Fukumoto, D., Suzuki, T., & Ozaki, K. (2020b). Analyzing upward deviation of actual vs predicted drug sales in Japan for a reasonable drug-pricing policy. *Therapeutic Innovation & Regulatory Science, 54*(3), 544-551. doi: 10.1177/2168479019860123

[99] Shibata, S., Kawaguchi, H., Uemura, R., & Suzuki, T. (2016). Emerging growth of orphan drugs for neurological diseases in Japan: potential benefits for both patients and pharmaceutical companies. *Journal of Regulatory Science, 4*(3), 7-13. doi: 10.21423/jrs-v04n03p007

[100] Shibata, S., Matsushita, M., Saito, Y., & Suzuki, T. (2017). Optimal anti-cancer drug profiles for effective penetration of the anti-cancer drug market by generic drugs in Japan. *Therapeutic Innovation & Regulatory*

Science, 52(4), 442-448. doi: 10.1177/2168479017749513

[101] Shibata, S., Matsushita, M., Saito, Y., & Suzuki, T. (2018). Anticancer drug prescription patterns in Japan: future directions in cancer therapy. *Therapeutic Innovation & Regulatory Science, 52*(6), 718-723. doi: 10.1177/2168479017751404

[102] Shibata, S., Wayama, Y., Tsuyuki, A., Matsushita, M., Chiba, K., Matsuki, E., Okamoto, S., & Suzuki, T. (2017). An empirical study of the prescription pattern of drugs for hematological malignancies in Japan from 2010-2014. *Biological and Pharmaceutical Bulletin, 40*(6), 894-901. doi: 10.1248/bpb.b17-00111

[103] Shirotani, M., Kurokawa, T., & Chiba, K. (2014). Comparison of global versus Asian clinical trial strategies supportive of registration of drugs in Japan. *The Journal of Clinical Pharmacology, 54*(7), 753-764. doi: 10.1002/jcph.273

[104] Shirotani, M., Suwa, T., Kurokawa, T., & Chiba, K. (2014). Efficient clinical trials in Japan: bridging studies versus participation in global clinical trials. *The Journal of Clinical Pharmacology, 54*(4), 438-445. doi: 10.1002/jcph.216

[105] Suzuki, M., & Nakamura, H. (1998). German reference price system and the effects on drug prices, prescription volume, and R&D incentives (in Japanese). *Iryo To Shakai, 8*(3), 17-38.

[106] Takayama, A., Kobayashi, E., Nakamura, T., & Narukawa, M. (2017). Quantitative assessment of premium rates for clinical usefulness in new drug price calculation in Japan. *Therapeutic Innovation & Regulatory Science, 51*(5), 582-588. doi: 10.1177/2168479017696270

[107] Takayama, A., & Narukawa, M. (2016a). Investigation of factors affecting the degree of price gap between the national health insurance reimbursement price and the actual market price of new drugs (in Japanese). *Regulatory Science of Medical Products, 6*(3), 295-305. doi: 10.14982/rsmp.6.295

[108] Takayama, A., & Narukawa, M. (2016b). Pharmaceutical Pricing and Reimbursement in Japan: For Faster, More Complete Access to New Drugs. *Therapeutic Innovation & Regulatory Science, 50*(3), 361-367. doi: 10.1177/2168479015619202

[109] Takayama, A., & Narukawa, M. (2017). Comparison of New Drug Accessibility and Price Between Japan and Major European Countries. *Therapeutic Innovation & Regulatory Science, 51*(5), 604-611. doi: 10.1177/2168479017706716

[110] Teramae, F., Makino, T., Lim, Y., Sengoku, S., & Kodama, K. (2020). International Strategy for Sustainable Growth in Multinational Pharmaceutical Companies. *Sustainability, 12*(3), 867. doi: 10.3390/su12030867

[111] Thomas, L. G., III. (2004). Are we all global now? Local vs. foreign sources of corporate competence: the case of the Japanese pharmaceutical industry. *Strategic Management Journal, 25*(8-9), 865-886. doi: 10.1002/smj.420

[112] Thomke, S., & Kuemmerle, W. (2002). Asset Accumulation, Interdependence and Technological Change: Evidence from Pharmaceutical Drug Discovery. *Strategic Management Journal, 23*(7), 619-635. doi: 10.1002/smj.242

[113] Thakor, R. T., Anaya, N., Zhang, Y., Vilanilam, C., Siah, K. W., Wong, C. H., & Lo, A. W. (2017). Just how good an investment is the biopharmaceutical sector? *Nature Biotechnology, 35*(12), 1149-1157. doi: 10.1038/nbt.4023

[114] Tominaga, T., Ando, Y., & Kondo, T. (2012). International Vision and Strategy for Drug Regulatory Authority: The PMDA's International Vision. *Clinical Pharmacology & Therapeutics, 92*(3), 349-351. doi: 10.1038/clpt.2012.90

[115] Ueno, T., Asahina, Y., Tanaka, A., Yamada, H., Nakamura, M., & Uyama, Y. (2014). Significant Differences in Drug Lag in Clinical Development Among Various Strategies Used for Regulatory Submissions in Japan. *Clinical Pharmacology & Therapeutics, 95*(5), 533-541. doi: 10.1038/clpt.2013.223

[116] Wakutsu, N., & Nakamura, H. (2015a). Analyzing the benefits from new NHI drug pricing system in Japan: factor decomposition and simulation (in Japanese). *Iryo To Shakai, 25*(2), 205-220. doi: 10.4091/iken.25.205

[117] Wakutsu, N., & Nakamura, H. (2015b). New NHI drug-pricing system in Japan: incentives for R&D and budget neutrality. *International Journal of Economic Policy Studies, 10*(1), 1-12. doi: 10.1007/BF03405759

[118] Wettstein, D. J., & Boes, S. (2019). Effectiveness of national pricing policies for patent-protected pharmaceuticals in the OECD: a systematic literature review. *Applied Health Economics and Health Policy, 17*(2), 143-162. doi: 10.1007/s40258-018-0437-z

[119] Wong, C. H., Siah, K. W., & Lo, A. W. (2019). Estimation of clinical trial success rates and related parameters. *Biostatistics, 20*(2), 273-286. doi: 10.1093/biostatistics/kxx069

[120] Wright, D. J. (2004). The drug bargaining game: pharmaceutical regulation in Australia. *Journal of Health Economics, 23*(4), 785-813. doi: 10.1016/j.jhealeco.2003.11.003

[121] Xin, Y. J., Hubbard-Lucey, V. M., & Tang, J. (2019). Immuno-oncology drug development goes global. *Nature Reviews Drug discovery, 18*(12), 899-900. doi: 10.1038/d41573-019-00167-9

[122] Yamashita, K., Kaneko, M., & Narukawa, M. (2019). A Significant Anticancer Drug Approval Lag Between Japan and the United States Still Exists for Minor Cancers. *Clinical Pharmacology & Therapeutics, 105*(1), 153-160. doi: 10.1002/cpt.1136