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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

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ABSTRACT

To stimulate clinical development, the Japanese government introduced "pricing premium for the promotion of new drug development and elimination/resolution of off-label use" in 2010. Using statistical analysis, we aimed to verify the acceleration of clinical development in therapeutic areas that are positive factors for receiving reward premiums. We defined "encouragement for clinical development" as the Pharmaceuticals and Medical Devices Agency (PMDA) review time in each therapeutic area compared with that in all therapeutic areas together. The dataset for this research was created from publicly available information on the PMDA website. New molecule entities (NMEs) between 2000 and 2016 in Japan were selected as the drugs of interest. Univariate regression analysis, Wilcoxon signed-rank test, and logistic regression analysis were conducted. The number of NMEs has been decreasing over time except for **B** (blood and blood-forming organs). The review time was significantly shorter for **A** (alimentary tract and metabolism), **B**, **J** (anti-infective for systemic use), and **L** (antineoplastic and immunomodulating agents) compared with that for all anatomical therapeutic chemical (ATC) codes together. The review time was significantly longer for **C** (cardiovascular system), and **S** (sensory organs). From logistic regression analysis, **A**, **B**, **J**, and **L** were identified as significant positive factors to shorten the review time. In conclusion, the present study has demonstrated that clinical development in Japan has been encouraged in therapeutic areas with unmet medical needs as the PMDA review time is shortened. This study assessing the review time per ATC code is consistent with our first report where the review time per office of new drug was investigated.

Keywords: review time, clinical development, regulatory science, drug pricing, PMDA

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INTRODUCTION

Japan has the largest drug market share after the United States and its market structure is unique among the developed countries. In Japan, cardiovascular drugs are profitable while they are not profitable in other developed countries (1). Historically, Japan suffered from a so-called "drug lag," consisting of a 5–10 year delay between marketing approval after new drug application (NDA) in Europe or the US and that in Japan. Moreover, some products were not available at all in Japan.

In this context, Japan has been striving to streamline the approval process by taking the following multiple measures: establishing an international vision of PMDA to join the global development seamlessly (2), increasing the number of reviewers at Pharmaceuticals and Medical Devices Agency (PMDA) (3), introducing prior assessment consultation before NDA (4), creating guidelines such as the "Basic Principles in Global Clinical Trials" (5), and offering the Sakigake Designation system (6). As a result, Japan has currently the shortest review time among major developed countries' regulatory agencies such as EMA, FDA, PMDA, Health Canada, and Swissmedic and the Australian TGA (7). In 2010, the government introduced the "Pricing premium for the promotion of new drug development and elimination/resolution of off-label use (pricing premiums)" (8). Figure 1 depicts this system that makes the Japanese market more attractive for investments from pharmaceutical companies. When the pricing premium is awarded, the drug prices increase (Figure .1, a), thereby enabling pharmaceutical companies to recover the research and development (R&D) cost right after launching new drugs and eventually "reinvent" them for the "next" new drugs (Figure .1, b).

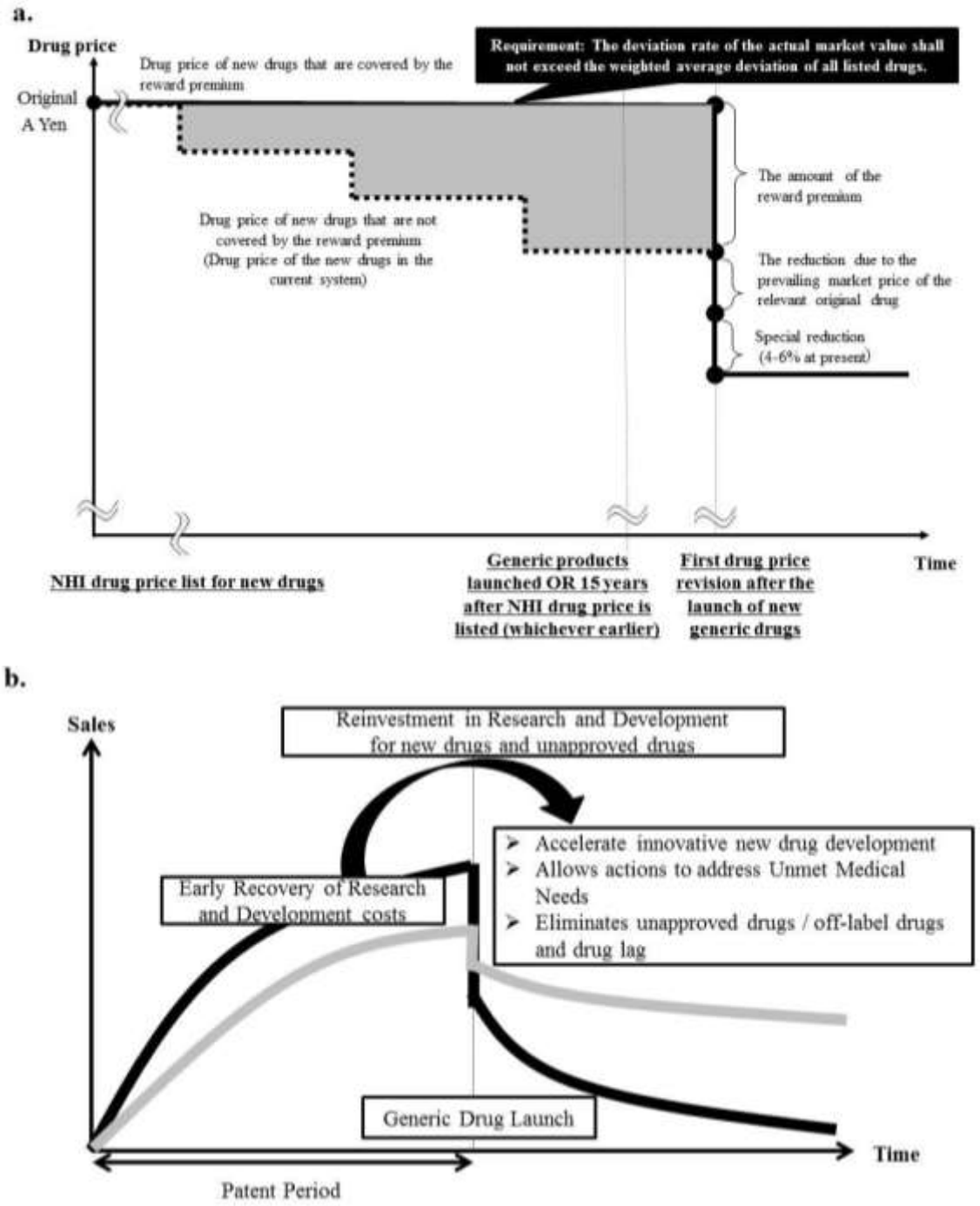


Figure 1: Concept of pricing premium for the promotion of new drug development and Elimination/resolution of off-label use (a. drug price transition, b. sales transition) (8)

According to previous reports, this premium system will likely be applicable to drugs in therapeutic areas with high unmet medical needs, such as oncology or neurology. The system is allowing pharmaceutical companies to make profits if they have successfully developed drugs in these therapeutic areas taking into account the increasing healthcare costs in Japan (9-11). Thus, in addition to benefiting the business of pharmaceutical companies, this pricing premium system

can also benefit patients in Japan. With this current Japanese pharmaceutical market opportunity, clinical drug development in neuroscience, neurology, and oncology seems to have been encouraged and related drug availabilities have improved (12-14). However, to the best of our knowledge, the relationship between the therapeutic areas identified as contributing factors for receiving reward premiums and clinical developments has not been evaluated through statistical analyses. Thus, it remains unclear whether this reward premium system does stimulate R&D of drugs in neuroscience, neurology, and oncology.

Here, we defined "encouragement of clinical development" as the PMDA review time for each therapeutic area compared with that for all therapeutic areas together and we tried to statistically verify the acceleration of clinical development in therapeutic areas that are positive factors for receiving reward premiums. Our first report provided evidence from the viewpoint of the Office of New Drug. This second report is a statistical investigation of the review times from the perspective of anatomical therapeutic chemical (ATC) codes and compares the results with those reported in the first report to investigate whether the reward premium system is working in Japan. We consider that these two consecutive reports provide important perspectives from the regulatory science point of view. While most policies are not perfect at their planning stage, a scientific evaluation can help in fine-tuning the contents and propose improvements based on the result outcomes (15).

MATERIALS AND METHOD

The dataset for this research was generated from publicly available information on the PMDA website (http://www.pmda.go.jp/english/). New molecule entities (NMEs) between 2000 and 2016 in Japan were selected as the drugs of interest. They were categorized according to the first level of the ATC classification system, which is the pharmaceutical coding system operated by the World Health Organization. The first level uses a one-letter code to indicate the main anatomical group on which a drug acts as presented in Table 1.

The number of NMEs per year was calculated. For trend analysis of the number of NMEs approved in each ATC code, univariate regression analysis was conducted (*$p < 0.05$, **$p < 0.01$).

Each review time was also calculated. The review time was defined as the period (in months) between NDA and marketing approval. The review times were presented using box plots with the top, middle, and bottom representing the 75th percentile, median, and 25th percentile, respectively. Error bars represent the 90th and 10th percentiles. The review time for each ATC

code was compared with the median value using the Wilcoxon signed-rank test (*$p < 0.05$, **$p < 0.01$).

For logistic regression analysis, a stepwise method was used to examine several variables for investigating which factors are significant explanatory variables. Table 2 summarizes binary variables selected for the logistic regression analysis. Using the logistic regression model to estimate the coefficient, the estimates were converted to odds ratio for the drug profiles that impacted the shortening of the review time.

All statistical analyses were performed using the statistical software IBM SPSS Statistics (software version released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

RESULTS AND DISCUSSION

Table 3 presents the number of NMEs approved between 2000 and 2016 in Japan. Numbers have been decreasing over time except for **B** (blood and blood-forming organs). In particular, a significant downward trend was confirmed for **A** (alimentary tract and metabolism) and **V** (Various).

Figure 2 presents the review time between 2000 and 2016 per each ATC code. The review time was significantly shorter for **A** (median: 12 months), **B** (median: 11 months), **J** (anti-infectives for systemic use) (median: 10 months), and **L** (antineoplastic and immunomodulating agents) (median: 11 months) compared with that for all ATC codes together (median: 13 months). The review time was significantly longer for **C** (cardiovascular system) (median: 15 months) and for **S** (sensory organs) (median: 19 months). The peak medians for each ATC code were 57 (**A**), 119 (**B**), 66 (**C**), 57 (**D**), 49 (**G**), 63 (**H**), 75 (**J**), 0 (**K**), 66 (**L**), 49 (**M**), 123 (**N**), 16 (**P**), 101 (**R**), 67 (**S**), and 135 (**V**) months. The minimum values were 7 (**A**), 6 (**B**), 6 (**C**), 9 (**D**), 9 (**G**), 9 (**H**), 1 (**J**), 0 (**K**), 5 (**L**), 10 (**M**), 5 (**N**), 8 (**P**), 8 (**R**), 10 (**S**), and 6 (**V**) months.

Figure 3 describes the time course change in the review time for each ATC code. We confirmed that review times shortened over time for all ATC code with ranges narrowing over the years as well.

Figure 4 shows the result of the multivariate analysis using a stepwise method for each ATC code. **A**, **B**, **J**, and **L** were significantly more likely to have a shorter review time.

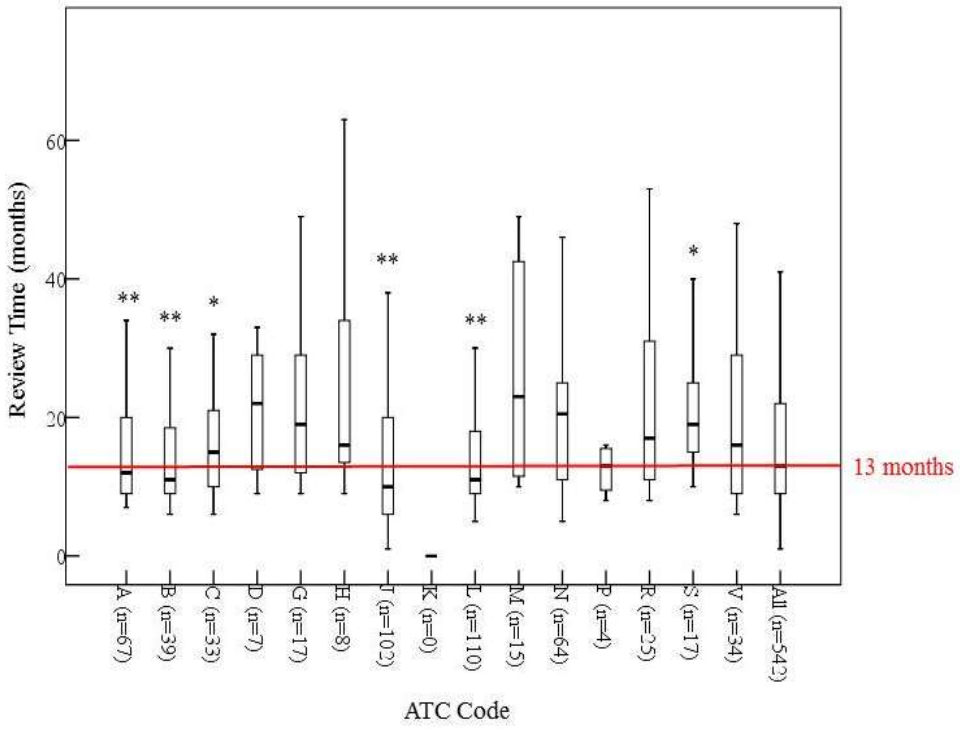
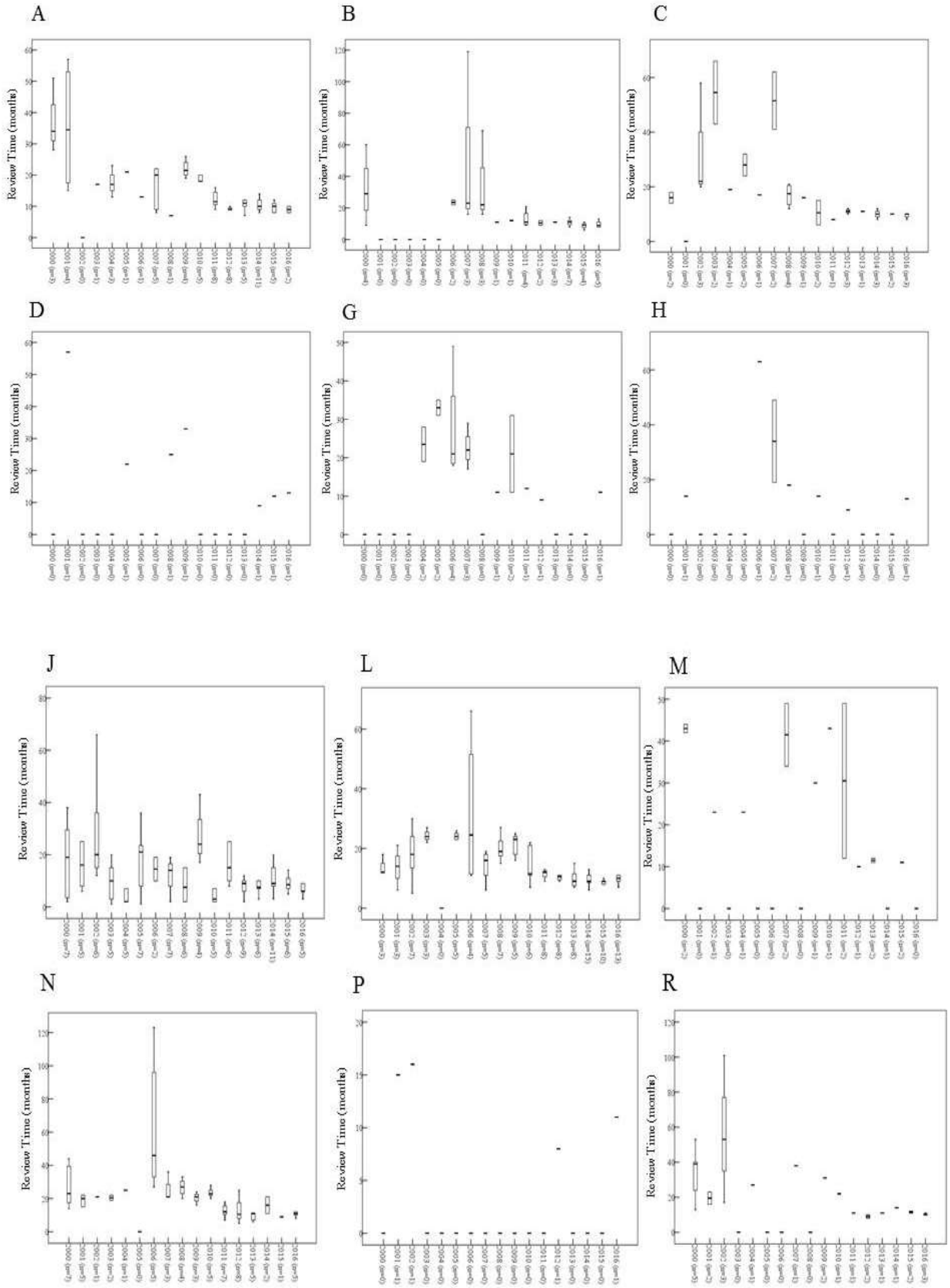


Figure 2: Review times per ATC code

In this box plot, the top, middle, and bottom represent the 75th percentile, median, and 25th percentile, respectively. Error bars represent the 90th and 10th percentiles. For analysis, each category was compared with the median value of all categories (13 months) using the Wilcoxon signed-rank test. *$p < 0.05$, **$p < 0.01$


A
B
C
D
G
H
J
L
M
N
P
R
Review Time (months)

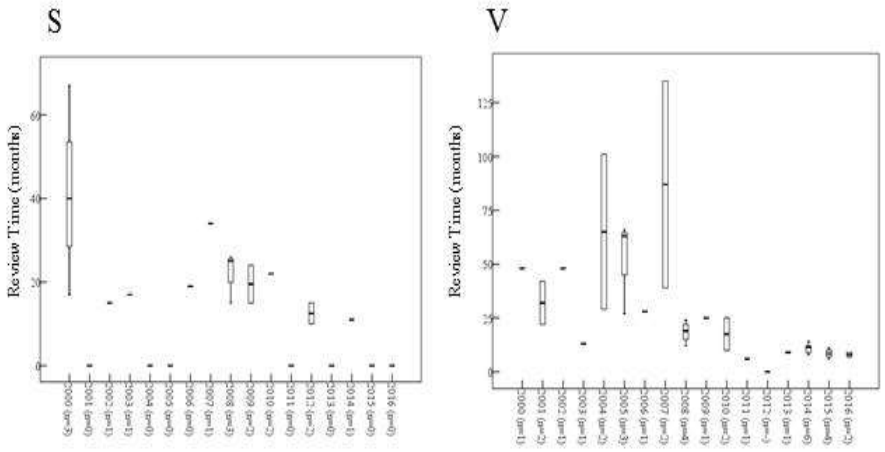
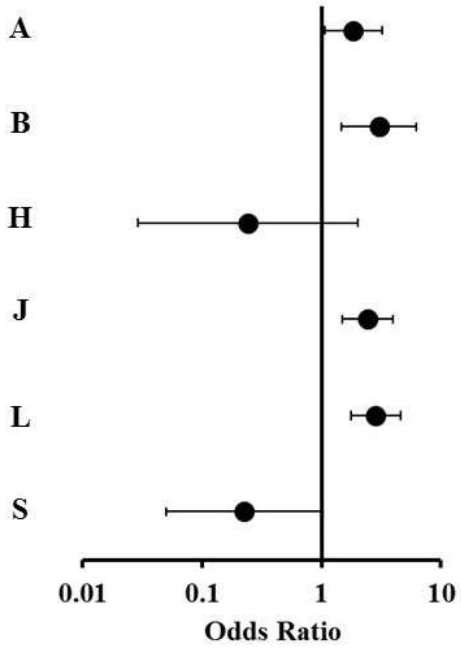


Figure 3: Time course of review times for each ATC code

In this box plot, the top, middle, and bottom represent the 75th percentile, median, and 25th percentile, respectively.

Table 1: ATC classification system: first level

Code	Therapeutic areas
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 insulin
J	Anti-infective 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



	OR	95% CI upper	95% CI lower	*p* values
A	**1.848**	**3.231**	**1.056**	**0.031**
B	**3.016**	**6.164**	**1.476**	**0.002**
H	**0.241**	**2.000**	**0.029**	**0.188**
J	**2.413**	**3.931**	**1.481**	**0.000**
L	**2.843**	**4.602**	**1.756**	**0.000**
S	**0.225**	**1.013**	**0.050**	**0.052**

Figure 4: Odds ratio for the profiles that accelerated the review time

Table 2: Summary of binary variables selected for logistic regression analysis

Objective variable	**Category**	**n**
Review time (< 13 months)	**Yes = 1**	**266**
	No = 0	**276**
Exploratory variable	**Category**	**n**
A	Yes = 1	67
	No = 0	475
B	Yes = 1	39
	No = 0	503
C	Yes = 1	33
	No = 0	509
D	Yes = 1	7
	No = 0	535
G	Yes = 1	17
	No = 0	525
H	Yes = 1	8
	No = 0	534
J	Yes = 1	102
	No = 0	440
K	Yes = 1	0
	No = 0	542
L	Yes = 1	110
	No = 0	432
M	Yes = 1	15
	No = 0	527
N	Yes = 1	64
	No = 0	478
P	Yes = 1	4
	No = 0	538
R	Yes = 1	25
	No = 0	517
S	Yes = 1	17
	No = 0	525
V	Yes = 1	34
	No = 0	508

Table 3: Number of NMEs in Japan between 2000 and 2016 categorized per ATC code

Year	ATC code													
	A	B	C	D	G	H	J	L	M	N	P	R	S	V
2000	34	29	16	0	0	0	19	12	43	23	0	39	40	48
2001	35	0	0	57	0	14	16	14	0	20	15	20	0	32
2002	0	0	22	0	0	0	20	18	23	21	16	53	15	48
2003	17	0	55	0	0	0	10	24	0	21	0	0	17	13
2004	17	0	19	0	24	0	2	0	23	25	0	27	0	65
2005	21	0	28	22	33	0	21	24	0	0	0	0	0	63
2006	13	24	17	0	21	63	15	25	0	46	0	0	19	28
2007	20	23	52	0	22	34	14	16	42	21	0	38	34	87
2008	7	22	18	25	0	18	8	19	0	27	0	0	25	19
2009	22	11	16	33	11	0	24	23	30	21	0	31	20	25
2010	18	12	11	0	21	14	3	12	43	23	0	22	22	18
2011	12	11	8	0	12	0	15	12	31	12	0	11	0	6
2012	9	11	11	0	9	9	9	11	10	11	8	9	13	0
2013	11	11	11	0	0	0	8	9	12	11	0	11	0	9
2014	10	11	10	9	0	0	9	9	0	16	0	14	11	12
2015	10	9	10	12	0	0	9	9	11	9	0	12	0	9
2016	9	9	10	13	11	13	6	10	0	11	11	10	0	8
Univariate regression analysis	Y = −0.96*X + 1944.8 (*p < 0.05)	Y = 0.16*X − 309.1	Y = −1.00*X − 2036.3	Y = −0.47*X − 945.2	Y = −0.11*X + 236.0	Y = −0.22*X + 452.6	Y = −0.57*X + 1159.0	Y = −0.47*X + 954.5	Y = −0.56*X + 1147.7	Y = −0.78*X + 1588.7	Y = −0.20*X + 401.6	Y = −1.15*X + 2325.7	Y = −0.94*X + 1907.5	Y = −3.01*X + 6082.4 (**p < 0.01)

Y: the number of the NMEs; X: year; *p < 0.05; **p < 0.01

DISCUSSION

The present study shows that the reward premium system that was introduced in 2010 has been working well in delivering innovative drugs to the Japanese market, In particular, we could verify through evaluation of the PMDA review time that drug developments in therapeutic areas that are considered to be significant positive factors for receiving the reward premiums have been encouraged. However, authors do not mean that this encouragement has not been put on the other therapeutic areas, just because the review time was significantly shorter in **L** that is one of the positive factors to be designated by the reward premium system. Actually, therapeutic areas **A**, **B**, and **J**, which are not positive factors, have been stimulated likely because they comprise urgent medical needs indications. **A** and **B** include "inborn errors of metabolism" and "gastrointestinal disorders" which reportedly account for 17% of the marketing authorizations from 2006 to 2011 in the US (2nd largest share) (16), and **J** includes fatal infectious and parasitic diseases, such as human immunodeficiency virus and hepatitis C virus, for which a similar number of drugs were approved in the US and Japan (17). Therefore, clinical development in Japan has not been biased solely toward therapeutic areas that are considered to be contributing factors for receiving the reward premiums. Indeed, we consider that the reward premium system has been boosting effective clinical development of innovative drugs in Japan than can make profits through this premium system. These new development trends may lead to the shortening of PMDA review time in addition to improving performance because of the multiple countermeasures taken by PMDA(18).

There are several limitations in this study. It is well known that "drug lags" consists of lags in drug development (LDD) and lags in drug review (LDR). LDD can be shortened by joining global trials (19) and LDR can be improved via improvement of the clinical development strategy for NDA (20). Generally, lags have to be discussed considering both LDD and LDR. However, this research was not conducted in the light of these perspectives because the primary objective of this study was to evaluate whether the reward premium system can accelerate the clinical development of drugs which are considered as positive contributing factors to be designated by this premium system. Contributing factors for shortening the review time in Japan under this premium system remain to be identified in the future.

This study provides important new insight for pharmaceutical companies that are targeting Japanese pharmaceutical markets in highlighting the rationale to initiate clinical developments, while making profits for next R&D and continuously meeting unmet medical needs in Japan.

Price regulation differs across countries: in France, Italy, and Japan, the government sets and controls the drug price while other countries, such as Germany, the Netherlands, and New Zealand, use reference prices allowing pharmaceutical companies to set a price above the reference price. The price control in Japan renders this country less attractive from the marketing point of view for global companies (21-23). However, the Japanese premium system can ensure profits to pharmaceutical companies if they have successfully launched innovative drugs that are targeting unmet medical needs. Even though the Japanese pharmaceutical market is strictly regulated unlike the US market where the drug price can be set through negotiating with the government, Japan can reach high sale levels like the US (24). In Japan, the prices of NMEs indicated for unmet medical needs can be higher because of the limited number of patients (25). Together with these insights, our findings suggest that the Japanese pharmaceutical market became more attractive for pharmaceutical companies, enabling them to develop NMEs in Japan simultaneously with other countries.

To summarize, investment has become more competitive in Japan. A major reason is that the Japanese market status represents a fairly predictable environment because of the regulations, and more importantly, innovation can be rewarded through the reward premium system.

CONCLUSION

In conclusion, the present study demonstrates that clinical development in Japan has been encouraged to target unmet medical needs by assessing the review time per ATC code. This is consistent with the results of our first report where the Office of New Drug review time was investigated.

CONFLICT OF INTEREST

Shoyo Shibata is an employee of Chugai Pharmaceutical Co., Ltd. However, his being part of the company has not influenced the results or discussion in this study. Koji Chiba and Takeshi Suzuki have nothing to disclose. This research was supported in part by Keio Gakuji Academic Development Funds and Ministry of Education, Culture, Sports, Science and Technology (MEXT), supported program for the strategic research foundation at private universities. The authors would like to thank Akane Koitabashi (Division of Basic Biological Sciences, Faculty of Pharmacy, Keio University) for her support and assistance with this research.

REFERENCES

1. Shibata S, Uemura R, Suzuki T. Comparative analysis between the top-selling drugs in the Japanese pharmaceutical market and those in the United States, the United Kingdom,

France, and Germany. Ther Innov Regul Sci, 2016; 50:221-227.

2. Tominaga T, Ando Y, Kondo T. International vision and strategy for drug regulatory authority: the PMDA's international vision. Clin Pharmacol Ther, 2012; 92:349-351. doi: 10.1038/clpt.2012.90.
3. Ichimaru K, Toyoshima S, Uyama Y. PMDA's challenge to accelerate clinical development and review of new drugs in Japan. Clin Pharmacol Ther, 2010; 88:454-457. doi: 10.1038/clpt.2010.190.
4. Pharmaceuticals and Medical Devices Agency. "Announcement of drug evaluation prior consultation survey overview." March 19, 2002. <http://www.pmda.go.jp/operations/shonin/info/consult/file/h21pas_survey.pdf> cited 13 May, 2017.
5. Ministry of Health, Labour and Welfare. "Basic principles on global clinical trials. September 28, 2007." <www.pmda.go.jp/operations/notice/2007/file/0928010-e.pdf> cited 13 May, 2017.
6. Kondo H, Hata T, Ito K, Koike H, Kono N. The current status of Sakigake Designation in Japan, PRIME in the European union, and Breakthrough Therapy Designation in the United States. Ther Innov Regul Sci, 2017; 51:51-54.
7. Bujar M, McAuslane N, Liberti L. R&D Briefing 59: The impact of the evolving regulatory environment on the approval of new medicines across six major authorities 2006-2015. Centre for Innovation in Regulatory Science. (2016).
8. Central Social Insurance Medical Council. "Minutes of Special Committee on Drug Prices." 23 Jun, 2010. Tokyo, Japan: Central Social Insurance Medical Council (Chuikyo).
9. Shibata S, Uemura R, Suzuki T. Factors that affect the acquisition of reward premiums for promotion of innovative drug discovery in Japan. Ther Innov Regul Sci, 2016; 50:56-65.
10. Shibata S, Uemura R, Suzuki T. Impact of premium rewards for the promotion of innovative drug discovery on the Japanese pharmaceutical market: an analysis by therapeutic area. Ther Innov Regul Sci, 2016; 50:49-55.
11. Shibata S, Uemura R, Suzuki T. Evaluating the effectiveness of repricing for market expansion in the Japanese drug pricing system. Ther Innov Regul Sci, 2016; 50:751-758.
12. Shibata S, Kawaguchi H, Uemura R, Suzuki T. Emerging growth of orphan drugs for neurological diseases in Japan: potential benefits for both patients and pharmaceutical

companies. Journal of Regulatory Science, 2016; 4:7-13.

13. Shibata S, Uemura R, Chiba K, Suzuki T. 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, 2016; 4:1-9.
14. Shibata S, Wayama Y, Tsuyuki A, Matsushita M, Chiba K, Matsuki E, et al. An empirical study of the prescription pattern of drugs for hematological malignancies in Japan from 2010–2014. Biol Pharm Bull, 2017; in press.
15. Obama B. United States Health Care ReformProgress to Date and Next Steps. JAMA, 2016; 316:525-532.
16. Melnikova I. Rare diseases and orphan drugs. Nat Rev Drug Discov, 2012; 11:267-268.
17. Anderson R, Brooks-Rooney C. The Differences between Infectious & Parasitic Drug Approvals in Japan and the USA. Value Health, 2014; 17:A808. doi: 10.1016/j.jval.2014.08.533.
18. Ichimaru K, Toyoshima S, Uyama Y. PMDA's challenge to accelerate clinical development and review of new drugs in Japan. Clin Pharmacol Ther, 2010; 88:454-457. doi: 10.1038/clpt.2010.190.
19. Hirai Y, Kinoshita H, Kusama M, Yasuda K, Sugiyama Y, Ono S. Delays in new drug applications in Japan and industrial R&D strategies. Clin Pharmacol Ther, 2010; 87:212-218. doi: 10.1038/clpt.2009.215.
20. Ueno T, Asahina Y, Tanaka A, Yamada H, Nakamura M, Uyama Y. Significant differences in drug lag in clinical development among various strategies used for regulatory submissions in Japan. Clin Pharmacol Ther, 2014; 95: 533-541. doi: 10.1038/clpt.2013.223.
21. Takayama A, Narukawa M. Pharmaceutical pricing and reimbursement in Japan for faster, more complete access to new drugs. Ther Innov Regul Sci, 2016; 50:361-367.
22. Chintagunta PK, Desiraju R. Strategic pricing and detailing behavior in international markets. Marketing Science, 2005; 24:67-80.
23. Sethuraman R, Tellis GJ, Briesch RA. How well does advertising work? Generalizations from meta-analysis of brand advertising elasticity's. J Mark Res, 2011; 48:457-471.
24. Ding, M.; Eliashberg, J.; Stremersch, S., Innovation and marketing in the pharmaceutical industry: emerging practices, research and policies. Springer, New York, 2014.
25. Kato Y, Matsui T, Hane Y, Abe J, Ueda N, Sasaoka S, et al. Analysis of New Drug Price

Calculation According to National Health Insurance (NHI) Drug Price List in Japan. RSMP, 2016; 6:171-183.

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