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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

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ABSTRACT

In 2010, a premium rewards system for the promotion of innovative drug discovery was introduced in Japan, which aimed to further the development of innovative new medicines to meet the high level of unmet medical needs present in Japan. Previous research indicated that anti-cancer agents, immune-suppressants, and neuroscience drugs comprised the drug categories that significantly contributed to receive this reward premium. In this study, the number of new molecule entities (NMEs) approved in Japan between 2000 and 2015, along with their review times by the Pharmaceuticals and Medical Devices Agency (PMDA), were investigated to elucidate the actual clinical development status in Japan under this reward system. The dataset used in this study was created from publicly-available information on the PMDA website. For analysis, univariate regression analysis and Wilcoxon signed-rank test were used. Significant upward trends were observed in the total number of NMEs approved by the Offices of New Drug III, IV, V, and the Vaccines and Blood Products Office. No significant differences in the number of NMEs between 2000 and 2015 for each New Drug Office were observed. The median review time was 14 months; the maximum review time was 21 months (Office of New Drug III) and the minimum review time was 12 months (Offices of New Drug IV and V), excluding the Office of Vaccines and Blood Products (11 months). The review period was significantly shortened over time in the Offices of New Drug I and II. Our study suggests that the development of new drugs in therapeutic areas with high unmet medical needs has been adequately promoted in Japan, along with reasonably shortened PMDA review times.

Keywords: Japanese pharmaceutical companies, clinical development, drug development, drug pricing, PMDA

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INTRODUCTION

The Japanese pharmaceutical industry is known to be unique among other developed countries. There are two main aspects that have established this uniqueness; one is the drug pricing system and the other is market characteristics. For the drug pricing system, when a new drug is launched onto the market, its price is determined based on those of comparable drugs, which are selected from the National Health Insurance (NHI) price list in terms of indications, chemical structure, and mode of action. In addition, the new drug is evaluated in terms of innovativeness, usefulness, and market potential. Premiums can be granted when the new drug meets certain requirements. One of these premium systems is called the "Reward premiums for the promotion of innovative drug discovery and resolution of off-label use issues, etc", which was introduced in 2010. If this system is applied to a drug, the drug price goes up so that the company can recover costs early and re-invest in the research and development of unapproved or innovative drugs (1). It has been reported that orphan drugs and drugs targeting specific therapeutic areas, such immunology, neuroscience, and oncology, are likely to receive these rewards (2, 3). For market characteristics, Japan has a unique market among developed countries, with more cardiovascular, but less drugs in neuroscience/oncology, ranked among the best-selling drugs in the Japanese market (4). However, the promotion of drug development in these areas is evident, suggesting that the Japanese market is becoming similar to the global market with high profitability in these therapeutic areas (4, 5).

As described above, anti-cancer agents, immune-suppressants, and drugs in neuroscience have been identified as significantly contributing factors for receiving reward premiums. However, it is unclear if the actual clinical development status of these therapeutic areas with high unmet medical needs has been adequately stimulated in Japan. In this study, the number of new molecule entities (NMEs) approved in Japan between 2000 and 2015, along with their review times by the Pharmaceuticals and Medical Devices Agency (PMDA), were investigated to assess whether clinical development has been stimulated under this reward system. Review time was assessed to evaluate the performance of the various New Drug Offices in the PMDA to determine whether differences exist for reviewing New Drug Applications (NDAs) under this reward system.

MATERIALS AND METHOD

The dataset used in this study was created from publicly-available information on the PMDA website (http://www.pmda.go.jp/english/). New Molecule Entities (NMEs) approved between

2000 and 2015 were selected as the drugs of interest. The number of NMEs per year and the New Drug Office was calculated. Table 1 presents review categories of new drugs. The review time as the period (in months) between the NDA and marketing approval were defined and calculated based on the information obtained from the review report. Review time was evaluated for each New Drug Office. For trend analysis of the number of NMEs approved in each New Drug Office, univariate regression analysis was applied: $*p < 0.05$, $**p < 0.01$.

The review times were presented using box plots with the top, middle, and bottom representing the 75th percentile, the median, and the 25th percentile, respectively. Error bars represent the 90th and 10th percentiles. For analysis, univariate regression analysis was conducted to clarify trends in review times: $*p < 0.05$, $**p < 0.01$. The review time of each year/group was compared with the median value by using the Wilcoxon signed-rank test: $*p < 0.05$, $**p < 0.01$.

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

Figure 1 presents the number of NMEs approved between 2000 and 2015. The number has been increasing over time. For each New Drug Office, the largest was I (119), followed in order by II (105), IV (103), V (73), III (57), Vaccines and Blood Products (44), and Cellular and Tissue-based Products (0).

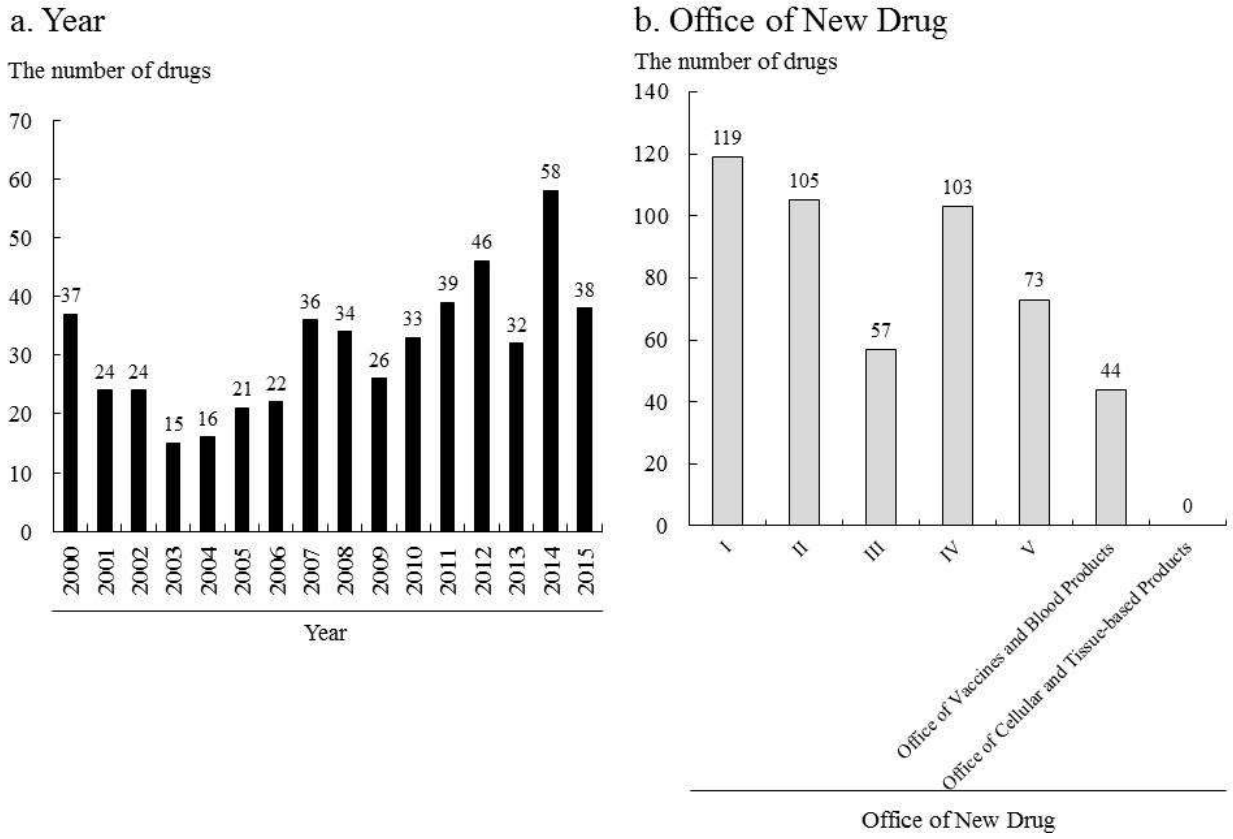

Figure 1: Number of NMEs approved between 2000 and 2015

The number of NMEs categorized by the New Drug Offices per year is shown in Table 2. The significant upward trends were confirmed in the total number of NEMs approved by Offices of New Drug III, IV, V, and Vaccines and Blood Products.

The time course of review times between 2000 and 2015 is presented in Figure 2. From univariate regression analysis, the review times were described as follows: Review time = -1.15 * (Year) + 2319.78 ($p < 0.01$). The review time significantly shortened over time. In addition, the range has been becoming narrower over the time.

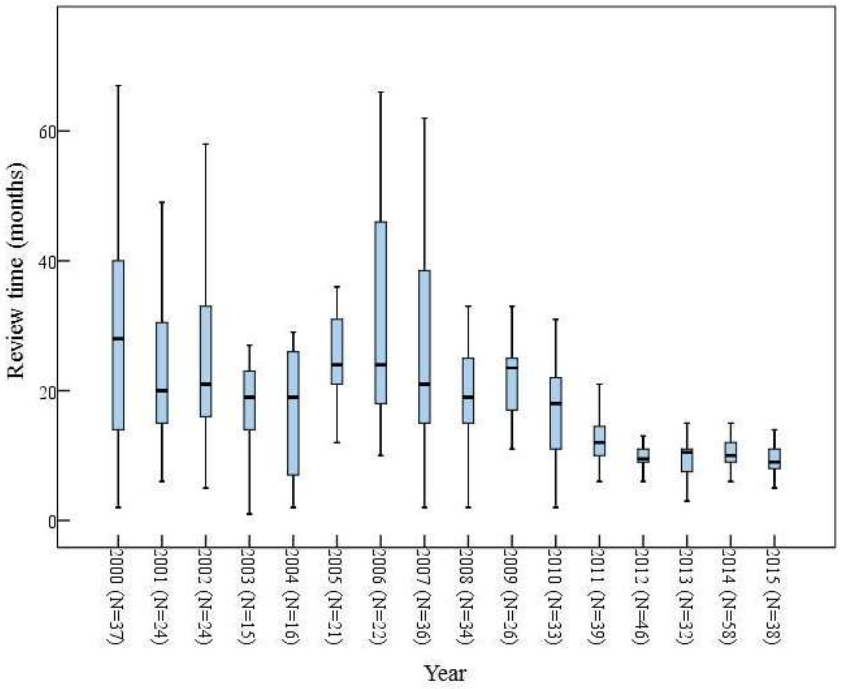

Figure 2: The time course of review between 2000 and 2015

Figure 3 presents the review time per New Drug Office. The review time was significantly shorter in the Offices of New Drug I (Median; 13 months), IV (Median; 12 months), and V (Median; 12 months), compared to all the Offices together (Median; 14 months). The peak medians for each Office of New Drug were 66, 123, 96, 101, 135, and 119 months, respectively. The minimums were 1, 6, 5, 1, 5, and 2 months, respectively.

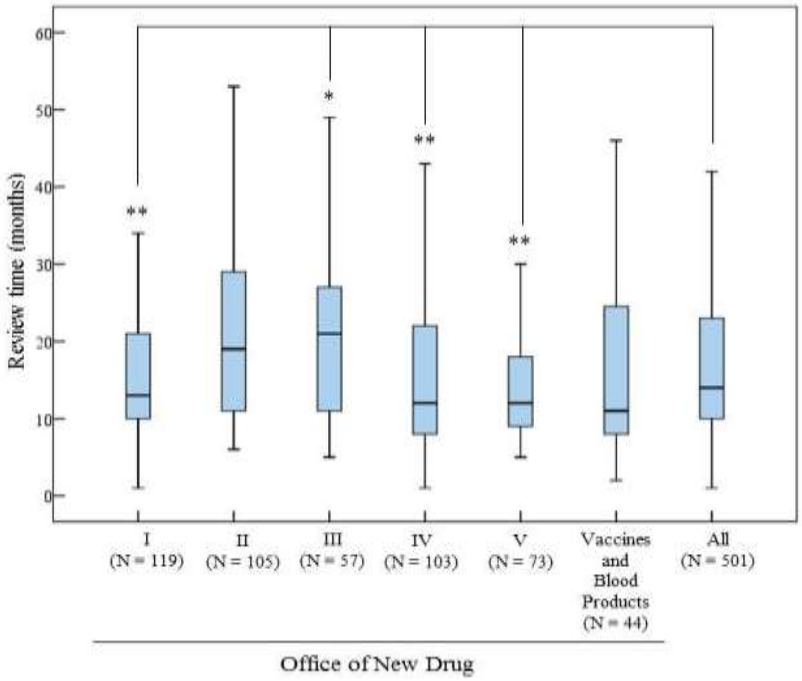

Figure 3: Presents the review time per New Drug Office

The time course of the review time for each New Drug Office between 2000 and 2015 is shown in Figure 4. From univariate regression analysis, review times for each New Drug Office were described as follows: Review time (Office of New Drug I) = -0.95 * (Year) + 1919.60 ($p < 0.01$); Review time (Office of New Drug II) = -1.52 * (Year) + 3071.52 ($p < 0.01$); Review time (Office of New Drug III) = -0.67 * (Year) + 1358.30; Review time (Office of New Drug IV) = -0.33 * (Year) + 683.58; Review time (Office of New Drug V) = -0.35 * (Year) + 723.91; Review time (Office of Vaccines and Blood Products) = -0.41 * (Year) + 815.89. Review times shortened over time for all New Drug Offices with ranges narrowing over the years as well.

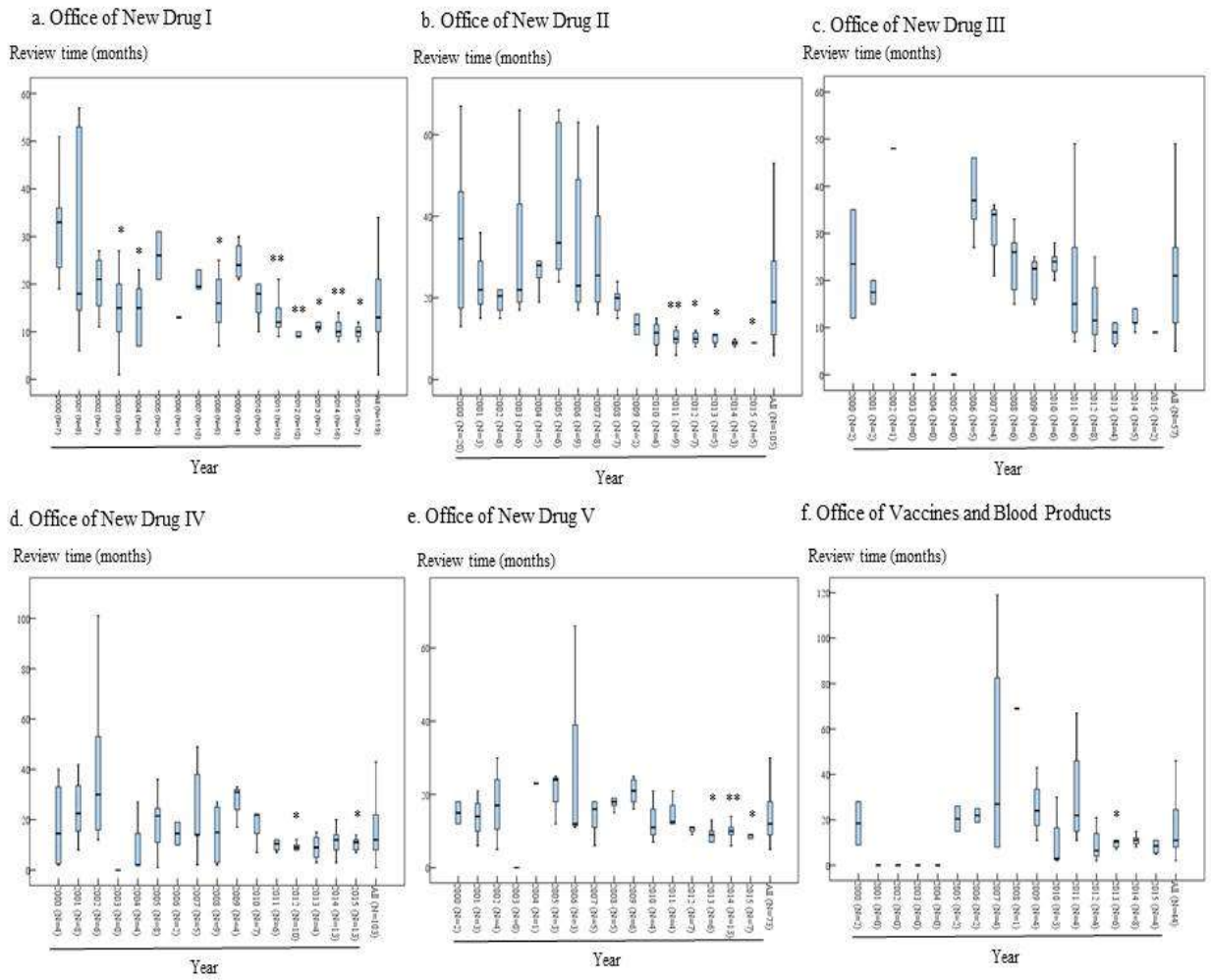

Figure 4: Review time for each New Drug Office between 2000 and 2015

The present study clarified that there were no significant differences between New Drug Offices in the number of NMEs, suggesting that the development of new drugs in Japan is not one-sided, although the premium rewards system is likely to only be applied to drugs that are orphan drugs

or targeted towards neuroscience, immunology, or oncology (2). However, the significant upward trend was confirmed in the total number of NEMs approved by the Offices of New Drug III, IV, V, and Vaccines and Blood Products. This result also indicates that the drug profiles identified as contributing factors for receiving reward premiums were appropriate, and, indeed, clinical development in these therapeutic areas has been stimulated. This is consistent with the perspective obtained from a previous report (2). Takayama et al. reported that the average time between approval and National Health Insurance (NHI) listing has been shortened in NMEs approved in Japan between October and December 2014 (6), indicating that the price setting in Japan reflects the true value of new medicine. This can make access to innovative drugs by all patients in Japan possible. In addition, according to several previous reports, with increasing knowledge on the molecular mechanisms underlying diseases, which leads to increased drug targets (7, 8), the number of compounds in clinical development, particularly in oncology and neuroscience, indeed continues to increase at the global level (9, 10). Developing innovative, new drugs is one of the key components for research-based pharmaceutical companies. They are struggling to develop new drugs by collaborating with academia, creating opportunities through mergers and acquisitions (11), and combining experience strategies (12) to increase the efficiency of their research and development departments. In this context, together with the fact that, at present, review times in the PMDA are the shortest among major regulatory agencies (13), it is important that drug prices be set high enough for pharmaceutical companies to recover research and development costs and secure adequate investments. However, it must also be low enough to let the patients that truly need the drugs obtain them for a reasonable cost. In this context, to summarize, the present study revealed that the premium rewards system is working well in Japan since its introduction in 2010.

The present study also revealed that the review time for NMEs by the PMDA has been gradually shortening, and the range becoming narrower. In order to reduce drug lag, Japan changed its government policies by creating guidelines such as the “Basic Principles in Global Clinical Trials” (14) etc., which allows Japan to join global development and establish an international vision of PMDA to align the development strategies of global companies (15). This has increased the number of reviewers in the PMDA (16) and introduced a prior assessment consultation, which takes place before the submission of a formal NDA (17). In addition, this policy has advanced regulatory science for effective decision making despite limited information in all phases of clinical development (18, 19). Through these countermeasures, review times

have been substantially shortening from a median review time of 22 months (2009) to 9 months (2013) for NMEs (20), with an increasing number in Japan joining global clinical trials (21, 22).

Table 3 presents the summary of review times for each Office with the results of the trend analysis. For pharmaceutical products, the median review time in the Offices of New Drug I, IV, and V was significantly shorter compared to the overall review time and, more importantly, although the significant downward trend was confirmed only in the Offices of New Drug I and II, the range for all Offices has been gradually shortening. Now that the PMDA struggles to shorten the review times to as short as possible, it is important for the pharmaceutical companies to create adequate clinical development strategies depending on therapeutic areas since drugs in neuroscience have the largest lag, while cardiovascular drugs have the shortest (23). Review times for drugs approved with conditions was short compared with those without conditions for approval (24). It is notable that the review times for oncology drugs have also been shortening. Although previous reports revealed that the anti-cancer drugs have a larger drug lag compared with those in other therapeutic areas as of 2011 (25), this is because the introduction of the revised "Guideline for Clinical Evaluation of Anti-cancer Drugs" issued in 2005 has worked well (26) and encouraged oncology clinical development in global clinical trials by proceeding the harmonization of endpoints, which can be one of the barriers in participating in global trials (27). Drug lags in neuroscience drugs were also reported to be quite substantial as of 2011 (28). However, currently, review times in this therapeutic area have also been shorter. For endpoints, it is also important that PMDA consultation meetings are held as frequently as possible between pharmaceutical companies and the PMDA to discuss what is the optimal strategy for a particular drug when it comes to reducing drug lag as well as review times by the PMDA (29). Drug lag is known to consist of delays in development time as well as review time. Now that the review times are short enough, delays in development time are one of the key factors for Japanese patients to receive the benefits of these new treatments.

As of 2015, there are no specific products launched in the Office of Cellular and Tissue-based Products. However, the Japanese regulatory conditions have been aligning with other regulatory authorities, which will allow these products to be developed and delivered effectively in Japan (30, 31).

The authors of the current study believe that the premium rewards system encourages clinical development in specific areas with high unmet medical needs. In addition, review times in the PMDA have been short enough in all New Drug Offices, thus the clinical development of innovative new drugs, including cellular and tissue-based products, should be accelerated in

Japan, and this will bring high profits to the pharmaceutical companies, which is one of the key drivers for the research and development of the "next" innovative drug in Japan. However, the relationship between this system and review time was not statistically analyzed in this article. Although further studies should be conducted, the findings of this study have provided the future clinical development directions in Japan.

CONCLUSION

In conclusion, our study suggests that the development of new drugs in therapeutic areas with high unmet medical needs has indeed been adequately promoted in Japan. In addition, review times in the PMDA are reasonably short to not impede drug development.

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.

AUTHOR NOTE

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REFERENCES

1. Central Social Insurance Medical Council. "Minutes of Special Committee on Drug Prices." 23 Jun, 2010. Tokyo, Japan: Central Social Insurance Medical Council (Chuikyo).
2. 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.
3. 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.
4. 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.

5. 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.
6. 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.
7. Landry Y, Gies JP. Drugs and their molecular targets: an updated overview. Fundam Clin Pharmacol, 2008; 22:1-18.
8. Overington JP, Al-Lazikani B, Hopkins AL. How many drug targets are there? Nat Rev Drug Discov, 2006; 5:993-996.
9. Berggren R, Moller M, Moss R, Poda P, Smietana K. Outlook for the next 5 years in drug innovation. Nat Rev Drug Discov, 2012; 11:435-436.
10. Lafferty-Whyte K, Mormeneo D, Del Fresno Marimon M. Opportunities and challenges of the 2016 target landscape. Nat Rev Drug Discov, 2017; 16:10-11.
11. Schuhmacher A, Gassmann O, Hinder M. Changing R&D models in research-based pharmaceutical companies. J Transl Med, 2016; 14:105.
12. Dahlin E, Nelson GM, Haynes M, Sargeant F. Success rates for product development strategies in new drug development. J Clin Pharm Ther, 2016; 41:198-202.
13. 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).
14. 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 5 March, 2017.
15. 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.
16. 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.
17. 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 5 March, 2017.
18. Tominaga T, Asahina Y, Uyama Y, Kondo T. Regulatory science as a bridge between

science and society. Clin Pharmacol Ther, 2011; 90:29-31.

19. Tominaga T, Ando Y, Nagai N, Sato J, Kondo T. Balancing societal needs and regulatory certainty: the case study of peramivir in Japan. Clin Pharmacol Ther, 2013; 93:342-344.
20. Poirier AF. Closing the drug lag for new drug submission and review in Japan: An industry perspective. Clin Pharmacol Ther, 2015; 98:486-488.
21. Ando Y, Uyama Y. Multiregional clinical trials: Japanese perspective on drug development strategy and sample size for Japanese subjects. J Biopharm Stat, 2012; 22:977-987.
22. Asano K, Tanaka A, Sato T, Uyama Y. Regulatory challenges in the review of data from global clinical trials: the PMDA perspective. Clin Pharmacol Ther, 2013; 94:195-198.
23. 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.
24. 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. J Regulatory Sci 2016;4:1-9.
25. Yonemori K, Hirakawa A, Ando M, Hirata T, Yunokawa M, Shimizu C *et al*. The notorious "drug lag" for oncology drugs in Japan. Invest New Drugs,2011; 29:706-712.
26. Ministry of Health, Labour and Welfare. "Guideline for Clinical Evaluation of Anti-cancer Drugs." (Japanese) November 1, 2005. <https://www.pmda.go.jp/files/000206740.pdf> cited 5 March, 2017.
27. Shimazawa R, Ikeda M. Japan lags behind the UK in neurological drug approvals. Br J Clin Pharmacol, 2011; 71:473-475.
28. Girman CJ, Ibia E, Menjoge S, Mak C, Chen J, Agarwal A, et al. Impact of different regulatory requirements for trial endpoints in multiregional clinical trials. Drug Inf J, 2011; 45:587-594.
29. Sugita T. Recent trends and special topics in new drug review in PMDA. GaBI Journal, 2013; 2:99-100.
30. Matsuda T, Aruga A. Comparison of Regulations for the Development of Oncolytic Virus Therapy in the United States, the European Union, and Japan. Journal of Regulatory Science, 2016; 4:1-9.

31. Oye KA, Eichler HG, Hoos A, Mori Y, Mullin TM, Pearson M. Pharmaceuticals Licensing and Reimbursement in the European Union, United States, and Japan. Clin Pharmacol Ther, 2016; 100:626-632