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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

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Abstract

We examined conditional approval and all-case surveillance designations for new molecular entities investigated between 2000 and 2014 in Japan. Using univariate or multivariate logistic-regression analysis, this study attempted to clarify profiles that affect the receipt of these designations, and to provide guidance for effectively using conditional approval and all-case surveillance designations. Analysis showed that the highest number of drugs to which these systems were applied was category L (Antineoplastic and immunomodulating agents) of the Anatomical Therapeutic Chemical Classification System. Orphan drug designation (ODD) and L drugs were significantly correlated with the receipt of both conditional approval and all-case surveillance. These designations shortened the review time. Positive factors that shortened the period of review included ODD, using global data, and joining a global study. Bridging strategy was the only negative factor. Utilization of this Japan-specific PMS system can shorten drug lag, thereby securing the safety of Japanese subjects.

Keywords:
drug development, all-case surveillance, conditional approval, regulatory review time, drug lag, PMDA

1. Introduction

Although ”drug lag” has been extensively examined, it remains as one of the important problems that have yet to be solved. Moreover, social concerns have been raised in a country with a wide drug lag like Japan [1], as compared to those in the EU and the United States(US) [2]. One of the factors responsible for this drug lag is the approval delay, which is due to the actual review time required for these approvals[3]. However, review time, which is defined as the duration between the New Drug Application (NDA) and the approval, has declined in Japan over the period from 2000 until 2009, with a shortened time found for drugs that have been designated as priority review[4]. This is directly related to the Japanese regulatory agency Pharmaceuticals and Medical Devices Agency (PMDA), which has made large strides towards shortening the review time through the implementation of multiple countermeasures [5].

Recently, clinical trials have been conducted globally in order to recruit subjects over a shorter period of time, thereby reducing the overall developmental period [6, 7]. The Ministry of Health, Labour and Welfare in Japan issued a notification that encouraged the Japanese pharmaceutical industry to join global studies in a timely manner, with the aim of simultaneous launches [8]. This means that a larger number of compounds will be approved for use in Japan with less Japanese and more foreign data used in the NDA. As a result, this should lead to more new drugs that will be available for Japanese patients without any extended delays.

The regulatory authorities of the EU (European Medicines Agency: EMA) and the US (Food and Drug Administration: FDA) evaluated the use of global trials and decided to focus more attention on the handling of clinical data obtained from studies conducted in regions other than the EU and the US, with the EMA actually issuing both a concept paper [9] and a reflection paper on this process [10]. Based on this change, clinical trials are currently transitioning from regional studies

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in the EU and the US to global studies that involve all countries in the world including US, EU and Japan. Furthermore, there have been many discussions on the planning, implementation, and use of the data analysis results from these studies [7, 11, 12]. Starting in the 2000s, Japan began participating in global studies [13], which has led to a decrease in the amount of Japanese-only clinical data that is being submitted for NDAs. However, it is important that additional Japanese data to be collected after approvals that are based on global trials, particularly from a safety point of view. The PMDA has requested that pharmaceutical companies perform post-marketing surveillance (PMS) studies in Japan, with the specific aim of investigating the safety, efficacy, and pharmacokinetic (PK)/pharmacodynamic (PD) data for Japanese subjects after marketing approvals based on global trials. When PMS is required, there are several conditions that new drugs must meet in order to gain marketing approval, and this is referred to as conditional approval. When the PMDA gives a new drug a conditional approval, this means that the pharmaceutical companies must perform PMS studies that will be able to adequately collect additional data. An all-case surveillance is a PMS study designation in which all of the collected data comes from cases where the dosing has been further investigated after marketing approval. This all-case surveillance is a unique system to Japan and has been done primarily because of the small number of Japanese subjects in the initial clinical trials [14]. This system is also applicable to the accumulation of additional safety data for orphan drugs and antineoplastic agents [15]. Although the purpose of this survey is to improve the outcome via the proper use of pharmaceutical products based on sufficient clinical data, the majority of health care professionals are not aware of the necessity of this survey [16].

The conditional approval and all-case surveillance system can be applied to drugs that have less Japanese data, thereby shortening the review time, and thus, can lead to a reduced amount of time required to examine NDA documents by the reviewers. In addition, in Japan, PMS is considered to affect the nature of clinical trials and the approval process, which can be important in terms of improving the efficiency of drug development. Therefore, we initially investigated the current status of new molecular entities (NMEs) that received conditional approval and all-case surveillance designations. By examining the potential factors that were collected between 2000 until 2014, we were able to utilize these findings to define guidelines for effectively using this system. To investigate whether this system worked well with regard to delivering innovative drugs to Japanese patients in a timely manner, we then statistically evaluated whether conditional approval and all-case surveillance had an effect on the review time. We also analyzed other factors that may have had an effect during the review period.

As far as we know, this is the first study to report on the potential factors that can affect receiving a conditional approval and all-case surveillance designation. This study initially examined the latest and largest NME datasets, which were obtained between 2000 and 2014, and then used the information to statistically evaluate the impact of several factors including conditional approvals and all-case surveillance on the review time.

2. Materials and Methods

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

Table 1 presents the information obtained from a review report of the NMEs that were approved between 2000 and 2014, which includes company profile, conditional approval, all-case surveillance, orphan drug designation (ODD), priority review, expedited review, normal review, using global data for NDA, adopting a bridging strategy, and participating in a global study. We defined the review time as the period (in months) between the NDA and the marketing approval. The approval dates in the US were obtained from the website of the FDA: (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/).

NMEs were categorized according to the first level of the Anatomical Therapeutic Chemical (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: A is for Alimentary tract and metabolism, B for Blood and blood forming organs, C for Cardiovascular system, D for Dermatologicals, G for Genitourinary system and sex hormones, H for Systemic hormonal preparations, excluding sex hormones and insulins, J for Anti-infectives for systemic use, K for Transfusion, L for Antineoplastic and immunomodulating agents, M for Musculoskeletal system, N for Nervous system,, R for Respiratory system,, S for Sensory organs, T for Diagnostic medicine, and V for Various.

Logistic regression was used for examining hypotheses about relationships between categorical outcome variables and categorical predictor variables. After using either the univariate or multivariate logistic-regression model to estimate the coefficient, we then converted the estimates to the odds ratio for the drug profiles that impacted both receiving a conditional approval and all-case surveillance and the shortening of the review time. The models adequacy was evaluated through the use of Hosmer-Lemeshow goodness-of-fit statistics when using a multivariate logit regression analysis. This goodness-of-fit test produces a p-value and if it is below 0.05, the model is not adequate. However, if it is above 0.05, then this model passes the test and is considered to be adequate.

In the first step, a simple logistic regression was conducted on several parameters to calculate the unadjusted odds ratio. In the second part of the analysis, we used the stepwise method to examine several variables that were collected based on the first simple logistic regression analysis in order to investigate which factors were significant explanatory variables. Data obtained from the initial simple logistic regression with p values > 0.2 were excluded from this analysis. Table 2 summarizes the binary variables selected for the logistic regression analysis.

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.).

Conditional Approval	n	%
Yes	174	37
No	294	63
All-Case Surveillance		
Yes	121	26
No	347	74
Company Profile [#]		
Global	275	59
Domestic	193	41
Orphan Drug Designation		
Yes	108	23
No	360	77
Priority Review		
Yes	44	9
No	424	91
Expedited Review		
Yes	13	3
No	455	97
Normal Review		
Yes	411	88
No	57	12
Global Data		
Yes	222	47
No	246	53
Bridging Study		
Yes	26	6
No	442	94
Global Study		
Yes	45	10
No	423	90
ATC Code		
A	55	12
B	31	7
C	25	5
D	7	1
G	11	2
H	13	3
J	94	20
L	84	18
M	17	4
N	63	13
P	0	0
R	23	5
S	16	3
V	29	6

Table 1. Profile of investigational objects used in this research.
New drugs obtained marketing approval between 2000 and 2014.
Abbreviation: ATC, Anatomical Therapeutic Chemical Classification System.
[#] Domestic companies are defined as companies headquartered in Japan, and global companies are headquartered outside of Japan.

Review time of orphan drugs (OD)/non-orphan drugs, drugs with/without conditional approval, and drugs with/without all-case surveillance (A) and according to the ATC code (B). (A) Significant differences between OD and non-OD, conditional approval drugs and non-conditional approval drugs, and all-case surveillance drugs and non-all-case surveillance drugs were determined by using a Students t-test, with *p< 0.05, **p< 0.01 set as the levels of significance (n = 468 for all drugs, 108 for OD, 360 for non-OD, 174 for conditional approval, 294 for non-conditional approval, 121 for all-case surveillance, and 347 for non-all-case surveillance).

3. Results

The drug profiles that were compiled according to the code of the ATC Classification System are presented in Table 3. J, L, and N were ranked as the top 3 categories for the number of NMEs developed during the period from 2000 until 2014. The rates for conditional approval, all-case surveillance, and ODD were the highest for L. Priority reviews primarily occurred for the J and L drugs. J drugs accounted for the largest percentage of drugs given an expedited review.

When using global data for the NDA, the top three NMEs included the L, J, and A drugs. The number of NDAs that included a bridging strategy and a global study was small on average, with no significant difference confirmed for their impact.

The results of a simple logistic regression analysis and the odds ratio calculated for the drug profiles that impacted the receipt of a conditional approval are shown in Figure 1. Positive factors included company profile, ODD, priority review, and L, while negative factors were normal review, C, and N. The adjusted odds ratios that were calculated from a multiple regression analysis performed using the above results are also shown in Figure 1. Positive factors included ODD and L, while negative factors included normal review and N.

The odds ratio for the drug characteristics that affected the designation of all-case surveillance that was obtained from the simple logit analysis are presented in Figure 2. Positive parameters were company profile, ODD, priority review, L, and global data, while the only negative factor was found to be N. The ad-

Objective Variable			
Conditional Approval	No = 0, yes = 1	Review time (≥21 months)	No = 0, yes = 1
All-Case Surveillance	No = 0, yes = 1		
Explanatory Variables			
Company Profile #	Domestic = 0, global = 1	Conditional Approval	No = 0, yes = 1
Orphan Drug Designation (ODD)	No = 0, yes = 1	All-Case Surveillance	No = 0, yes = 1
Priority Review	No = 0, yes = 1	Company Profile #	Domestic = 0, global = 1
Expedited Review	No = 0, yes = 1	Orphan Drug Designation (ODD)	No = 0, yes = 1
Normal Review	No = 0, yes = 1	Priority Review	No = 0, yes = 1
ATC Code	No = 0, yes = 1	Expedited Review	No = 0, yes = 1
Global Data	No = 0, yes = 1	Normal Review	No = 0, yes = 1
Bridging Study	No = 0, yes = 1	ATC Code	No = 0, yes = 1
Global Study	No = 0, yes = 1	Global Data	No = 0, yes = 1
		Bridging Study	No = 0, yes = 1
		Global Study	No = 0, yes = 1

Table 2. Summary of binary variables selected for logistic regression analysis.
Abbreviation: ATC, Anatomical Therapeutic Chemical Classification System.
Domestic companies are defined as companies headquartered in Japan, and global companies are headquartered outside of Japan.

justed odds ratio for the drug profiles impacting the receipt of all-case surveillance are also shown in Figure 2. ODD, L, V, and global data were positive factors, while normal review was a negative factor for an all-case surveillance designation.

Overall, the factors that significantly affected receiving a conditional approval and an all-case surveillance were as follows. Common positive factors included ODD and L while the primary negative factor was a normal review. Global data was significantly positive for receiving an all-case surveillance, while N was a negative factor for designation as a conditional approval.

The analysis results for orphan drug (OD) and non-OD review times, conditional and non-conditional approval drugs, and drugs designated or not designated as all-case surveillance are shown in Figure 3A. Factors that significantly reduced the review time included ODD, conditional approval, and all-case surveillance.

The NME review times according to the ATC code are shown in Figure 3B. J and L drugs had a significantly shorter review time, while the R drugs exhibited a significantly longer review time as compared with the average review time for all NMEs.

The odds ratios for the drug profiles that affected the review period are shown in Figure 4. Profiles that shortened the review time included company profile, conditional approval, all-case surveillance, ODD, priority review, A, L, and bridging studies. Normal review, N, and R were all shown to increase the review time.

The adjusted odds ratios for the characteristics that also affected the review time are also shown in Figure 4. ODD, priority review, A, global data, and global studies decreased the review time, while bridging studies increased the review time.

Overall, the positive factors that significantly reduced the review time included ODD, A, global data, and global study. In contrast, bridging studies increased the review time.

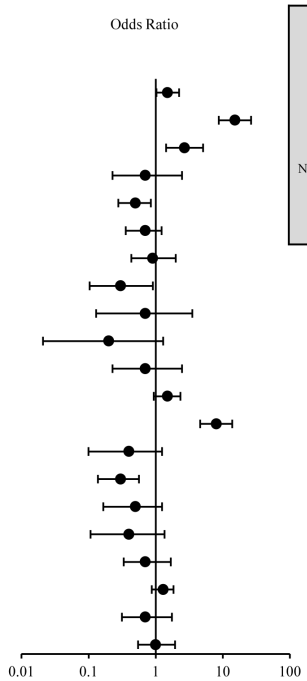
4. Discussion

The concept of drug lag, which refers to a delay in the launch of new drugs, was first introduced in the 1970s [17]. This lag is considered to consist of three types of delays that include the timing related to starting development, the developmental period, and the review period [3]. Although there have been a large number of papers published on drug lag, the majority have focused on particular therapeutic areas [18, 19, 20, 21]. Our current study focused primarily on the impact of the current status of conditional approval and all-case surveillance, and the effects caused by the Japan-specific PMS system. To understand the impact of the PMS system on drug lag comprehensively, we first investigated the factors that affected the receipt of a conditional approval and all-case surveillance in order to provide suggestions for better utilization of this Japan-specific PMS system.

The common positive factors associated with receiving conditional approval and all-case surveillance were ODD and L (Figures 1 and 2). Since ODs have fewer clinical trials and subjects compared with non-ODs [22], it is reasonable to conduct PMS studies for these types of drugs in order to collect more data after their initial launch. It is notable that the L drugs were significantly associated with the application of these systems. This is partly because improvement of the development strategy for oncology drugs has enabled Japan to participate in global studies, which has led to a shortening of the development period due to having to use less Japanese data for an NDA

Univariate Analysis

Explanatory Variables	95% CI			
	Odds ratio	Lower limit	Upper limit	*p*
Company Profile	1.5	1.0	2.2	0.04
ODD	15.2	8.7	26.3	0.00
Priority Review	2.7	1.4	5.1	0.00
Expedited Review	0.7	0.2	2.5	0.63
Normal Review	0.5	0.3	0.8	0.01
A	0.7	0.4	1.2	0.19
B	0.9	0.4	2.0	0.84
C	0.3	0.1	0.9	0.03
D	0.7	0.1	3.5	0.64
G	0.2	0.0	1.3	0.09
H	0.7	0.2	2.5	0.63
J	1.5	0.9	2.3	0.09
L	8.0	4.6	13.8	0.00
M	0.4	0.1	1.2	0.10
N	0.3	0.1	0.6	0.00
R	0.5	0.2	1.2	0.12
S	0.4	0.1	1.3	0.13
V	0.7	0.3	1.7	0.48
Global Data	1.3	0.9	1.8	0.22
Bridging Study	0.7	0.3	1.7	0.49
Global Study	1.0	0.5	1.9	0.93



Multivariate Analysis

Explanatory Variables	95% CI			
	Odds ratio	Lower limit	Upper limit	*p*
ODD	17.4	9.6	31.6	0.00
Normal Review	0.3	0.1	0.5	0.00
L	4.9	2.6	9.2	0.00
N	0.5	0.2	1.0	0.06

Hosmer-Lemeshow test

χ^2	df	*p*
7.2	4	0.1

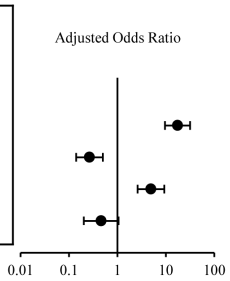
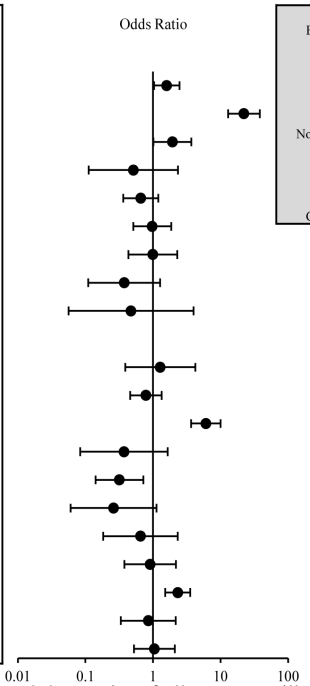


Figure 1. Odds ratio for the drug profiles that impacted the receipt of a conditional approval. Univariate and multivariate logistic-regression models were used to estimate the coefficient, with the values then converted to the odds ratio for the designation of a conditional approval with the potential predictors described in the table.

Univariate Analysis

Explanatory Variables	95% CI			
	Odds ratio	Lower limit	Upper limit	*p*
Company Profile	1.6	1.0	2.5	0.03
ODD	22.2	13.0	38.1	0.00
Priority Review	1.9	1.0	3.7	0.04
Expedited Review	0.5	0.1	2.3	0.39
Normal Review	0.7	0.4	1.2	0.17
A	1.0	0.5	1.9	0.94
B	1.0	0.4	2.3	0.99
C	0.4	0.1	1.3	0.12
D	0.5	0.1	4.0	0.49
G	0.0	0.0		1.00
H	1.3	0.4	4.2	0.68
J	0.8	0.5	1.3	0.38
L	6.1	3.7	10.0	0.00
M	0.4	0.1	1.7	0.19
N	0.3	0.1	0.7	0.01
R	0.3	0.1	1.1	0.07
S	0.7	0.2	2.3	0.51
V	0.9	0.4	2.2	0.83
Global Data	2.3	1.5	3.6	0.00
Bridging Study	0.9	0.3	2.2	0.74
Global Study	1.0	0.5	2.1	0.90



Multivariate Analysis

Explanatory Variables	95% CI			
	Odds ratio	Lower limit	Upper limit	*p*
ODD	36.2	18.7	70.3	0.00
Normal Review	0.2	0.1	0.4	0.00
L	3.8	2.0	7.4	0.00
V	4.4	1.5	12.7	0.00
Global Data	2.6	1.4	4.6	0.00

Hosmer-Lemeshow test

$\chi 2$	df	*p*
5.7	4	0.2

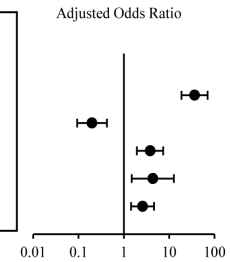


Figure 2. Odds ratio for the drug profiles that impacted the receipt of all-case surveillance. Univariate and multivariate logistic-regression models were used to estimate the coefficient, with the values then converted to the odds ratio for the designation of all-case surveillance with the potential predictors described in the table.

	All	Conditional Approval		All-Case Surveillance		Orphan Drug Designation		Priority Review		Expedited Review		Global Data		Bridging Study		Global Study	
ATC code	n	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
A	55	16	29.1	14	25.5	12	21.8	1	1.8	0	0	35	63.6	3	5.5	8	14.5
B	31	11	35.5	8	25.8	9	29.0	2	6.5	1	3.2	20	64.5	1	3.2	7	22.6
C	25	4	16.0	3	12.0	3	12.0	0	0	0	0	9	36.0	0	0	1	4.0
D	7	2	28.6	1	14.3	0	0	0	0	0	0	0	0	0	0	0	0
G	11	1	9.1	0	0.0	0	0	0	0	0	0	8	72.7	3	27.3	2	18.2
H	13	4	30.8	4	30.8	5	38.5	0	0	0	0	6	46.2	1	7.7	0	0
J	94	42	44.7	21	22.3	26	27.7	23	24.5	7	7.4	38	40.4	2	2.1	5	5.3
L	84	64	76.2	49	58.3	39	46.4	17	20.2	0	0	51	60.7	4	4.8	13	15.5
M	17	3	17.6	2	11.8	0	0	0	0	0	0	6	35.3	3	17.6	1	5.9
N	63	10	15.9	7	11.1	8	12.7	0	0	3	4.8	27	42.9	6	9.5	3	4.8
P	0	0	0.0	0	0.0	0	0	0	0	0	0	0	0	0	0	0	0
R	23	5	21.7	2	8.7	2	8.7	0	0	0	0	10	43.5	0	0	4	17.4
S	16	3	18.8	3	18.8	2	12.5	0	0	0	0	5	31.3	1	6.3	1	6.3
V	29	9	31.0	7	24.1	2	6.9	1	3.4	2	6.9	7	24.1	2	6.9	0	0

Table 3. Numbers and ratios of drugs categorized by drug profiles according to ATC code.
Abbreviation: ATC, Anatomical Therapeutic Chemical Classification System.

[23]. Therefore, if NDAs for other category drugs are more frequently submitted by pharmaceutical companies using foreign studies combined with data from Japanese studies, or if these companies utilize the results from foreign trials instead of waiting for local Japan studies, these drugs will more rapidly gain conditional approval and all-case surveillance. The use of a global study was another positive factor for receiving all-case surveillance. As compared to global studies, the amount of Japanese data that is available is often very small, which shows the benefit of applying global studies for development strategy. However, we confirmed that conditional approval and all-case surveillance were not applicable for drugs such as L and OD when they were initially launched in the US and/or there were safety concerns that were predictable from the precedents or their mode of actions (for example: Betaferone, Stromectol, Gonalef, Modiodal, Volibris, Apokyn, Remicade, Leustatin, Pirespa, and Bosulif), suggesting that these drugs should enter the market as quickly as possible with PMS follow up to ensure reasonable safety.

Regarding the negative factors, the most common was a normal review, which indicates that while securing safety, the NMEs need to be delivered to patients as soon as possible in order to receive a conditional approval and all-case surveillance designation. Another negative factor for conditional approval was N, which suggests that global studies are likely to be used for an NDA (Table 3). However, the number of Japanese patients that are receiving N drugs is high since Japan is an aging society and thus, sufficient Japanese efficacy, safety, and PK/PD data should be obtained in this therapeutic area. As shown in Figure 3A, these systems led to a significant reduction in the review time, which suggests that utilization of these PMS studies can lead to a reduction in drug lag in Japan. Regarding the review time, J and L drugs had a shorter review time compared with the other drug categories. The drugs in these categories can meet high unmet medical needs, such as drugs used for HIV, HCV, and oncology. As a result, these circumstances can lead to shorter review times. In addition, there were a large number of drugs in J and L that received conditional approval and all-case surveillance (Table 3), which should contribute to a shortening of the review time. Although our findings also suggested that using global data or participating in global studies reduced the review time, the use of bridging strategies did not. These findings are consistent with a previous study that focused on oncology drugs [24], and another research report that demonstrated that compounds with a Japanese origin tended to have less drug lag [25]. Another positive factor for shortening the review period was A, which encompasses the second largest share of drugs used to treat rare metabolic and endocrine-related diseases [26, 27].

In order to shorten the development period, we have attempted to determine the best environment for clinical trials, along with trying to improve the efficiency of data collection for

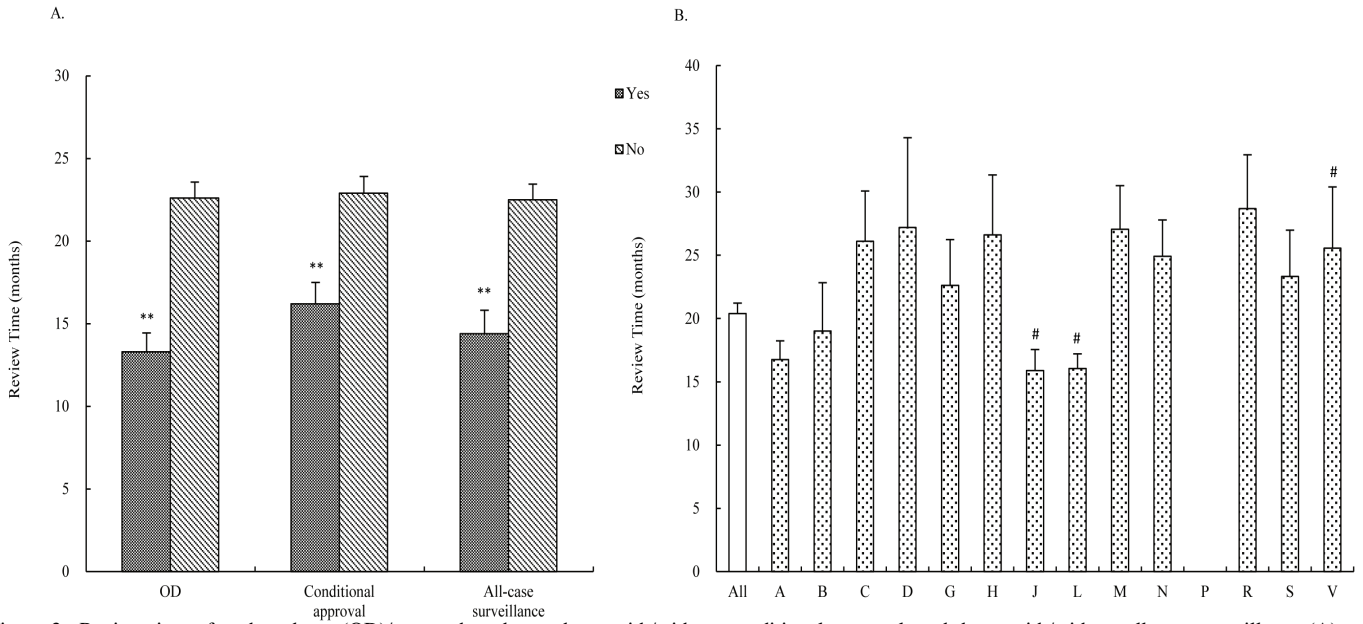
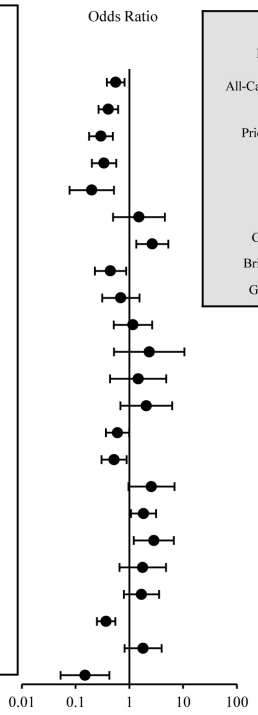


Figure 3. Review time of orphan drugs (OD)/non-orphan drugs, drugs with/without conditional approval, and drugs with/without all-case surveillance (A) and according to the ATC code (B). (A) Significant differences between OD and non-OD, conditional approval drugs and non-conditional approval drugs, and all-case surveillance drugs and non-all-case surveillance drugs were determined by using a Students t-test, with *p<0.05, **p<0.01 set as the levels of significance (n = 468 for all drugs, 108 for OD, 360 for non-OD, 174 for conditional approval, 294 for non-conditional approval, 121 for all-case surveillance, and 347 for non-all-case surveillance) (B) Significant differences between all of the drugs and each code were determined by a one-way ANOVA with Tukeys test, with the significance set as #p<0.05 (n = 468 for all drugs, 55 for A, 31 for B, 25 for C, 7 for D, 11 for G, 13 for H, 94 for J, 84 for L, 17 for M, 63 for N, 0 for P, 23 for R, 16 for S and 29 for V). See Table 1 caption for explanation of the ATC code.

Univariate Analysis

Explanatory Variables	Odds ratio	95% CI Lower limit	95% CI Upper Limit	p
Company Profile	0.6	0.4	0.8	0.00
Conditional Approval	0.4	0.3	0.6	0.00
All-Case Surveillance	0.3	0.2	0.5	0.00
ODD	0.3	0.2	0.6	0.00
Priority Review	0.2	0.1	0.5	0.00
Expedited Review	1.5	0.5	4.6	0.47
Normal Review	2.7	1.3	5.3	0.01
A	0.4	0.2	0.9	0.02
B	0.7	0.3	1.5	0.37
C	1.2	0.5	2.7	0.71
D	2.3	0.5	10.6	0.27
G	1.5	0.4	4.9	0.54
H	2.1	0.7	6.3	0.20
J	0.6	0.4	1.0	0.05
L	0.5	0.3	0.9	0.02
M	2.6	1.0	6.9	0.06
N	1.8	1.1	3.1	0.03
R	2.9	1.2	6.7	0.02
S	1.8	0.7	4.8	0.26
V	1.7	0.8	3.6	0.18
Global Data	0.4	0.2	0.5	0.00
Bridging Study	1.8	0.8	4.0	0.15
Global Study	0.1	0.1	0.4	0.00



Multivariate Analysis

Explanatory Variables	Odds ratio	95% CI Lower limit	95% CI Upper Limit	p
All-Case Surveillance	0.5	0.3	1.1	0.07
ODD	0.4	0.2	0.9	0.02
Priority Review	0.2	0.1	0.6	0.00
A	0.4	0.2	0.9	0.02
J	0.7	0.4	1.2	0.15
R	2.4	0.9	6.5	0.08
Global Data	0.5	0.3	0.8	0.00
Bridging Study	2.8	1.1	7.1	0.03
Global Study	0.2	0.1	0.5	0.00

Hosmer-Lemeshow test

χ^2	df	p
7.2	4	0.1

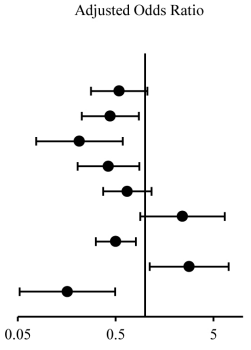


Figure 4. Odds ratio for the drug profiles that accelerated the review time. Univariate or multivariate logistic-regression models were used to estimate the coefficient, with the values then converted to the odds ratio of the acceleration of the review time with the potential predictors described in the table.

the NDA. Based on this aspect, the use of conditional approval and all-case surveillance is important when submitting foreign data. However, specific guidelines that provide details on how to effectively use this system have yet to be created. This article provided guidelines so that PMS system in Japan can be utilized to help deliver innovative drugs to Japanese patients with the least amount of delay. Our current research verified that conditional approval and all-case surveillance shortened the review period. Since conditional approval can be given to drugs that are submitted together with global data, this suggests that conditional approval can contribute to a shortening of the development time and a reduction of the approval period for new drugs.

Considering that Japan has fallen behind with regard to the global development of new drugs, its participation in global studies can assist in the developmental process and reduce the drug lag [28]. Thus, there needs to be a more positive and effective use of these systems in Japan if the country hopes to catch up with the new development that is now being undertaken globally. Achieving this will require an increase in the cost and burden on the pharmaceutical industry [14]. However, this by itself might be advantageous, as it could lead to an acceleration of market approvals in Japan. Thus, we need to seriously consider which of the drugs need to be subjected to these systems, in addition to determining the balance that will be necessary in order to evaluate the drug safety profile between a clinical trial and PMS studies. In the US, there is an opinion that granting an extension of the exclusive marketing rights to those drugs whose long-term safety profile is confirmed in PMS studies would be viewed as an incentive by pharmaceutical companies, while another opinion is that conditional approvals need to be systematized [29, 30].

As several papers have reported [31, 32], approved doses in Japan differ from those reported in the US and EU. Moreover, the doses in Japan are likely to be lower than those that have been approved in Western countries. However, it should be noted that the approved doses in the US are sometimes reduced after marketing approvals are granted. One of the reasons for this is that the maximum tolerated doses estimated by the phase 1 study tend to be taken as recommended doses [33, 34]. Therefore, it is important to collect clinical data during PMS for Japanese patients when there are simultaneous launches due to the participation of Japan in global studies. Needless to say, it is also important to consider the balance between the risks and benefits by launching NMEs in Japan without delay through global trials, since the dose approved in Japan may be changed after conducting the all-case surveillance for several months.

There were two major limitations for our current research. First, we only focused on NMEs. Second, not all of the drugs approved between 2000 and 2014 including drugs that expanded upon the indications, and in addition, there was no comparative analysis of these drugs done between the US and EU. Additional research based on the perspective of these limitations will need to be undertaken in our future studies.

5. Conclusion

The current study clarified the factors affecting the receipt of conditional approval and all-case surveillance, in addition to examining the effects that these factors potentially have on the review time. There was a significant positive correlation between ODD and category L and the receipt of conditional approval and all-case surveillance. However, the PMS examined in this study did not take into consideration ODD and L drugs that have already been launched in the US or the associated safety data that had been previously extrapolated. The review time was significantly reduced by conditional approval and all-case surveillance. Utilization of this PMS system can help deliver innovative drugs to Japanese patients with the shortest possible delay and help solve or provide better solutions for drug lag problems, thereby securing the safety of Japanese subjects and potentially contributing to a better quality of life for these patients.

6. Declaration of Conflicting Interest

The authors declare no conflicts of interest. This research was supported in part by Keio Gakuji Academic Development Funds and MEXT-Supported Program for the Strategic Research Foundation at Private Universities.

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8. Article information

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