TDL.ORG TEXAS DIGITAL LIBRARY

Journal of Regulatory Science

http:\\journalofregulatoryscience.org

Journal of Regulatory Science 8 (2020) 1–9

Regulatory Science

Potential Impact of Accelerated Approval on the Drug Lags for Anticancer Drugs Between the United States and Japan

Takashi Nagasawa[a,*], Atsushi Aruga[a]

[a] *Joint Graduate School of Tokyo Women's Medical University and Waseda University, Tokyo, Japan*

Abstract

The term 'drug lag' represents the difference in the timing of drug approval among countries. The impact of accelerated approvals on the drug lag for anticancer drugs between the United States (U.S.) and Japan was evaluated using publicly available information to identify anticancer drugs approved in the U.S. or Japan between January 2006 and March 2017. A logistic regression analysis was conducted to determine the association between the oncology drugs lags and potential factors, including accelerated approval. The median drug lag was 805 days. The drug lag was extended for drugs that were approved in the U.S. under accelerated approval (884 days) compared to the standard approval (606 days). A total of 170 approvals were available for the analysis of drug lags. A multivariate logistic regression analysis revealed that the following factors contributed significantly to the drug lags ($p<0.05$): accelerated approval (odds ratio [OR] 4.48), Phase III study (OR 3.69), major cancer (OR 0.38), and international/global development (OR 0.32). Accelerated approval in the U.S. is one of the significant factors that extend the drug lags for anticancer drugs. The current drug development and approval process in Japan may have advantages, however, since a new regulation to reduce drug lag for anticancer drugs, the conditional early approval system, may help minimize drug lags and support decision making not only for regulators but also pharmaceutical companies.

Keywords: accelerated approval, anticancer drug, drug lag, Japan, oncology

1. Introduction

The term 'drug lag' refers to the difference in the timing of a drug's approval among countries. A delay in the approval or launch of a new drug results in the loss of patients' opportunity to be treated with the drug, even as patients in another country may benefit from the same drug approved therein. Cancer is one of the major life-threatening diseases worldwide, presenting a high, unmet medical need. Over 14.1 million people are diagnosed with cancer worldwide each year, and the associated mortality exceeds 8.2 million individuals [2]. Research has indicated that approximately one half of the people in Japan are at risk of developing cancer in their lifetimes, and one third of those affected may die due to cancer [16, 22]. Systemic anticancer therapy in an advanced or metastatic cancer setting can prolong a patients' survival and maintain their quality of life by preventing cancer growth. Ideally, all cancer patients should have access to anticancer therapies without delays in the availability of anticancer drugs, which can be a direct threat to the patients' lives.

In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) and the Ministry of Health, Labour and Welfare (MHLW) are the regulatory bodies with important roles in the review and approval of new drugs. Drug lags have been a topic of interest for researchers but are also an urgent issue to be resolved among regulators. Japan's regulatory authorities have taken several steps to minimize the drug lags [26], including the publication of several relevant guidelines such as the notification of the International Conference on Harmonization (ICH) E5 guideline (including Q&A) [10, 31], and a guidance that was made effective in 2006 regarding the clinical evaluation of anticancer drugs, which promoted the acceleration of oncology drug development and approval [19]. In addition, in an effort to accelerate the clinical development of unapproved drugs, a Committee for Unapproved Drugs was formed in 2010 by the MHLW [17]. A designation system named 'Sakigake' was introduced with the goal of accelerating the development and launch time for innovative drug candidates by conducting priority consultations, prior assessments, and priority reviews [18].

In the United States, the Food and Drug Administration (FDA) has four pathways for expediting the development and approvals of drugs that address serious or life-threatening con-

*Corresponding author: Takashi Nagasawa,
Email: Takashi.Nagasawa@pfizer.com

ditions [29]. Of these pathways, the designation 'breakthrough therapy' applies to drugs that have demonstrated substantial improvement over existing therapies, based on preliminary clinical or non-clinical evidence. The 'accelerated approval' pathway is not a designation; rather, it is a unique system that permits the FDA to grant marketing authorization for a drug that has shown a clinical meaningful benefit by surrogate endpoints in early-stage clinical trials. Until recently, Japan did not have an approval system equivalent to the accelerated approval system in the U.S.

Several studies suggested that drug lags have been caused by several factors, including delays in the initiation of clinical trials among countries and longer review periods between new drug applications and drugs approvals [12, 14, 20, 23, 30, 34]. In addition to these potential factors, it has been hypothesized that the lack of an accelerated approval pathway in Japan contributes to the drug lags between Japan and the U.S., especially for anticancer drugs. Although in the European Union (EU), the European Medicines Agency (EMA) has introduced a conditional marketing authorization system that is similar to the U.S. accelerated approval pathway, it has been suggested that the drug lags between Japan and the U.S. are more significant compared to those between Japan and the EU [7, 29]. In the present study, we investigated how accelerated approval affects the drug lags for anticancer drugs between the U.S. and Japan.

2. Methods

The present study targeted anticancer drugs for systemic therapy to treat malignant tumors (except generics) that were approved in the U.S or Japan between January 1, 2006 and March 31, 2017. The approvals for both new therapeutic indications and supplemental indications were included because a single drug might have received multiple approvals for multiple indications during the study period. The information and data analyzed in this study for approved drugs were collected from the lists of approved products, approval letters, review reports, common technical documents, package inserts, and New Drug Application (NDA) and Biologic License Application (BLA) approval reports from the public websites of Japan's PMDA and the U.S. FDA. Taking into account the potential effects of other confounding factors on the drug lags, data was analyzed not only for the dates of regulatory approval and the type of approval (U.S. only), but also for drug indications (e.g., tumor type), drug development style (international/global development and local/bridging strategy), and pivotal trials of drug efficacy evaluations (i.e., the development phase, study design and endpoint). 'Major cancer' was defined as non-small-cell lung cancer, gastric cancer, colorectal cancer, and breast cancer, based on the Guidelines for the Clinical Evaluation of Anticancer Drugs [19]. Complete information about the drug development style was not always available in the FDA's review reports, and all of the drug development styles used in the U.S. were classified as 'international/global' in the present study. The public-knowledge-based application ("Kochi application") was a unique supplemental NDA system in Japan; an additional indication could be granted without conducting all or some clinical trials for drugs whose off-label use is publicly recognized as medically and pharmaceutically validated based on sufficient evidence, such as approvals and substantial clinical use in Western countries (e.g., U.S.), reliable scientific publications or review articles in the international journals, and/or reliable clinical study results conducted by publicly-owned research projects. Because of non-availability of clinical data package, the approvals based on Kochi application was excluded.

'Drug lag' was defined as the approval lag between the two countries, calculated by subtracting each drug approval date in the U.S. from its approval date in Japan. If a drug was approved earlier in Japan than in the U.S., the value was negative. Since some of the drugs were approved in one country within the study period but were not yet approved in the other country, the data collection period was extended until March 31, 2019. If a drug was still not approved by that time, that cut-off date was entered to calculate the drug lags. For investigation of factors that may be associated with a drug lag, the drugs for which there was unavailability of a complete set of information about the clinical data package (i.e., the pivotal study and development style) were excluded. Also excluded were the drugs for which approval was obtained in the U.S. or Japan, but for which development had not begun in the other country. The various drug lag values were not distributed normally, and included several extreme values (Figure. 1); therefore, a logistic regression analysis was conducted. The values were dichotomized using cut-offs: 0: ≤two years; 1: >two years.

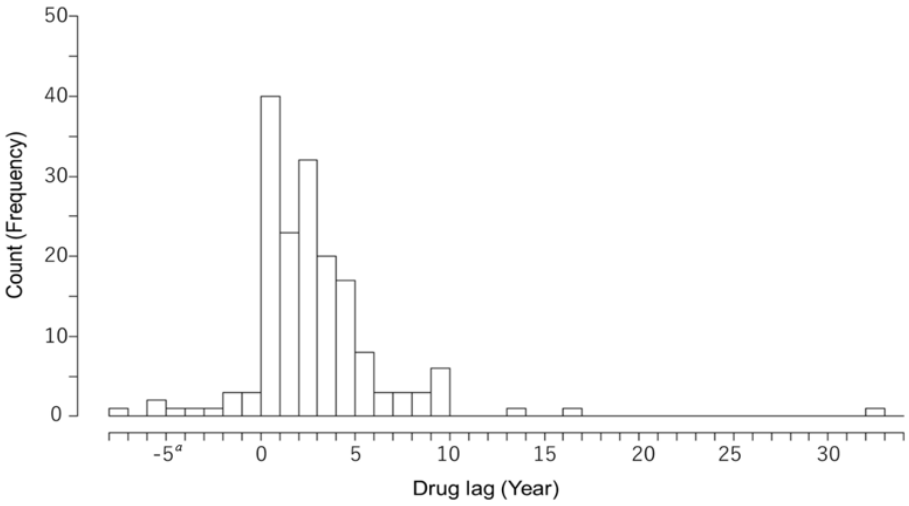
The logistic regression analysis was applied with the binary response of the drug lag and the factors defined above as explanatory variables. A stepwise logistic regression analysis for the selection of predictive variables that may affect the drug lags was conducted. Probability (p)-values <0.05 were accepted as significant. The statistical analyses were performed using Microsoft Excel for Office 365 ver. 1902 and R ver. 3.5.0.

3. Results

The study identified 145 drugs approved in the U.S. and 128 drugs approved in Japan (total = 273 drug approvals). The characteristics of the approved drugs are summarized in Table 1.

The number of drug approvals during each 3-year period from 2006 to 2017 tended to increase in both countries. The vast majority of the drugs (>90 percent) were approved earlier in the U.S. than in Japan. Of the 145 approvals in the U.S., 29 indications were still not approved in Japan as of March 31, 2017. Approximately 30 percent of the drug approvals were accelerated approvals, and the majority of drugs (69.7 percent) were indicated for the treatment of solid tumors. Approximately 30 percent of the approvals were for major cancer indications.

A small between-country difference regarding the pivotal studies for the drug efficacy evaluations was observed. Approximately 80 percent of approvals in Japan were based on late-phase (i.e., Phase III) studies, whereas in the U.S., approximately 35 percent were based on data from early-phase (Phase



[a]Each bar represents the frequencies of the drug lags divided into a year. A negative drug lag value indicates that the drug was approved earlier in Japan vs. the U.S.

Figure 1: Distribution of 170 Anticancer Drugs by the Drug Lag

I or II) studies. Global or international development was used in approximately one-third of the total number of approvals in Japan (34.4 percent).

We were able to analyze the drug lags for a total of 170 approved indications. Each drug lag (in days) by factors is presented using descriptive statistics in Table 2. The median drug lag was 805 days (range -2,556 to 11,831 days). The average drug lag was 1020.9 days (standard deviation [SD] 1,387 days) suggesting greater variability and several extreme values. The drug lag was extended for the drugs that were approved under U.S. accelerated approval (median drug lag, 894 days) compared to the U.S. standard approval (median, 606 days). The proportion of approvals with a drug lag of more than two years was 71.9 percent for the accelerated approvals and 47.8 percent for the standard approvals. Relatively shorter drug lags were observed for solid tumor (649 vs. 1,116 days), major cancer indication (459 vs. 894 days), and international/global development (497 vs. 1,116 days), compared to the other factors.

Before conducting a multivariate logistic regression analysis with all factors as explanatory variables, a univariate logistic regression was performed with each factor, including 'accelerated approval' (Table 3). The coefficient of accelerated approval showed a significant result that contributed to the extension of a drug lag (regression coefficient = 1.03, p = 0.003). "Solid tumor", "major cancer", and "international/global development" were revealed as having significant coefficients that contributed to the shortening of a drug lag ($p<0.05$).

A multivariate logistic regression analysis was then performed to identify the coefficients among the above factors that contributed the most (Table 4). The results of the analysis demonstrated that accelerated approval (odds ratio [OR] 4.48 [95 percent CI: 0.61, 2.39], regression coefficient = 1.50, p = 0.0009) and pivotal Phase III study (OR 3.69 [95 percent CI: 0.03, 2.59], regression coefficient = 1.12, p = 0.045), significantly extended the drug lag, whereas major cancer (OR 0.38 [95 percent CI: -1.78, -0.16], regression coefficient = -0.97, p = 0.019), and international/global development (OR 0.32 [95 percent CI: -1.85, 0.40], regression coefficient = -1.12, p = 0.0024), significantly reduced the drug lag.

4. Discussion

Drug lag has been a social issue and a research focus in Japan for many years [28]. The PMDA remains committed to enhancing consultation services and strengthening the organizational structure to improve both the predictability of drug development and the quality of reviews in order to help resolve the development lag. According to the latest PMDA's five-year report of the drug lag calculation (for all drugs approved in 2013-2017), the drug lags had gradually decreased to 0.4 years by 2017, and the largest drug lag (1.7 years) was observed in 2015 [25]. For anticancer drugs, Maeda et al. (2015) and Ueno et al. (2014) have reported that approximately two-year drug lags existed [14, 30]. The current study confirmed that the median drug lag in anticancer drug still remains at 805 days, and most of the drugs (92.9 percent) were approved earlier in the U.S.; 29 indications were still not approved in Japan. Cancer is one of the major life-threatening diseases worldwide, including Japan, and anticancer therapies help prolong patient's survival and maintain their quality of life (QOL). Represented by the cases of imatinib for chronic myeloid leukemia or crizotinib for ALK positive non-small-cell lung cancer, the new anticancer therapy drastically changed treatment paradigm and improved patients' QOL or survival [3, 27]. Thus, delays in the availability of anticancer drugs can socially and clinically impact cancer patients' lives. Further efforts are needed to resolve this issue.

The present study demonstrated that accelerated approval is one of the significant factors associated with drug lags. To the best of our knowledge, no studies have reported that differences in the approval system between the U.S. and Japan have

	U.S.		Japan	
	n	(%)	n	(%)
Approval years:				
2006-2008	22	(15.2)	15	(11.7)
2009-2011	28	(19.3)	28	(21.9)
2012-2014	44	(30.3)	42	(32.8)
2015-2017	51	(35.2)	43	(33.6)
Earlier approval in Japan	10	(6.9)	11	(8.6)
Earlier approval in the U.S.	135	(93.1)	117	(91.4)
Not yet approved	3		29	
Type of approval:				
U.S. accelerated approval	46	(31.7)	39	(30.5)
Indication				
Tumor types:				
Solid tumor	101	(69.7)	86	(67.2)
Major cancer [a]	43	(29.7)	39	(30.5)
Hematological tumor	44	(30.3)	42	(32.8)
Clinical data package: Pivotal study for efficacy evaluation				
Development phase:				
Phase III (Late phase)	94	(64.8)	100	(78.1)
Phase I or II (Early phase)	51	(35.2)	28	(21.9)
Study design:				
Randomized	107	(73.8)	93	(72.7)
Single arm	38	(26.2)	35	(27.3)
Study endpoint:				
Time-to-event (e.g., PFS [b] , OS [c] , etc.)	94	(64.8)	81	(63.3)
Surrogate (Response rate)	49	(33.8)	40	(31.3)
Surrogate (Others)	2	(1.4)	7	(5.5)
Development style:				
Local/bridging	-	-	84	(65.6)
International/global	145	(100)	44	(34.4)

[a]Major cancers included non-small-cell lung cancer, gastric cancer, colorectal cancer and breast cancer.
[b]PFS = progression-free survival
[c]OS = overall survival

Table 1: Characteristics of the 273 Oncology Drugs Approved in the U.S. (n=145) and Japan (n=128)

affected the drug lags; this is the first study that demonstrates that accelerated approval is one of the significant factors associated with drug lags. It was known that the drug lags were based on complex mechanisms and various factors: a delay in drug development [20, 34] and a delay in submission [8, 21] (i.e., the development lag), a longer review period (i.e., the review lag) [34], the drug development strategy (local or bridging strategy, global strategy) [13, 14], and the size of patient population (i.e., major or minor cancer) [21, 33]. Thus, in order to identify the factors that contributed the most to the drug lags, a multivariate analysis was conducted that could adjust for confounding effects among factors. For the logistic regression analyses, a cutoff value of two years was used to classify anticancer drugs into two groups (a drug lag ≤2 years and >2 years), because two years as a drug lag was likely to be the important threshold for anticancer drugs, considering the fact that the maximum drug lag during the last five years in Japan was 1.7 years [25], and the situation where patients with life-threatening diseases

				Drug lag between the U.S. and Japan (days)			Proportion of approvals with a drug lag of >2 years
	Factor	**n**	**(%)**	**Median**	**(Min,**	**Max)**	**% (n/N)**
Overall and Approval timing		170		805	(-2,556,	11,831)	-
	U.S. first	158	(92.9)	889	(32,	11,831)	-
	Japan first	12	(7.1)	-638	(-2,556,	-24)	-
Approval category in the U.S.	Accelerated approval	57	(33.5)	894	(-524,	4,891)	71.9 (41/57)
	Standard approval	113	(66.5)	606	(-2,556,	11,831)	47.8 (54/113)
Tumor type	Solid tumor	117	(68.8)	659	(-2,106,	11,831)	48.7 (57/117)
	Hematological tumor	53	(31.2)	1,116	(-2,556,	5,869)	71.7 (38/53)
Patient population	Major cancer	51	(30.0)	459	(-2,106,	3,442)	37.3 (19/51)
	Minor cancer *(other than major)*	119	(70.0)	894	(-2,556,	11,831)	63.9 (76/119)
Development phase	Phase III *(Late phase)*	126	(74.1)	783	(-2,106,	5,869)	55.6 (70/126)
	Phase I or II *(Early phase)*	44	(25.9)	790	(-2,556	11,831)	56.8 (25/44)
Study design	Randomized	122	(71.8)	774	(-2,106,	4,891)	52.5 (64/122)
	Single-arm	48	(28.2)	911	(-2,556,	11,831)	64.6 (31/48)
Study endpoint	Time-to-event	110	(64.7)	792	(-2,106,	4,891)	54.5 (60/110)
	Others	60	(35.3)	808	(-2,5556,	11,831)	58.3 (35/60)
Development style	Local/bridging	89	(52.4)	1,116	(-2,556,	11,831)	62.9 (56/89)
	International/global	81	(47.6)	497	(-2,106	3,113)	19.8 (16/81)

Table 2: Summary of drug lags by potential factors

such as cancer are unable to receive new anticancer drugs for more than two years - the significant social and clinical impacts discussed above.

Our analysis also showed that the global development strategy was a factor for shortening the drug lags. The bridging strategy was introduced in Japan after the implementation of the ICH E5 guideline in 1998 [10], and this strategy contributed to the approval of many anticancer drugs that had not been approved. However, there was only a modest impact on the drug lags because the bridging study in Japan was conducted after the results of the overseas Phase III study became available [13]. In recent years, the global development strategy became more common rather than the bridging strategy. The global development strategy enables simultaneous application in multiple regions and greatly decreased the drug lags [1, 9, 30]. The global development strategy can also be used to mitigate the development lag. For example, even if a Phase I study has begun in the U.S., and Japan has not participated in that study, a simultaneous application may be possible by participating in a registrational, global Phase III study. However, the global development strategy may not always be effective, especially for drugs that are used to treat life-threatening diseases such as cancer, because the accelerated approval system in the U.S. allows the FDA to approve anticancer drugs with the data obtained in early stage clinical trials (Phase I/II studies). We observed that even when the global development strategy was applied, drug lags of approximately 859 days existed for anticancer drugs that were approved under the accelerated approval system in the U.S. (data not shown). We also observed that 78.1 percent of the clinical data packages in Japan contained Phase III studies, whereas in the U.S., 35.2 percent of the drug approvals were based on data from early-phase studies. This result suggests that the FDA was relatively active, approving anticancer drugs based on the results from early-stage clinical trials, which seemed to be supported by the regulation on accelerated approval. Taking the past and present findings together, it is apparent that the presence of an accelerated approval system is important for resolving drug lags and for regulators' decision making regarding what level of evidence is to be required for a drug's approval.

From industries' perspective, the clinical development guidance, regulatory systems, and laws in the regions are the key factors when making decisions for investment. The FDA introduced the breakthrough therapy designation in 2012 to accelerate drug development for life-threatening diseases. The FDA provides organizational support and intensive guidance for a designated drug that may demonstrate substantial improvement over the standard therapies. Similarly, "Enhanced early dialogue to facilitate accelerated assessment of PRIority MEdicines (PRIME)" was introduced in the EU [4], and in Japan, the Sakigake Designation System (as a pilot run) [18] has been introduced (Table 5). The accelerated approval system

Variable	Coefficient	Standard error	z-value	p-value
Accelerated approval in the U.S.	1.03	0.35	2.94	0.003 [a]
Solid tumor	-0.98	0.36	-2.75	0.006 [a]
Major cancer	-1.09	0.35	-3.15	0.017 [a]
Phase III (Late phase)	-0.05	0.35	-0.15	0.885
Single-arm study	0.50	0.35	1.43	0.154
Time-to-event endpoint	-0.15	0.32	-0.48	0.635
International/global development	-1.00	0.32	3.14	0.002 [a]

[a] $0.001 \leq p < 0.01$

Table 3: Univariate logistic regression analysis investigating factors that impact drug lags

Variable	Coefficient	Odds ratio	(95% CI)	p-value
(Intercept)	-1.07	0.34	(-2.68, 0.54)	0.191
Accelerated approval in the U.S.	1.50	4.48	(0.61, 2.39)	0.001 [a]
Solid tumor	-0.44	0.64	(-1.34, 0.46)	0.335
Major cancer	-0.97	0.38	(-1.78, -0.16)	0.019 [b]
Phase III (Late phase)	1.31	3.69	(0.03, 2.59)	0.045 [b]
Single-arm study	1.34	3.81	(-0.08, 2.75)	0.06
Time-to-event endpoint	1.06	2.89	(-0.13, 2.25)	0.081
International/global development	-1.12	0.32	(-1.85, 0.40)	0.002 [c]

[a] $p < 0.001$
[b] $0.01 \leq p < 0.05$
[c] $0.001 \leq p < 0.01$

Table 4: Multivariate logistic regression analysis investigating factors that impact drug lags

in the U.S. was introduced in 1996. In Europe, conditional marketing authorization was introduced in 2006 [5], but there was no similar approval system in Japan. One possible reason for the lack of early approval pathway in Japan is that the PMDA has depended on the use of the Guidelines for the Evaluation of Anticancer Drugs effective in 2006. This guideline requires the results of a confirmatory (Phase III) trial at the time of submission for a major cancer indication; however this requirement can be waived if the target number of patients is too small to conduct a confirmatory trial, resulting in the need for a case-by-case discussion with the PMDA [19]. We found that 21.9 percent of approvals were based on the results of early-stage trials (except for four randomized trials, most of the studies were small-sized single-arm trials evaluating tumor response as a primary endpoint), suggesting that those approvals were supported by this guideline. The full development conducted in Japan has the advantage of being able to produce results more safely and reliably than the accelerated approval. Yamada et al. (2010) indicated the benefit of access to safety data accumulated in other countries as a trade-off for delay in access to new drugs in Japan [32]. Okubo et al. (2019) reported that drugs developed under a bridging strategy tended to show lower risks, and that local clinical studies may play a substantial role in achieving optimization of post-marketing drug use [24]. In addition, a case-by-case discussion with the PMDA may support flexible drug development and allow regulators making a flexible decision upon drug approval. As a trade-off, the decision-making process may not be transparent. A concrete regulatory guidance helps guide pharmaceutical companies to establish a drug development strategy, especially in the era of global drug development and simultaneous regulatory submission. Furthermore, the requirement of Phase III may cause delay in access to a promising drug, resulting in missing treatment opportunity for patients suffering from life-threatening major cancer.

The conditional early approval system was introduced in Japan in October 2017 to improve the predictability of drug development, and the system could grant regular approval to promising drugs with approval conditions [15]. The designation criteria include drugs that treat serious diseases for which there are limited treatment options and drugs for which it is not possible to conduct clinical trials or for which clinical trials take too long because the number of patients is small (Table 5). Although the conditional early approval system was implemented and the qualifying criteria looked similar to that in the U.S., it is not comparable to the U.S. accelerated approval. Specifically, Japan's conditional early approval system is not legally institutionalized, and verification of the clinical benefit by post-marketing confirmatory trials is not always a mandatory condition, which is required in the U.S. accelerated approval system [29]. As of September 2019, only two products,

Country	**U.S.**	**EU**	**Japan**
Drag development acceleration program	**Breakthrough Therapy**	**PRIME**	**Sakigake**
Year introduced	2012	2016	2015
Features	(a) Intensive guidance on efficient drug development (b) Organizational commitment (c) Rolling review (d) Other actions to expedite review	(a) Enhanced interaction and early dialogue with developers of promising medicines (b) Optimized development plans and speedier evaluations so that these medicines can reach patients earlier	(a) Developed ahead of the world (b) Designated at an early stage of clinical trials, and aimed for early commercialization with various types of support (for example, six months review period)
Accelerated approval program	**Accelerated Approval**	**Conditional Marketing Authorization**	**Conditional Early Approval**
Year introduced	1996	2006	2017
Qualifying criteria	(a) Generally, provides a meaningful advantage over available therapies (b) Demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or or other clinical benefit	(a) The risk-benefit balance of the product is positive (b) It is likely that the applicant will be able to provide comprehensive data (c) Fulfilment of unmet medical need (d) The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required	(a) High medical benefits as a result of comprehensive evaluation (b) It is difficult to conduct a confirmatory clinical trial, or it takes a considerable time because the number of patients is too small (d) A certain level of efficacy and safety are demonstrated based on the results of clinical trials other than confirmatory clinical trials

Table 5: Comparison of expedited programs for serious conditions in the U.S., EU, and Japan

lorlatinib and pembrolizumab, have been approved under the conditional early approval system in Japan. Both drugs were also granted accelerated approval in the U.S. Lorlatinib was approved earlier in Japan; the drug lag was -41 days (Japan approval: Sept. 21, 2018 and U.S. approval: Nov. 2, 2018). For pembrolizumab, the drug lag was 578 days (Japan approval: Dec. 21, 2018 and U.S. approval: May 23, 2017). Although the numbers of cases are limited, the conditional early approval system may help pharmaceutical companies predict drug development and submission paths and also help regulators make approval decisions with the data obtained in early stage trials, leading to a reduction of the drug lags for anticancer drugs. On the other hand, one should be cautious about potential unidentified risks for the drugs approved with the limited clinical data. In 2002, gefitinib was approved in Japan ahead of the western countries, with pivotal Phase II data. After the approval, the risk of treatment-related deaths with interstitial lung disease were reported, and the follow-up Phase III study indicated that gefitinib was not effective in patients without epidermal growth factor receptor (EGFR) active mutations [6, 11]. The mechanism of safety monitoring or surveillance at the post-marketing setting may become more important for the accelerated approvals. A requirement of post-marketing confirmatory study should be discussed when Japan's conditional early approval system is legally institutionalized. Further regulatory science activity is warranted among stakeholders, including regulators and industries.

Our study has a limitation in that it targeted only anticancer drugs, and the results may not be applicable to other drug categories. In addition, only drugs that have received regulatory approval in the U.S. and Japan were examined. Terminated or discontinued drugs were not evaluated, and drugs approved in the EU were not included. In addition, the business decisions made by pharmaceutical companies were not included as a potential factor associated with development lags because the development and submission strategies, as well as investment decisions, by pharmaceutical companies, were not publicly available. However, to avoid a possible confounding effect that may be associated with the business decision, drugs for which clinical development has not been initiated in either country during the study period were excluded.

5. Conclusion

We characterized approximately 140 oncology drugs approved in the U.S. and 130 oncology drugs approved in Japan

over the past 11 years. There was an approximate two-year gap in drug approval between the U.S. and Japan for the oncology drugs. The application of accelerated approvals in the U.S. was shown to be one of the significant factors that extended the lags between the U.S. and Japan in their approvals of anticancer drugs. Although there are advantages in the way of anticancer drug development and case-by-case based discussion with PMDA in Japan, new regulations may be needed to resolve the drug lag for anticancer drugs. The newly launched conditional accelerated approval system in Japan may help minimize the drug lags and support decision making not only for regulators but also pharmaceutical companies.

6. Declaration of Conflicting Interest

The authors declare no conflicts of interest. No funding support was obtained for this research.

7. Disclaimer

Takashi Nagasawa is an employee of Pfizer R&D Japan G.K. His affiliation and the company did not influence the results or discussion in this paper

8. Acknowledgement

We thank Norisuke Kawai, an employee of Pfizer R&D Japan G.K. who provided technical advice on the statistical analyses.

9. Article Information

This article was received January 5, 2020, in revised form March 27, 2020, and made available online August 12, 2020.

10. References

[1] Asano, K., Tanaka, A., Sato, T., & Uyama, Y. (2013). Regulatory Challenges in the Review of Data From Global Clinical Trials: The PMDA Perspective. *Clinical Pharmacology and Therapeutics, 94*(2), 195-198. doi: 10.1038/clpt.2013.106

[2] Cancer Today. (2012). Cancer Fact Sheet. Retrieved September 30, 2019 from https://gco.iarc.fr/today/fact-sheets-cancers

[3] Druker, B. J., Guilhot, F., O'Brien, S. G., Gathmann, I., Kantarjian, H., Gattermann, N., Deininger, M. W. N., Silver, R. T., Goldman, J. M., Stone, R. M., Cervantes, F., Hochhaus, A., Powell, B. L., Gabrilove, J. L., Rousselot, P., Reiffers, J., Cornelissen, J. J., Hughes, T., Agis, H., Fischer, T., Verhoef, G., Shepherd, J., Saglio, G., Gratwohl, A., Nielsen, J. L., Radich, J. P., Simonsson, B., Taylor, K., Baccarani, M., So, C., Letvak, L., & Larson, R. A. (2006). Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia. *New England Journal of Medicine, 355*(23), 2408-2417. doi: 10.1056/NEJMoa062867

[4] European Medicines Agency. (2018). *Enhanced early dialogue to facilitate accelerated assessment of PRIority Medicines (PRIME)*. Retrieved September 30, 2019 from https://www.ema.europa.eu/documents/regulatory-procedural-guideline/enhanced-early-dialogue-facilitate-accelerated-assessment-priority-medicines-prime_en.pdf

[5] European Medicines Agency. (2016). *Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004*. Retrieved September 30, 2019 from https://www.ema.europa.eu/documents/scientific-guideline/guideline-scientific-application-practical-arrangements-necessary-implement-commission-regulation-ec/2006-conditional-marketing-authorisation-medicinal-products-human-use-falling_en.pdf

[6] Fukuoka, M., Wu, Y-L, Thongprasert, S., Sunpaweravong, P., Leong, S-S., Sriuranpong, V., Chao, T-Y, Nakagawa, K., Chu, D-T., Saijo, N., Duffield, E. L., Rukazenkov, Y., Speake, G., Jiang, H., Armour, A. A., To, K-F., Yang, J. C-H., & Mok, T. S. K. (2011). Biomarker Analyses and Final Overall Survival Results From a Phase III, Randomized, Open-Label, First-Line Study of Gefitinib Versus carboplatin/paclitaxel in Clinically Selected Patients With Advanced Non-Small-Cell Lung Cancer in Asia (IPASS). *Journal of Clinical Oncology, 29*(21), 2866-2874. doi: 10.1200/JCO.2010.33.4235

[7] Hartmann, M., Mayer-Nicolai, C., & Pfaff, O. (2013). Approval Probabilities and Regulatory Review Patterns for Anticancer Drugs in the European Union. *Critical Reviews in Oncology/Hematology, 87*(2), 112-121. doi: 10.1016/j.critrevonc.2013.01.004

[8] 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 US. *Health Policy, 104*(3), 241-246. doi: 10.1016/j.healthpol.2011.11.008

[9] Honig, P.K. (2014). Recent Trends and Success Factors in Reducing the Lag Time to Approval of New Drugs in Japan. *Clinical Pharmacology and Therapeutics, 95*(5), 467-469. doi: 10.1038/clpt.2013.256

[10] International Conference of Harmonization Expert Working Group. *Ethnic Factors in the Acceptability of Foreign Clinical Data E5 (R1)*. Retrieved September 30, 2019 from https://www.pmda.go.jp/files/000156836.pdf

[11] Inoue, A., Saijo, Y., Maemondo, M., Gomi, K., Tokue, Y., Kimura, Y., Ebina, M., Kikuchi, T., Moriya, T., & Nukiwa, T. (2003). Severe Acute Interstitial Pneumonia and Gefitinib. *Lancet, 361*(9352), 137-139. doi: 10.1016/S0140-6736(03)12190-3

[12] Kawabata-Shoda, E., Masuda, S., & Kimura, H. (2012). Anticancer Drug Development From Traditional Cytotoxic to Targeted Therapies: Evidence of Shorter Drug Research and Development Time, and Shorter Drug Lag in Japan. *Clinical Pharmacology and Therapeutics, 37*(5), 547-552. doi: 10.1111/j.1365-2710.2012.01332.x

[13] 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

[14] Maeda, H., & Kurokawa, T. (2015). 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

[15] Ministry of Health, Labour and Welfare. (2017). *Conditional Early Approval System for Drugs* (in Japanese). Retrieved September 30, 2019 from https://www.pmda.go.jp/files/000220723.pdf

[16] Ministry of Health, Labour and Welfare. (2017). *Demographic Statistics (Confirmed Number) in 2017* (in Japanese). Retrieved September 30, 2019 from https://www.mhlw.go.jp/toukei/saikin/hw/jinkou/kakutei17/index.html

[17] Ministry of Health, Labour and Welfare. (n.d.). *Review Meeting for Unapproved and Off-label Drugs with High Medical Need* (in Japanese). Retrieved September 30, 2019 from http://www.mhlw.go.jp/stf/shingi/other-iyaku_128701.html

[18] Ministry of Health, Labour and Welfare. (n.d.). *Sakigake Designation System* (in Japanese). Retrieved September 30, 2019 from http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/topics/tp150514-01.html

[19] Ministry of Health, Labour and Welfare. (2005). *The Revision of the Guideline for Clinical Evaluation Methods of Anticancer Drugs in Japan* (in Japanese). Retrieved September 30, 2019 from https://www.pmda.go.jp/files/000206740.pdf

[20] Nakajima, K., Dagher, R., Strawn, L., Urushidani, J., Kurokawa, T., & Chiba, K. (2015). The Relationship Between Development Start

Lag and Approval Lag in Oncology Drug Development in Japan. *Therapeutic Innovation and Regulatory Science, 49*(6), 911-919. doi: 10.1177/2168479015579518

[21] Nakayama, H., Matsumaru, N., & Tsukamoto, K. (2019). The Drug Lag and Associated Factors for Orphan Anticancer Drugs in Japan Compared to the United States. *Investigational New Drugs, 37*(5), 1086-1093. doi: 10.1007/s10637-018-0612-y

[22] National Cancer Center. Cancer Information Service (in Japanese). Retrieved September 30, 2019 from http://ganjoho.jp/reg_stat/statistics/stat/summary.html

[23] Ohwaki, K., & Nakabayashi, T. (2014). Relationship Between Drug Lag and Factors Associated With Clinical Trials in Japan. *Journal of Clinical Pharmacy and Therapeutics, 39*(6), 649-652. doi: 10.1111/jcpt.12202

[24] Okubo, T. K., & Ono S. (2019). Analysis of Global Drug Development Pathways and Postmarketing Safety in Japan: Local Studies May Reduce Drug-Related Deaths. *Clinical and Translational Science, 12*(4), 408-415. doi: 10.1111/cts.12631

[25] Pharmaceuticals and Medical Devices Agency. Estimation of Drug Lag (in Japanese). Retrieved September 30, 2019 from https://www.pmda.go.jp/files/000227686.pdf

[26] Sinha, G. (2010). Japan Works To Shorten "Drug Lag", Boost Trials of New Drugs. *Journal of the National Cancer Institute, 102*(3), 148-151. doi: 10.1093/jnci/djq017

[27] Solomon, B. J., Mok, T., Kim, D-W., Wu, Y-L., Nakagawa, K., Mekhail, T., Felip, E., Cappuzzo, F., Paolini, J., Usari, T., Iyer, S., Reisman, A., Wilner, K. D., Tursi, J., & Blackhall, F. (2014). First-line Crizotinib Versus Chemotherapy in ALK-positive Lung Cancer. *The New England Journal of Medicine, 371*(23), 2167-2177. doi: 10.1056/NEJMoa1408440

[28] Tsuji, K., & Tsutani, K. (2008). Follow the leader. *Nature, 453*, 851-852.

[29] U.S. Food and Drug Administration. (2014, May). Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics. Retrieved September 30, 2019 from https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf

[30] 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 and Therapeutics, 95*(5), 533-541. doi: 10.1038/clpt.2013.223

[31] Uyama, Y., Shibata, T., Nagai, N., Hanaoka, H., Toyoshima, S., & Mori, K. (2005) Successful bridging strategy based on ICH E5 guideline for drugs approved in Japan. *Clinical Pharmacology and Therapeutics, 78*(2), 102-113. doi: 10.1016/j.clpt.2005.04.001

[32] Yamada, T., Kusama, M., Hirai, Y., Arnold, F., Sugiyama, Y. & Ono, S. (2010). Analysis of Pharmaceutical Safety-Related Regulatory Actions in Japan: Do Tradeoffs Exist Between Safer Drugs and Launch Delay? *The Annals of Pharmacotherapy, 44*(12), 1976-1985. doi: 10.1345/aph.1P153

[33] Yamashita, K., Kaneko, M., & Nakamura, M. (2019). A Significant Anticancer Drug Approval Lag Between Japan and the United States Still Exists for Minor Cancers. *Clinical Pharmacology and Therapeutics, 105*(1), 153-60. doi: 10.1002/cpt.1136

[34] Yonemori, K., Hirakawa, A., Ando, M., Hirata, T. Yunokawa, M., Shimizu, C., Katsumata, N., Tamura, L., & Fujiwara, Y. (2011). The Notorious "Drug Lag" for Oncology Drugs in Japan. *Investigational New Drugs, 29*(4), 706-712. doi: 10.1007/s10637-011-9638-0