Investigational New Drugs (2019) 37:1086–1093
https://doi.org/10.1007/s10637-018-0612-y

PHASE III STUDIES

The drug lag and associated factors for orphan anticancer drugs in Japan compared to the United States

Hiroki Nakayama[1] · Naoki Matsumaru[2] · Katsura Tsukamoto[2]

Received: 6 April 2018 / Accepted: 24 May 2018 / Published online: 31 May 2018

Summary

The approval of orphan anticancer drugs in Japan has increased to meet high social demand. Drug lag, namely the approval lag of new drugs, is recognized as a social issue in Japan. We investigated the approval lag and its components, submission lag and review-time lag, between Japan and the United States (US) to reveal whether an approval lag still exists, and to identify potential factors that may contribute to reducing the approval lag. Anticancer drugs approved in Japan between April 2004 and November 2017 were investigated using publicly available information. Results showed that the median approval lag of orphan anticancer drugs in 2016–2017 was 727.0 days (interquartile range, IQR, 310.0–1054.3). The approval lag was significantly correlated with the submission lag (correlation coefficient = 1.00, $P < 0.001$) but not with the review-time lag (correlation coefficient = −0.16, $P = 0.22$). The submission lag was significantly longer for orphan anticancer drugs than non-orphan drugs (median, 712.5 days [IQR, 186.0–1448.3] vs. 387.0 days [92.8–1096.0], $P = 0.023$). External collaboration in drug development was associated with a longer submission lag (coefficient = 762.1, $P = 0.017$), while breakthrough therapy designation in the US was associated with a shorter submission lag (coefficient = −832.8, $P = 0.035$). In conclusion, we revealed that an approval lag for orphan anticancer drugs still existed in 2016–2017. A submission lag for orphan anticancer drugs was the main component affecting the approval lag, and was longer than that for non-orphan drugs. External collaboration in drug development may be a potential factor in reducing the submission lag for orphan anticancer drugs.

Keywords Cancer · Orphan drug · Drug lag · Japan · External collaboration · Breakthrough therapy designation

Introduction

The attention given to rare cancers has increased over the past decade, largely due to: (i) they collectively comprise 20% of cancers, (ii) their mortality rate is higher than that of common cancers, and (iii) proper therapeutic management is not readily available [1, 2]. Despite this increased attention, however, drug development for rare cancers remains insufficient. A major reason for this is that, due to their rarity, the cost of drug development for rare diseases cannot be recovered by the expected sales of the drug under normal market conditions [3].

Health authorities and regulatory agencies have introduced orphan drug designation systems to stimulate research and development (R&D) of drugs for rare diseases, including those for rare cancers in the United States (US) in 1983 and in Japan in 1993 [3]. Orphan drug designation provides pharmaceutical companies with incentives to conduct drug development for rare diseases. In Japan, these incentives include the following: (i) subsidy payment, (ii) extra guidance and consultation on R&D for the drugs, (iii) preferential tax treatment, (iv) priority review by the Pharmaceuticals and Medical Devices Agency (PMDA), and (v) extension of the re-examination period for up to ten years after approval of the drugs [4]. The number of drugs designated as orphan drugs has increased in the US and Japan since the designation systems were first put in place [5].

Drug lag, namely the approval lag of a drug as compared to other countries such as the US, is recognized as a social issue in Japan, in terms that the unavailability of new drugs due to

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10637-018-0612-y) contains supplementary material, which is available to authorized users.

✉ Hiroki Nakayama
hiroki.nakayama@astellas.com

[1] Healthcare Policy & CSR, Astellas Pharma Inc., 2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo 103-8411, Japan

[2] Global Regulatory Science, Gifu Pharmaceutical University, 1-25-4, Daigakunishi, Gifu 501-1196, Japan

the approval lag negatively impacts the population's health. An approval lag consists of two types of delay, a submission lag and a review-time lag [6].

Anticancer drugs are prescribed for the treatment of cancer, a life threatening disease. An approval lag for anticancer drugs therefore constitutes a direct threat to life, and has historically attracted substantial attention [7]. While several studies have examined the approval lag and its components for anticancer drugs [7–9], we are unaware of any studies which have investigated the lag for orphan anticancer drugs, despite the increasing approval of orphan anticancer drugs in Japan [10].

In this study, we first investigated whether an approval lag for orphan anticancer drugs still exists. Second, we compared the submission lag between orphan and non-orphan anticancer drugs. We also analyzed factors associated with the submission lag for orphan anticancer drugs. We specifically investigated the lag between Japan and the US because the approval lag for anticancer drugs is longer between Japan and the US than that between Japan and the EU [7], and also because a larger number of new molecular entities are approved in the US than in the EU [11].

Materials and methods

Sample identification

This study targeted all anticancer drugs approved in Japan as new active ingredients or as a new indication from April 2004 to November 2017 for systemic therapy to treat malignant tumors. Figure 1 shows the flowchart of sample identification. Of 255 indications of 129 anticancer drugs approved in Japan, the following indications were excluded: (i) indications whose PMDA review reports were not available; (ii) indications that were approved for benign tumors, palliative therapy or supportive therapy, including adjuvant therapy; (iii) indications that were not approved for comparable indications in the US; and (iv) indications whose new drug application (NDA) or biologics license application (BLA) dates in the US were not available. As a result, 142 indications of 84 anticancer drugs were analyzed in this study.

Data collection

Data on anticancer drugs approved in Japan were obtained from lists of approved products, review reports, package inserts, and common technical documents available from the PMDA website. Information related to the review of drugs by the US Food and Drug Administration (FDA) was collected from approval letters, review reports, package inserts, and NDA and BLA approval reports available from the FDA website.

If several indications were approved in one NDA based on different pivotal studies, each indication was treated as a different NDA. The approval lag was calculated by subtracting the approval date in the US from that in Japan. The submission lag was calculated by subtracting the date of the NDA or BLA in the US from the date of the NDA in Japan. We defined review time as the period between the date of the NDA or BLA and approval in the US and between the date of the NDA and approval in Japan. We calculated the review-time lag by subtracting the review time by the FDA from that by the PMDA.

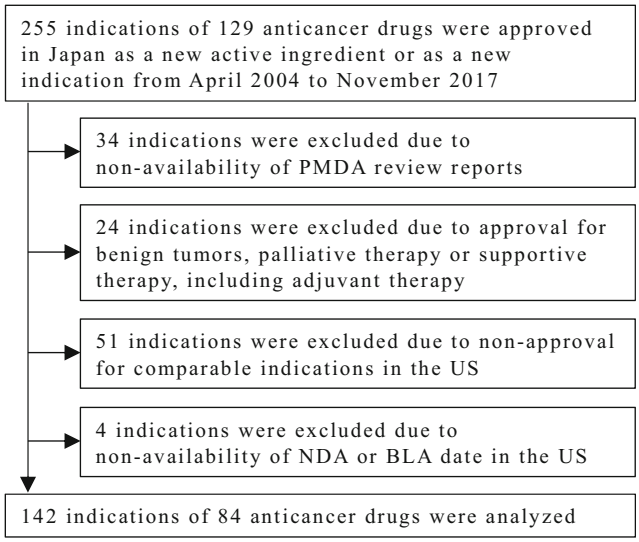

Fig. 1 Flowchart of sample identification

We defined an orphan anticancer drug as an anticancer drug designated as an orphan drug in Japan [4]. If the applicants of a drug were different between Japan and the US, the R&D strategy of the drug was recognized as an external collaboration, in reference to a previous study [12]. Development strategy consisted of four components: bridging strategy, global clinical trial, independent development in Japan, and public knowledge-based application. A bridging strategy is defined as a strategy that extrapolates foreign pivotal studies as the main clinical data in a data package in Japan. A public knowledge-based application is a system in Japan in which a current off-label use drug can be approved without further clinical studies if sufficient evidence for the drug is available and the drug is sufficiently well known [13]. Type of drug consisted of four kinds of drug, namely cytotoxic drug, hormonal drug/ antagonist, molecular targeted drug, and other anticancer drug. We defined a molecular targeted drug as a drug known to target a specific molecule, in reference to a past study [14].

Statistical analysis

Correlations between the approval lag and submission lag or review-time lag for orphan anticancer drugs were identified based on Pearson's product moment correlation coefficient.

The Mann-Whitney U test was used to compare the submission lag and review-time lag between orphan and non-orphan anticancer drugs. We used a multiple regression analysis to identify potential factors associated with a submission lag. Independent variables were selected using backward/forward stepwise selection according to Akaike's Information Criterion. All statistical analyses were performed using EZR software [15] version 1.36, with $\alpha = 0.05$ as the statistically significant threshold.

Given that the submission lag is caused by delays in or extended periods of clinical development in Japan [6], we hypothesized that it was potentially affected by the factors "company characteristics", "R&D strategy", "drug characteristics", and "regulatory status in the US." For company characteristics, we selected "company nationality" as an independent variable because a previous study reported a shorter submission lag in drug development by Japanese companies than non-Japanese companies [12]. Three independent variables were selected for the R&D strategy, namely "external collaboration", "bridging strategy", and "global clinical trial". A previous study demonstrated that an alliance or licensing for drug development has a major impact on the submission lag [12]. A bridging strategy tends to be adopted when there is a time lag in drug development [12], and is associated with a lag in the start of development of anticancer drugs in Japan [9]. In contrast, a global clinical trial is associated with a shorter submission lag [6]. Among drug characteristics, "cytotoxic drug" was used as an independent variable, because these drugs are

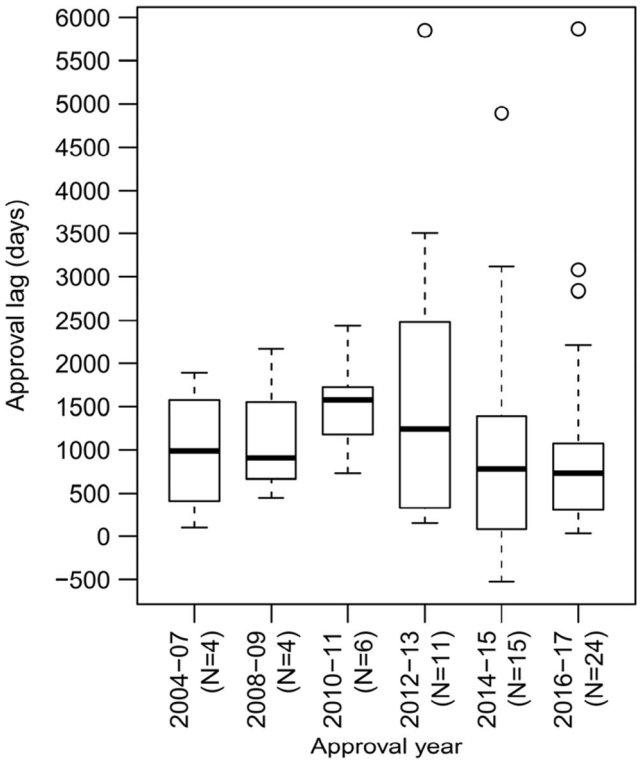

Fig. 2 Trend in the approval lag for orphan anticancer drugs between 2004 and 2017. The bold horizontal line in each box shows the median. The line at the upper edge of each box shows the 75th percentile and that at the lower edge shows the 25th percentile. The upper limit of the vertical line is the maximum value within the 75th percentile plus 1.5 times the interquartile range and that at the lower limit is the minimum value within the 25th percentile minus 1.5 times the interquartile range. The plotted points are outliers

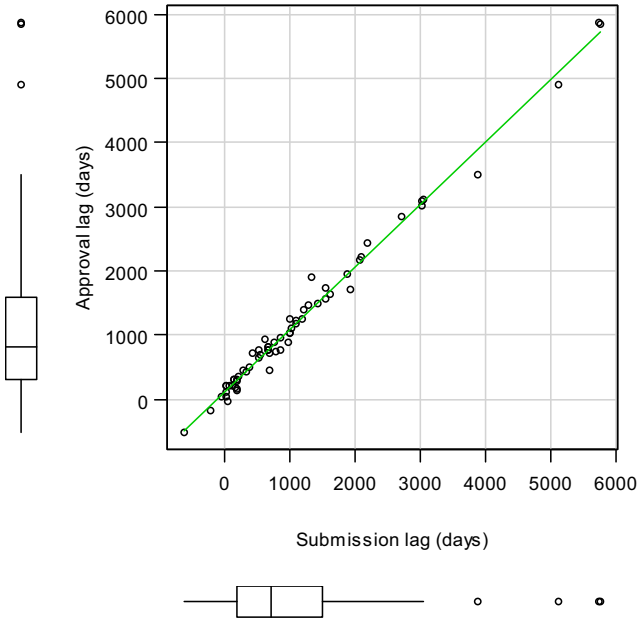

Fig. 3 Scatter plot of the approval lag and submission lag for orphan anticancer drugs. The diagonal line indicates the least-squares regression. The box-and-whisker plots on the left and bottom show the distribution of the approval lag and submission lag, respectively

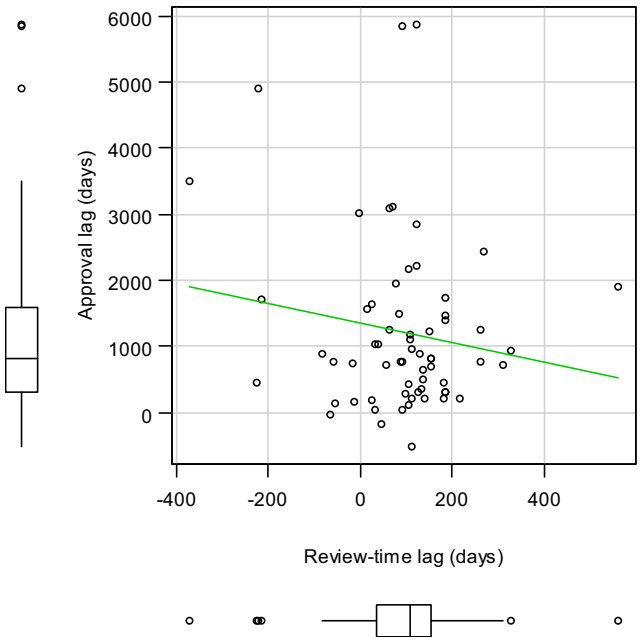

Fig. 4 Scatter plot of the approval lag and review-time lag for orphan anticancer drugs. The diagonal line indicates the least-squares regression. The box-and-whisker plots on the left and bottom show the distribution of the approval lag and review-time lag, respectively

Table 1 Summary of the analyzed anticancer drugs

Factor	Item	Anticancer drug *N* (%)	
		Orphan *N* = 64	Non-orphan *N* = 78
Company characteristics	Company nationality		
	Japanese	16 (25.0)	16 (20.5)
	Non-Japanese	48 (75.0)	62 (79.5)
R&D strategy	External collaboration		
	Yes	26 (40.6)	22 (28.2)
	No	38 (59.4)	56 (71.8)
	Development strategy		
	Bridging strategy	40 (62.5)	44 (56.4)
	Global clinical trial	16 (25.0)	30 (38.5)
	Independent development in Japan	7 (10.9)	2 (2.6)
	Public knowledge-based application	1 (1.6)	2 (2.6)
Drug characteristics	Type of tumor		
	Solid tumor	27 (42.2)	71 (91.0)
	Hematologic malignancy	37 (57.8)	7 (9.0)
	Type of drug		
	Cytotoxic drug	10 (15.6)	17 (21.8)
	Hormonal drug/antagonist	0 (0.0)	7 (9.0)
	Molecular targeted drug	49 (76.6)	49 (62.8)
	Other anticancer drug	5 (7.8)	5 (6.4)
Regulatory status in Japan	Type of NDA		
	iNDA	48 (75.0)	35 (44.9)
	sNDA	16 (25.0)	43 (55.1)
	Priority review by the PMDA		
	Yes	64 (100.0)	35 (44.9)
	No	0 (0.0)	43 (55.1)
	Development status in Japan at approval in the US		
	Approved	3 (4.7)	4 (5.1)
	Under review by the PMDA	9 (14.1)	25 (32.1)
	Under development	28 (43.8)	31 (39.7)
	Not developed	24 (37.5)	18 (23.1)
Regulatory status in the US	Orphan drug designation by the FDA		
	Yes	59 (92.2)	27 (34.6)
	Other	5 (7.8)	51 (65.4)
	Breakthrough therapy designation by the FDA		
	Yes	12 (18.8)	8 (10.3)
	Other	52 (81.2)	70 (89.7)
	Accelerated approval by the FDA		
	Yes	31 (48.4)	15 (19.2)
	Other	33 (51.6)	63 (80.8)
	Priority review by the FDA		
	Yes	53 (82.8)	60 (76.9)
	Other	11 (17.2)	18 (23.1)

FDA, US Food and Drug Administration; iNDA, initial new drug application; PMDA, Pharmaceuticals and Medical Devices Agency; R&D, research and development; sNDA, supplemental NDA; US, United States

associated with a greater lag at the start of the development of anticancer drugs in Japan [9]. Furthermore, we speculated that cytotoxic drugs may require longer clinical development in Japan, especially in dose escalation studies, compared to the

other types of drugs because of their narrow therapeutic range [14]. For regulatory status in the US, we selected "breakthrough therapy designation by the FDA" and "accelerated approval by the FDA" because these represent FDA programs intended to facilitate and expedite the development of new drugs [16].

Results

Approval lag for orphan anticancer drugs

From April 2004 to November 2017, 84 anticancer drugs were approved for 142 indications, of which 64 indications were for orphan anticancer drugs and 78 were for non-orphan drugs. A list of these 142 indications for 84 anticancer drugs and the factors analyzed in this study is shown in Table S1.

Figure 2 shows the trend in the approval lag for orphan anticancer drugs between 2004 and 2017. The median approval lag in 2016–2017 was 727.0 days (interquartile range, IQR, 310.0–1054.3).

We next investigated correlations between the approval lag and its components, submission lag and review-time lag, for orphan anticancer drugs. Figure 3 presents a scatter plot of the approval lag and submission lag for orphan anticancer drugs. Figure 4 shows a scatter plot of the approval lag and review-time lag for orphan anticancer drugs. The approval lag was significantly correlated with the submission lag (correlation coefficient = 1.00, $P < 0.001$), but was not correlated with the review-time lag (correlation coefficient = −0.16, $P = 0.22$). These results suggest that the submission lag is the main component affecting the approval lag for orphan anticancer drugs.

Comparison of the submission lag between orphan and non-orphan anticancer drugs

Based on our finding that the submission lag is the main component affecting the approval lag for orphan anticancer drugs, we compared the submission lag between orphan and non-orphan anticancer drugs. We also compared the review-time lag between orphan and non-orphan anticancer drugs as a supplemental analysis. Table 1 presents the characteristics of analyzed orphan and non-orphan anticancer drugs. Figure 5 compares the submission lag between orphan and non-orphan anticancer drugs, showing that this lag was significantly longer for orphan anticancer drugs than non-orphan drugs (median, 712.5 days [IQR, 186.0–1448.3] vs. 387.0 days [92.8–1096.0], $P = 0.023$). In contrast, the review-time lag was significantly shorter for orphan anticancer drugs than non-orphan drugs (median, 107.0 days [IQR, 36.0–152.0] vs. 157.5 days [61.5–215.5], $P = 0.018$).

Factors associated with the submission lag of orphan anticancer drugs

To investigate the longer submission lag of orphan anticancer drugs in more detail, we performed multiple regression analysis to identify factors associated with this lag. Table 2 shows the independent variables used to analyze orphan anticancer drugs. We observed a longer submission lag for external collaboration as R&D strategy than for non-external collaboration. In contrast, we saw a shorter lag for global clinical trial as development strategy than bridging strategy. Cytotoxic drugs had a longer submission lag than the other types of drug, including molecular targeted drugs. Orphan anticancer drugs designated as breakthrough therapy by the FDA had a shorter submission lag than drugs without breakthrough therapy designation, whereas accelerated approval did not appear to affect the submission lag.

Table 3 presents factors associated with the submission lag for orphan anticancer drugs. External collaboration was significantly associated with a longer submission lag (coefficient = 762.1, $P = 0.017$), while breakthrough therapy designation by the FDA was significantly associated with a shorter submission lag (coefficient = −832.8, $P = 0.035$).

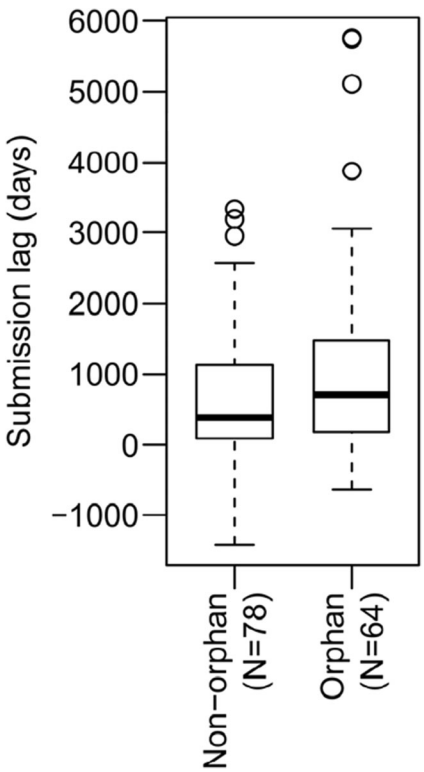

Fig. 5 Comparison of the submission lag between orphan and non-orphan anticancer drugs. The bold horizontal line in each box shows the median. The line at the upper edge of each box shows the 75th percentile and that at the lower edge shows the 25th percentile. The upper limit of the vertical line is the maximum value within the 75th percentile plus 1.5 times the interquartile range and that at the lower limit is the minimum value within the 25th percentile minus 1.5 times the interquartile range. The plotted points are outliers

Table 2 Independent variables for orphan anticancer drugs

Factor	Independent variables	*N*	Submission lag (median [IQR]) (days)
Company characteristics	Company nationality		
	Japanese	16	711.0 (35.8–2383.3)
	Non-Japanese	48	720.5 (249.0–1356.0)
R&D strategy	External collaboration		
	Yes	26	999.0 (660.8–2580.0)
	No	38	529.0 (165.8–1251.3)
	Development strategy		
	Bridging strategy	40	996.0 (586.3–1562.8)
	Global clinical trial	16	182.0 (118.0–602.5)
	Other	8	814.0 (−23.0–1928.5)
Drug characteristics	Type of drug		
	Cytotoxic drug	10	2444.0 (477.0–3015.8)
	Other	54	670.0 (186.0–1194.3)
Regulatory status in the US	Breakthrough therapy designation by the FDA		
	Yes	12	171.5 (98.0–382.8)
	Other	52	977.0 (486.5–1676.5)
	Accelerated approval by the FDA		
	Yes	31	753.0 (341.5–1305.0)
	Other	33	672.0 (178.0–1547.0)

FDA, US Food and Drug Administration; IQR, interquartile range; R&D, research and development; US, United States

To explore factors affecting relationships between submission lag and breakthrough therapy designation or accelerated approval, we conducted a supplemental analysis of development status in Japan at approval in the US of orphan anticancer drugs with or without breakthrough therapy designation and accelerated approval. As shown in Table 4, the percentage of orphan anticancer drugs with breakthrough therapy designation whose clinical development was started in Japan before approval in the US was higher than that of drugs without breakthrough therapy designation (91.7% vs. 55.8%). On the other hand, the percentage of orphan anticancer drugs with accelerated approval whose clinical development was started in Japan before approval in the US was almost the same as that of drugs without accelerated approval (61.3% vs. 63.6%).

Discussion

We demonstrated that submission lag is the main component affecting the approval lag for orphan anticancer drugs in Japan. Given that the submission lag is longer for orphan anticancer drugs than non-orphan drugs, we consider that the submission lag for orphan anticancer drugs can potentially be reduced. In contrast, the review-time lag was shorter for orphan anticancer drugs than non-orphan drugs. This is likely due to an incentive associated with orphan drug designation, namely priority review by the PMDA. All drugs designated as orphan drugs in Japan are reviewed under priority review: the target period is nine months, compared to the 12 months for normal review [17].

We identified two factors associated with the submission lag between Japan and the US for orphan anticancer drugs, "external collaboration" and "breakthrough therapy designation by the FDA". We speculate that this longer submission lag in Japan may be affected by cases of external collaboration

Table 3 Factors associated with the submission lag for orphan anticancer drugs

Independent variable	Coefficient	SE	*P* value
External collaboration			
Yes	762.1	311.1	0.017
Type of drug			
Cytotoxic drug	784.8	425.1	0.070
Breakthrough therapy designation by the FDA			
Yes	−832.8	386.7	0.035
Intercept	849.4	216.6	<0.001
N	64		
Adjusted R-squared	0.2242		
AIC	908.67		

AIC, Akaike's Information Criterion; FDA, US Food and Drug Administration; SE, standard error

Table 4 Development status in Japan at approval in the US of orphan anticancer drugs with or without breakthrough therapy designation and accelerated approval

Item	Breakthrough therapy designation *N* (%)		Accelerated approval *N* (%)	
	Yes	Other	Yes	Other
	N = 12	*N* = 52	*N* = 31	*N* = 33
Development status in Japan at approval in the US				
Approved	2 (16.7)	1 (1.9)	2 (6.5)	1 (3.0)
Under review by the PMDA	1 (8.3)	8 (15.4)	5 (16.1)	4 (12.1)
Under development	8 (66.7)	20 (38.5)	12 (38.7)	16 (48.5)
Not developed	1 (8.3)	23 (44.2)	12 (38.7)	12 (36.4)

PMDA, Pharmaceuticals and Medical Devices Agency; US, United States

in the development of an orphan anticancer drug that starts long after the approval of the drug in the US. For example, pralatrexate, an orphan anticancer drug approved in July 2017 in Japan for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma, had a long submission lag (2716 days). The applicant for the drug was Mundipharma K.K. in Japan and Allos Therapeutics, Inc. in the US. At the time of approval in the US in September 2009, development in Japan had not started. Mundipharma started clinical development in Japan after the execution of a license agreement with Allos Therapeutics in 2011 and filed the NDA in August 2016 in Japan [18–20]. Nevertheless, we consider that this type of external collaboration is necessary to resolve the existence of drugs or indications that are not approved in Japan but are approved in other countries. We also speculate that external collaboration might require more time for drug development than in-house development because (i) due diligence and deal negotiations are required before the start of external collaboration [12, 21] and (ii) all parties are required to reach consensus on decisions made during drug development. The submission lag may be reduced by establishing a skilled business development and alliance management team for efficient due diligence, deal negotiation, and alliance management. Flexible deal design to mitigate conflicts and realize a win-win philosophy may also be important in reducing the submission lag. Assuming that external collaboration will continue to play a major role in the pharmaceutical industry, these improvements for external collaboration are expected to reduce the submission lag for orphan anticancer drugs.

The breakthrough therapy designation is intended to expedite the development and review of drugs for serious or life-threatening conditions. The criteria for breakthrough therapy designation require preliminary clinical evidence demonstrating that the drug may substantially improve at least one clinically significant endpoint over available therapies. The FDA generally expects evidence derived from phase I or II studies [16]. It is acknowledged that one of the factors affecting submission lag is a lag in starting clinical development in Japan [9]. According to our analysis, the clinical development of almost all orphan anticancer drugs with breakthrough therapy designation in Japan is started before approval in the US, and their percentage is higher than that of drugs without breakthrough therapy designation. This might underlie an association between breakthrough therapy designation and a shorter submission lag. A previous study targeting general anticancer drugs supports our findings: the median difference in development start date between the US and Japan for anticancer drugs with breakthrough therapy designation was significantly shorter than that without breakthrough therapy designation [22].

Accelerated approval is a program started by the FDA to promote drug development for highly serious indications. This program allows the use of surrogate endpoints to evaluate drug efficacy [16]. Our analysis indicates that, unlike the case of breakthrough therapy designation, there is no clear difference in development status in Japan between orphan anticancer drugs with and without accelerated approval at the time of approval in the US. This might therefore underlie the lack of an association between accelerated approval and a shorter submission lag.

There are some limitations associated with this study. We only evaluated drugs that were successfully approved in both Japan and the US. Inclusion of drugs whose development failed or is ongoing in one country might have resulted in longer or shorter approval lag and submission lag, depending on the country where the drug development failed or the approval is delayed. Despite this exclusion of drugs with failed or ongoing development, however, we are confident that the data we analyzed were sufficient to achieve the purpose of this study.

In conclusion, we revealed that an approval lag for orphan anticancer drugs still existed in 2016–2017. Of the two components of approval lag for orphan anticancer drugs, submission lag was the main determinant, and was longer than that for non-orphan drugs. External collaboration in drug development was associated with a longer submission lag, while breakthrough therapy designation in the US was associated with a shorter submission lag. External collaboration in drug development may be a potential factor in reducing the submission lag for orphan anticancer drugs.

Acknowledgements The authors express their gratitude to Katsuya Nakano for his review of the study from a regulatory affairs viewpoint and to Makoto Tanaka for his useful suggestions.

Compliance with Ethical Standards

Conflict of Interest Hiroki Nakayama is an employee of Astellas Pharma Inc. Naoki Matsumaru declares that he has no conflict of interest. Katsura Tsukamoto declares that he has no conflict of interest. The Global Regulatory Science laboratory is financially maintained by donations from Otsuka Pharmaceuticals Co., Ltd.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Blay JY, Coindre JM, Ducimetiere F, Ray-Coquard I (2016) The value of research collaborations and consortia in rare cancers. Lancet Oncol 17(2):e62–e69. https://doi.org/10.1016/s1470-2045(15)00388-5
2. Gatta G, van der Zwan JM, Casali PG, Siesling S, Dei Tos AP, Kunkler I, Otter R, Licitra L, Mallone S, Tavilla A, Trama A, Capocaccia R (2011) Rare cancers are not so rare: the rare cancer burden in Europe. Eur J Cancer 47(17):2493–2511. https://doi.org/10.1016/j.ejca.2011.08.008
3. Heemstra HE, van Weely S, Buller HA, Leufkens HG, de Vrueh RL (2009) Translation of rare disease research into orphan drug development: disease matters. Drug Discov Today 14(23–24):1166–1173. https://doi.org/10.1016/j.drudis.2009.09.008
4. Ministry of Health, Labour and Welfare (2015) Overview of orphan drug/medical device designation system. (in Japanese) http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000068484.html Accessed 06 Feb 2018
5. Maeda K, Kaneko M, Narukawa M, Arato T (2017) Points to consider: efficacy and safety evaluations in the clinical development of ultra-orphan drugs. Orphanet J Rare Dis 12(1):143. https://doi.org/10.1186/s13023-017-0690-5
6. 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. Clin Pharmacol Ther 95(5):533–541. https://doi.org/10.1038/clpt.2013.223
7. Yonemori K, Hirakawa A, Ando M, Hirata T, Yunokawa M, Shimizu C, Katsumata N, Tamura K, Fujiwara Y (2011) The notorious "drug lag" for oncology drugs in Japan. Investig New Drugs 29(4):706–712. https://doi.org/10.1007/s10637-011-9638-0
8. 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. J Clin Pharm Ther 37(5):547–552. https://doi.org/10.1111/j.1365-2710.2012.01332.x
9. 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? Int J Clin Oncol 20(6):1072–1080. https://doi.org/10.1007/s10147-015-0825-4
10. Nakayama H, Tsukamoto K (2018) Unique characteristics of regulatory approval and pivotal studies of orphan anticancer drugs in Japan. Investig New Drugs. https://doi.org/10.1007/s10637-018-0603-z
11. Tsuji K, Tsutani K (2010) Approval of new drugs 1999-2007: comparison of the US, the EU and Japan situations. J Clin Pharm Ther 35(3):289–301. https://doi.org/10.1111/j.1365-2710.2009.01099.x
12. Hirai Y, Kinoshita H, Kusama M, Yasuda K, Sugiyama Y, Ono S (2010) Delays in new drug applications in Japan and industrial R&D strategies. Clin Pharmacol Ther 87(2):212–218. https://doi.org/10.1038/clpt.2009.215
13. Ito Y, Narimatsu H, Fukui T, Fukao A, Yoshioka T (2013) Critical review of 'Public domain application': a flexible drug approval system in Japan. Ann Oncol 24(5):1297–1305. https://doi.org/10.1093/annonc/mdt020
14. Maeda H, Kurokawa T (2014) Differences in maximum tolerated doses and approval doses of molecularly targeted oncology drug between Japan and Western countries. Investig New Drugs 32(4):661–669. https://doi.org/10.1007/s10637-014-0080-y
15. Kanda Y (2013) Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 48(3):452–458. https://doi.org/10.1038/bmt.2012.244
16. U.S. Food and Drug Administration (2014) Guidance for industry expedited programs for serious conditions – drugs and biologics. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf Accessed 06 Feb 2018
17. Ministry of Health, Labour and Welfare (2015) On the revision of the standard review timeline for new drug applications. (in Japanese) https://www.pmda.go.jp/files/000159256.pdf. Accessed 06 Feb 2018
18. Pharmaceuticals and Medical Devices Agency (2017) Review report for pralatrexate. (in Japanese) http://www.pmda.go.jp/drugs/2017/P20170605001/770098000_22900AMX00585_A100_1.pdf Accessed 06 Feb 2018
19. Mundipharma K.K. (2017) Common technical document for pralatrexate. (in Japanese) www.pmda.go.jp/drugs/2017/P20170605001/index.html Accessed 06 Feb 2018
20. U.S. Food and Drug Administration (2009) Approval letter for pralatrexate. https://www.accessdatafdagov/drugsatfda_docs/appletter/2009/022468s000ltr.pdf Accessed 06 Feb 2018
21. Jones A (2007) Minimizing leakage of value from R&D alliances. Nat Rev Drug Discov 6(9):711–719. https://doi.org/10.1038/nrd2357
22. Tanaka M, Matsumaru N, Tsukamoto K (2018) Influence of expedited programs in the United States on oncology drug development in Japan. Ther Innov Regul Sci. https://doi.org/10.1177/2168479018769288