Regular Article

Regional Disparity in First-in-Class Anticancer Drug Development in the US, EU, and Japan

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A cancer diagnosis is devastating for both patients and their caregivers. With high morbidity and mortality, cancer is a serious disease area with unmet medical needs. Thus, innovative anticancer drugs are in high demand worldwide but are unequally available. Our study focused on first-in-class (FIC) anticancer drugs and investigated their actual development situation in the United States (US), European Union (EU), and Japan over the last two decades to obtain fundamental information for understanding how the aforementioned demands are met, especially to eliminate drug lags among regions. We identified FIC anticancer drugs using pharmacological classes for the Japanese drug pricing system. Most FIC anticancer drugs were first approved in the US. The median approval time for anticancer drugs in new pharmacological classes during the last two decades in Japan (5072 d) was significantly different ($p = 0.043$) from that in the US (4253 d), though it was not significantly different from that in the EU (4655 d). Submission and approval lags between the US and Japan were more than 2.1 years, and those between the EU and Japan were more than 1.2 years. However, those between the US and the EU were less than 0.8 years. The development rate of FIC anticancer drugs in Japan is slower than in other regions. Even among developed countries, FIC anticancer drug lags exist. Considering the high impact of FIC anticancer drugs on society worldwide, we should work together to reduce drug lag among regions using an improved international cooperative framework.

Key words first-in-class, anticancer, regulatory policy, drug development, drug lag

INTRODUCTION

Pharmacotherapy in oncology has significantly progressed during the last decade, with innovative advances in the understanding of cancer molecular mechanisms and immunity and new modalities of drugs, including regenerative medicines and gene therapies. Some cancer types are curable with the correct combination of early detection by cancer screening, surgical treatment, radiation therapy, and pharmacotherapy. Cancer is the second cause of death worldwide, accounting for nearly 10 million deaths in 2020.[1,2] Owing to the severity of cancer-related distress, cancer patients and their caregivers live with a huge burden.[3,4] Therefore, cancer has a high impact on society with high medical needs globally. To overcome these unmet medical needs, new innovative anticancer drugs are being developed, approved, and used globally with the aim of minimal drug lag among regions.

Most of the research and development (R&D) of anticancer drugs are performed by private companies. Since they need to acquire a certain amount of profit from their investment, the companies make strategic R&D decisions, such as prioritized development in a particular region. The United States (US) is often the first approval region in the world primarily because it has the largest market with a free drug pricing system.[5] Moreover, various regulatory and industrial policies influence R&D plans. Regulatory authorities in some regions including the US, have expedited authorization procedures for innovative drugs. One typical example is the Breakthrough Therapy designation in the US, which was initiated in 2012. However, expedited programs mainly affect drug R&D in specific regions. Therefore, with respect to anticancer drugs in high demand worldwide, public and private sectors cooperate using the framework of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) to promote global development simultaneously. However, drug lag, defined as a drug approved in particular countries or regions that has not been approved in other countries or regions, is observed even among developed countries.[6,7]

Pharmaceutical companies often conduct R&D of me-too drugs (drugs similar to already-approved drugs) to make a profit and improve efficacy and/or safety. Since first-in-class (FIC) and me-too drugs have essentially different roles for patients and their caregivers,[8,9] we believe that these drugs should be treated separately when considering drug lag. FIC anticancer drugs are the last resort for desperate patients with serious conditions and no treatment options. Although the effects of me-too drugs are also non-negligible for some patients, giving them a secondary choice and more treatment options, the impact of early R&D of FIC drugs on public health around the world is enormous, incomparable with that of me-too drugs. Nevertheless, most of the studies on drug lag issues have been focused on new molecular entities (NMEs), including both FIC and me-too drugs. It is rational to distinguish FIC from all NMEs, to exclude me-too drugs, and explore the drug lag situation particularly with FIC anticancer drugs. In

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this study, focusing on FIC anticancer drugs, we investigated the actual anticancer drug approval situation in the US, European Union (EU), and Japan in the last two decades to further consider how to reduce inequality in how people worldwide obtain the latest innovative cancer pharmacotherapies.

MATERIALS AND METHODS

Materials All data were acquired from publicly available web pages of the Ministry of Health, Labour and Welfare (MHLW), Pharmaceuticals and Medical Devices Agency (PMDA), US Food and Drug Administration (FDA), and European Medicines Agency (EMA). We also surveyed other publicly available information such as companies' press releases and government news.

Identification of Pharmacological Classes for FIC Anticancer Drugs We used a unique Japanese drug pricing system to identify FIC anticancer drugs. As Japan has national health insurance (NHI), approved NMEs, including biologics for prescription drugs, are initially priced by the government. This price is set by referring to the drug classification used to select similar drugs.[10] We used that classification system (11th edition, listed until April 21, 2021, NHI drug price list) to determine the unique pharmacological class of the anticancer drug; "pharmacological effect 2" and "pharmacological effect 3" in the classification (Table 1) specify the unique pharmacological class. We then surveyed the approved anticancer drugs in Japan for each pharmacological class, and the earliest after 2000 was regarded as FIC anticancer drug in Japan. If the earliest was before 2000 in Japan, we excluded the corresponding pharmacological class from the analysis.

Next, we surveyed the approved anticancer drugs in the US or EU for the same pharmacological classification as that of Japan, and the earliest in the US and EU were identified as the FIC anticancer drug. If the identified FIC anticancer drug was approved before 2000 or drugs were approved in neither the US nor EU for a particular pharmacological class, we excluded further from the analysis. Each pharmacological class requires three FIC anticancer drugs approved after 2000 in each of three regions. Note that the three FIC anticancer drugs may not be the same because the approval order of drugs in a region can be different from each other and unique for each region.

Investigation of FIC Anticancer Drug Data For each FIC anticancer drug identified as described above, we recorded the approval date, submission date, and review time in the three regions (Supplementary Table). The lag days between approval and submission dates were calculated by subtracting one region from another, *i.e.*, subtracted US's date from Japan's date, US's date from EU's date, and EU's date from Japan's date. Since the FIC drug can be different in the three regions, we calculated FIC drug approval rate based on the approved new pharmacological classes in the three regions and compared them. We also investigated the status of orphan drug designations, expedited grant programs, and other relevant information (Supplementary Table).

Statistical Analyses The daily accumulation of approved new pharmacological classes for FIC anticancer drugs was analyzed using Kaplan–Meier plots and log-rank tests. To further explore the data, we analyzed the accumulation rates of new pharmacological classes for FIC by dividing them into two periods at the inflection point. The inflection point was determined visually from the plot representing the number of new pharmacological classes for FIC anticancer drugs approved yearly. Linear regression analysis was performed to determine the accumulation rate of approved new pharmacological classes from the slope of the approximate straight line. ANOVA was performed to test the difference of the speed among regions by comparing those slopes for the three regions. The regional differences on approval date, submission date and review time were analyzed using the Kruskal–Wallis test and *post-hoc* Steel–Dwass multiple comparison. All statistical analyses were performed using R (version 4.2.1) and EZR (version 1.55).[11] A p value less than 0.05 was considered statistically significant.

RESULTS

Figure 1 shows the flow chart representing the exclusion process of pharmacological classes for analyzing drug lags in Japan focusing on FIC anticancer drugs. At the time of December 31st, 2021, there are 96 pharmacological classes listed on the classification table, and 212 anticancer drugs are approved and available in Japan. Out of those classes, five classes for adjuvant and mixture drugs are excluded. Twenty-four classes are excluded because the earliest in Japan were approved before 2000, outside of the target period. Out of 57 classes, there are six classes such that no drug categorized in that pharmacological class has been approved in the US or EU. We further excluded five classes because the earliest in the US or EU were approved before 2000.

Forty-six pharmacological classes of FIC anticancer drugs were identified for analysis. Forty-one of the identified pharmacological classes had the same NME in all three study regions. Histone deacetylase, mammalian target of rapamycin (mTOR), myeloma cell proliferation, PD-1/PD-1 ligand binding, EGFR tyrosine kinase and tropomyosin receptor inhibitor classes differed NMEs in any of the three regions (see Supplementary Table for details). Forty FIC anticancer drugs were approved in the US first among the three regions. Figure 2 shows the growth in new pharmacological class approval rate, with a baseline of zero on December 31, 1999. Median days to the approval of a new pharmacological class in the US, EU, and Japan were 4252 [95% confidence interval (CI): 2629–4802], 4655 (95% CI: 3274–5066), and 5072 (95% CI: 4130–5474), respectively. There was a significant difference in median days to the approval between the US and Japan ($p = 0.043$); however, no significant difference was observed between the US and EU or the EU and Japan.

Since the inflection point of the Kaplan–Meier plots was in 2010 (Fig. 2), we divided the approval dates into two periods, with 2010 as the boundary, for further analysis. The accumulation rates of new pharmacological classes of FIC anticancer drugs in the three regions were distinct between pre-2010 and post-2010 periods. The linear regression of accumulation rates of new pharmacological classes and ANOVA revealed a significant difference in coefficients in the three regions pre-2010 period; however, no statistically significant difference was observed in the post-2010 period (Table 2). The proportion of FIC anticancer drugs with an orphan drug designation in the pre-2010 period was 66.7% in the US, 56.3% in the EU and 38.5% in Japan. This increased in the post-2010 period only in

Table 1. Pharmacological Class Determined by Drug Classification for Selecting Similar Drugs in Japan

Pharmacological class	Pharmacological effect 2	Pharmacological effect 3
1	Angiogenesis inhibition	VEGF inhibition
2	Angiogenesis inhibition	VEGF-A, VEGF-B, PIGF inhibition
3	Apoptosis induction	
4	BCL-2 inhibition	Apoptosis induction, cell cycle arrest
5	CDK inhibition	Tumor cell proliferation inhibition
6	Cell division inhibitory action	Inhibition of microtubule function through inhibition of tubulin polymerization
7	Cell division inhibitory action	Inhibition of microtubule function (selectively binds to CD30)
8	Cell division inhibition and antibody-dependent cellular cytotoxicity	
9	CTLA-4 binding inhibition	
10	EGFR inhibition	
11	Histone deacetylase inhibition	
12	Hormone like effect	Androgen synthase inhibition
13	Hormone like effect	Anti-androgen action/androgen receptor signal transduction inhibition
14	mTOR inhibition	Tumor cell proliferation inhibition, angiogenesis inhibition
15	Myeloma cell proliferation inhibition	
16	Nucleic acid synthesis inhibition	Binds to cytosine-rich DNA moieties
17	Nucleic acid synthesis inhibition	Double-stranded DNA cleavage action (selectively binds to CD22)
18	Nucleic acid synthesis inhibition	Inhibition of metabolism in nucleic acid synthesis process (inhibition of DNA polymerase activity, inhibition of ribonucleotide reductase)
19	Nucleic acid synthesis inhibition	Inhibition of metabolism in nucleic acid synthesis process (inhibition of dihydrofolate reduction, inhibition of TMP synthesis, inhibition of glycinamide/ribonucleotide/formintransferase)
20	Nucleic acid synthesis inhibition	Nucleotide excision repair mechanism inhibition
21	Nucleic acid synthesis inhibition	Protein synthesis inhibition (cell killing by uptake into RNA)
22	Nucleic acid synthesis inhibition and antibody-dependent cellular cytotoxicity	
23	PARP inhibition	Cell proliferation inhibition
24	PD-1/PD-1 ligand binding inhibition	Activation of cancer antigen-specific T cells and enhancement of cytotoxicity against cancer cells
25	Proteasome inhibition	
26	Ra accumulates in bone metastases and emits alpha rays	
27	Serin/topoisomerase inhibition	BRAF inhibition
28	Serin/topoisomerase inhibition	MEK inhibition
29	T cell-dependent cytotoxicity	
30	Tyrosine kinase inhibition	Anaplastic lymphoma kinase (ALK) inhibition
31	Tyrosine kinase inhibition	Angiogenesis inhibition, tumor cell proliferation inhibition, stromal cell signal transduction inhibition
32	Tyrosine kinase inhibition	Bcr-Abl tyrosine kinase inhibition
33	Tyrosine kinase inhibition	Bruton's tyrosine kinase inhibition
34	Tyrosine kinase inhibition	EGFR tyrosine kinase inhibition
35	Tyrosine kinase inhibition	EGFR tyrosine kinase inhibition with activated mutation and T790M mutation
36	Tyrosine kinase inhibition	EGFR/HER2 dual tyrosine kinase inhibition
37	Tyrosine kinase inhibition	FMS like tyrosine kinase 3 (FLT3) inhibition
38	Tyrosine kinase inhibition	Irreversible ErbB receptor tyrosine kinase inhibition
39	Tyrosine kinase inhibition	Janus kinase (JAK) inhibition
40	Tyrosine kinase inhibition	Raf kinase inhibition, VEGFR inhibition
41	Tyrosine kinase inhibition	Tropomyosin receptor kinase (TRK) inhibition
42	Tyrosine kinase inhibition	Tumor cell proliferation inhibition, angiogenesis inhibition
43	Tyrosine kinase inhibition	Tumor cell proliferation inhibition, angiogenesis inhibition (VEGFR inhibition)
44	Tyrosine kinase inhibition	VEGFR, PDGFR, c-Kit inhibition
45	Tyrosine kinase inhibition	VEGFR-2 inhibition
46	Y-labeled anti-CD20 antibody accumulates in CD20-positive B-cell tumors and emits beta rays	

VEGF: vascular endothelial growth factor, PIGF: placental growth factor, BCL-2: B-cell lymphoma 2, CDK: cyclin-dependent kinase, CTLA-4: cytotoxic T-lymphocyte-associated protein 4, EGFR: epidermal growth factor receptor, mTOR: mammalian target of rapamycin, TMP: thymidine monophosphate, PARP: poly (ADP-ribose) polymerase, PD-1: programmed cell death protein 1, BARF: B-Raf proto-oncogene, MEK: mitogen-activated protein kinase, Bcr-Abl: Breakpoint cluster region-Abelson, HER2: human epidermal growth factor receptor 2, PDGFR: platelet-derived growth factor receptor.

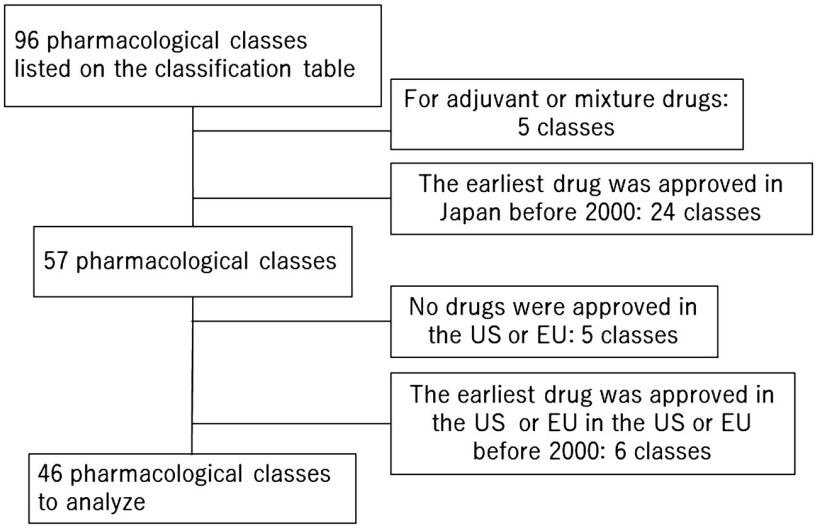

Fig. 1. Flow Chart of Pharmacological Classes to Include for Drug Lag Analysis among Three Regions, the US, EU, and Japan, Focusing on First-in-Class Anticancer Drugs

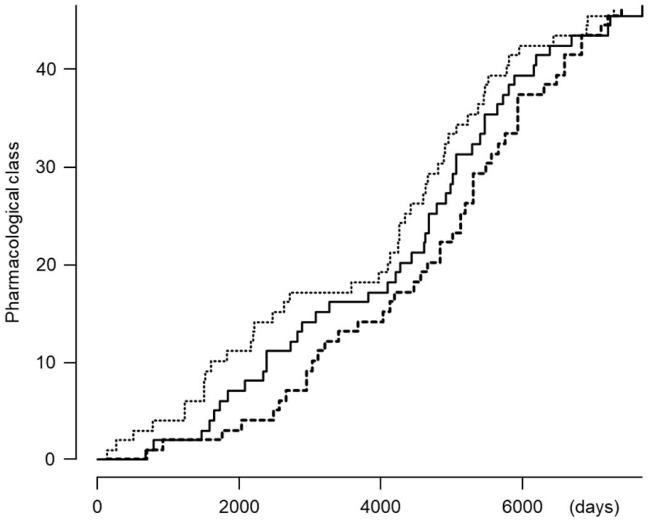

Fig. 2. The Accumulation of Approved New Pharmacological Classes of FIC Anticancer Drugs

Dotted, solid, and bold dotted lines are expressed the growth in pharmacological class approval rates in the US, EU, and Japan, respectively, with a baseline of zero in December 31, 1999. Statistically significant difference was observed between US and Japan by log-rank test ($p = 0.043$).

Table 2. Regional Difference of New Pharmacological Class Approval Pre- and Post-2010 Periods

		Coefficient [95% confidence interval] (10^{-3})	ANOVA
Pre-2010 period	US	5.52 [5.21, 5.84]	$p < 0.001$
	EU	4.29 [3.93, 4.66]	
	Japan	3.11 [2.7, 3.52]	
Post-2010 period	US	10.65 [9.74, 11.57]	$p = 0.342$
	EU	10.01 [9.4, 10.62]	
	Japan	10.25 [9.99, 10.5]	

Japan (US: 64.3%, EU: 36.7%, Japan: 51.5%).

We calculated the submission and approval lags of FIC anticancer drugs between the US and Japan, the US and EU, and Japan and EU (Fig. 3). The trend of the lag time between regions was almost the same for submission and approval; only the R&D time of FIC anticancer drugs in Japan was delayed compared to that of FIC anticancer drugs in the other regions. In contrast, the median review times for FIC anticancer drugs was 181.0, 317.5, and 413.5 d in the US, Japan and EU, respectively, with statistically significant differences (Fig. 4, $p < 0.001$).

DISCUSSION

In this study, we analyzed the approval status of FIC anticancer drugs in three developed regions, the US, EU, and Japan, focusing on the accumulation of approved new pharmacological classes and drug lag. For the former, we considered that each of the 46 pharmacological classes had the same value for patients and caregivers; thus, we investigated the differences in accumulation rate in the three regions as indicators of solution for unmet medical needs. The results indicated that the order of solutions availability for unmet medical needs was US, EU, followed by Japan; however, the situation in Japan improved after 2010. Comparing the percentage of R&D companies in Japan before and after 2010, we found that the percentage of Japanese domestic companies reached 33.3% in the post-2010 period, 1.44 times more than that in the pre-2010 period (see Supplementary Table for details). Regarding regulatory policies and activities, the Japanese government enforced the "Cancer Control Act" in 2007, and implemented the Basic Plan to Promote Cancer Control Programs.[12–14] This plan, including the promotion of cancer research activity, has been renewed every five years since its implementation and was active in 2022. Guidelines for using multiregional clinical trials (MRCT) that are relevant for simultaneous R&D beyond regions were issued in 2007, 2012, and 2014 in Japan, referring to ICH E5 Q&A#11.[15–17] The EMA has also published a reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU-population.[18] This information may contribute to improvement of the drug lag situation.

Submission and approval lags for FIC anticancer drugs were observed in the three regions. The results indicated that

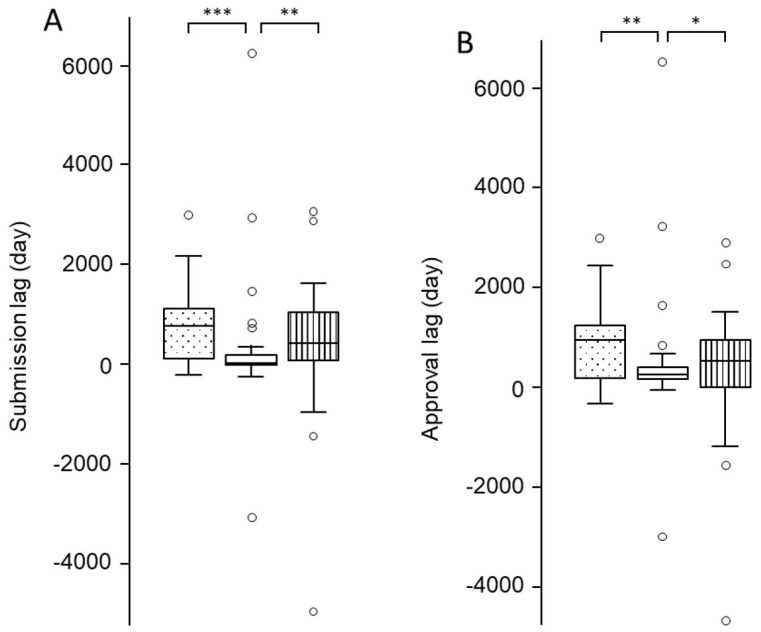

Fig. 3. Box-and-Whisker Plots of Submission Lag (A) and Approved Lag (B) of FIC Anticancer Drugs

Dotted, white and vertical lines boxes represent lag time among US and Japan, US and EU and Japan and EU, respectively. $*p<0.05$, $**p<0.01$, $***p<0.001$ by Steel–Dwass multiple comparison.

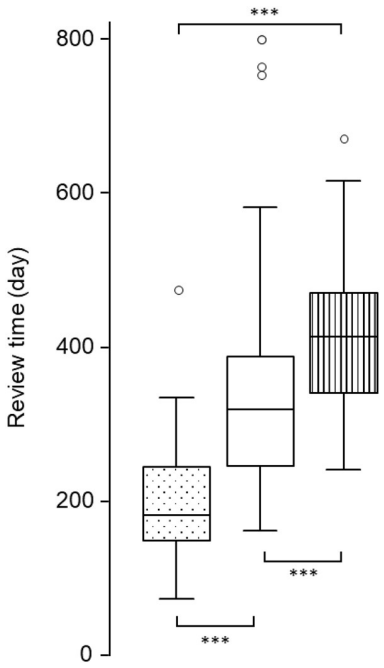

Fig. 4. Box-and-Whisker Plot of Review Time in Three Regions

Dotted, white and vertical lines boxes represent the review time in the US, Japan and EU, respectively. $***p<0.001$ by Steel–Dwass multiple comparison.

only the R&D time of FIC anticancer drugs in Japan lagged behind that of FIC anticancer drugs in the US and EU. There are several possible explanations to the reason why the R&D lags remained. Tsuji and Tsutani reported that new drugs of non-Japanese origin were delayed in approval in Japan because of delayed NDAs in Japan and costly and time-consuming clinical trials in Japan. Moreover, the lack of licensing opportunities was one of the major factors affecting drug lag in Japan, especially for new biopharmaceuticals.[19] Nakayama *et al.* appealed that orphan anticancer drug had longer submission and approval lags and 1/3 of drugs were developed by non-Japanese companies.[6] In this study, the situation was similar to those studies so that only 4 drugs (8.7% of total) were Japanese origin and 2/3 of the R&D companies in Japan submitted FIC anticancer drug applications as subsidiaries of foreign pharmaceutical companies. We could assume that R&D lags we observed are results of non-Japanese origin and/or development by non-Japanese companies.

It is known that using MRCTs including Japan as the implementation area is one of strategies for reducing drug lag in Japan. Rokuda *et al.* showed that more than 80% of pharmaceutical companies that operating MRCTs including Japan were non-Japanese firms.[20] Although even non-Japanese pharmaceutical companies are trying to accelerate drug development in Japan by utilizing MRCT, drug development in Japan is subject to regional barriers. Because Japan differs with respect to ethnicity and language from the US and EU, pharmaceutical companies need additional work for operating clinical studies and the NDA process in Japan, such as, to adjust dosage for the Asian population or to translate clinical study protocols, manuals, and documents into Japanese language. These burdensome works are sufficient excuses not to include Japan in MRCTs. In fact, Noguchi *et al.* reported that Japan is less able to participate in early phase MRCTs.[21]

In this study, we only surveyed FIC anticancer drugs approved by the EMA centralized procedure. The US and EU are multi-ethnic regions, and the official language for drug approval application and review is English. Interestingly, the submission lag between the US and EU was only 19.5 d; however, the approval lag between the US and EU was more than 9 months, with a longer review time in the EU than that in the US. This is a noteworthy difference between the FDA and the EMA. Longer review time for novel therapeutics required by the EMA than that for novel therapeutics required by the FDA has been observed in previous studies,[22–24] particularly

for anticancer drugs.[25,26] The longer review time for approval in the EU to some extent can be attributed to institutional differences among regions[23,27]; once the EMA issues a positive opinion, the European Commission has to adopt this opinion within 67 d before market authorization is granted. Hoekman *et al.* suggested that the EMA has difficulty dealing with high levels of uncertainty and may be more risk-averse than its US counterpart.[26]

It should be noted that the Breakthrough Therapy designation, which is considered the most powerful expedited regulatory program for innovative anticancer drug development in the US, was granted to only nine drugs in total and 42.9% of approvals after 2012 (see Supplementary Table for details). Our results suggested that none of the FIC anticancer drugs matched the Breakthrough Therapy designation criterion and that this program did not have a remarkable impact on the accumulation rate of new pharmacological classes.

There is a limitation in the method employed for identifying FIC anticancer drugs. We defined FIC as the first anticancer drug in a pharmacological class, based on the drug classification used for Japanese NHI drug price determination system. This classification is fundamental for the Japanese drug pricing system because the Japanese government sets a similar price if the drugs belong to the same classification. The drug classification is comprehensive enough to be applied to drugs in other countries. Although the FIC anticancer drugs we identified may not correspond to the FICs determined by the FDA or EMA, we believe that our method is useful for systematically identifying FICs in a uniform manner.

The effects and effective timing of policies vary. Therefore, our study revealed one possible explanation for drug lag in FIC anticancer drugs. We cannot rule out other possible explanations for the differences in anticancer drug R&D time among regions.

CONCLUSION

Considering the cultural, environmental and ethnic differences in each country or region, it is very important to analyze the approval or disapproval rates of FIC anticancer drugs in each country or region. Domestic promotion and initiation of cancer research performed by industry, government and academia can be key factors for prompt R&D and approval of FIC anticancer drugs in a region. With recent advances in the elucidation of the detailed genome and molecular mechanism of cancer pathology and immunology, various relevant data are accumulating, and the use of an integrated database has started. Owing to the high global medical need for cancer pharmacotherapies, it may be possible to consider using a "centralized procedure" to expand the EU approval system beyond the interests of each country. International organizations, such as the WHO and ICH, can take the initiative to address these challenges to achieve early and equitable patient access to FIC anticancer drugs worldwide.

Furthermore, various regulatory policies affect R&D time and plan. MRCT guidelines were issued for R&D in Japan. The guideline for MRCT based ICH E5 was revised to ICH E17 in 2017. However, it takes several years to achieve the actual effects of these regulatory measures on drug R&D and approval. Therefore, the effect of ICH E17 may be limited, and we will examine these effects in further studies.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials This article contains supplementary materials.

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