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Impact of Multiregional Clinical Trials on the Frequency of Revision of Package Inserts for New Efficacy Drugs in Japan and the United States

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The globalization of drug development has resulted in an increasing implementation of multiregional clinical trials (MCTs) in Japan. However, ethnic variations and low Japanese patient population in MCTs may impact post-marketing drug safety. This study compared the frequency of safety-related package insert revisions between drugs developed through MCTs and those developed otherwise (non-MCTs) in Japan and the United States. The analysis also investigated factors contributing to racial differences and the prevalence of MCTs. We retrospectively analyzed 227 new active-ingredient drugs approved in Japan between 2012 and 2021. Data on package insert revisions within 5 years of approval were collected from the Pharmaceuticals and Medical Devices Agency and the U.S. Food and Drug Administration databases. Comparisons were made by development method (MCT vs. non-MCT), metabolic enzyme polymorphisms, drug classification, approval process, and manufacturer. In Japan, the mean number of package insert revisions within 5 years was significantly higher for MCT drugs than for non-MCT drugs (0.28 vs. 0.17, p = 0.040). In the United States, no significant difference between MCT and non-MCT drugs was observed. Antineoplastic drugs and immunosuppressants demonstrated higher revision frequencies in both countries, with overall revisions greater in the United States than in Japan. MCT-developed drugs and antineoplastic/immunosuppressant drugs require careful post-marketing safety evaluation in Japanese patients. Differences in regulatory systems and post-marketing surveillance likely contribute to the observed variation in revision frequency between Japan and the United States.

Key words post-marketing safety evaluation, development strategy, multinational clinical trial, Japanese population, package insert revisions

INTRODUCTION

The globalization of drug development has recently advanced, and multiregional clinical trials (MCTs) have become the main approach for pharmaceutical development in Japan.[1)]

This trend is driven by the establishment of the ICH-E17 guidelines, which provide general principles for planning and designing MCTs.[2)] Additionally, efforts to streamline global development and address the "drug lag"—where drug approval in Japan is delayed compared to Western countries—have played a significant role.[3)]

MCTs are conducted using a single protocol across multiple countries and regions. This approach enabled rapid regulatory approval and market entry. However, the efficacy and safety of these drugs must be carefully evaluated, taking into account the ethnic differences among the participating regions.[4)]

Asian individuals including Japanese differ from Western populations in body composition and genetic polymorphisms of drug-metabolizing enzymes. These differences may influence the pharmacokinetics and pharmacodynamics.[5,6)] The ICH-E5 guideline shows the importance of ethnic factors when extrapolating foreign clinical data to Japan.[7)] Consequently, MCTs must include analyses involving Japanese participants.

Despite these requirements, the primary patient population in MCTs often consists of non-Japanese individuals, such as Westerners. The number of Japanese individuals tends to be lower than that of Western individuals. Nishida *et al*. analyzed the current status of development projects and MCTs in Japan.[8)] They reported that the proportion of Japanese participants in MCTs was lower than that in other countries, particularly for antineoplastic agents. Narukawa *et al*. employed ClinicalTrials.gov data to analyze Japan's participation rate in MCTs conducted by major foreign pharmaceutical companies.[9)] Their findings suggest that Japan's participation is increasing in phase 3 trials, but remains low in phase 2 trials, with the number of Japanese participants limited by the scale and regional composition of the trial. Under these circumstances, safety evaluations of MCTs in the Japanese popu-

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lation may be inadequate.

As MCTs employ a single protocol, most developed drugs are approved at the same dose across all participating regions. We previously examined the factors influencing dose differences between Japan and the United States (U.S.) for drugs approved in Japan between 2012 and 2021. Our analysis considered the development methods, pharmacological classification, review type, manufacturer, and metabolic enzymes. We noted that development via MCTs reduced the approved dose differences between Japan and the U.S.[10] However, cases exist where differences in pharmacokinetics were not reflected in the dose settings. For instance, rosuvastatin was approved at the same dose in both Japan and Western countries, despite a more than two-fold difference in the area under the concentration-time curve (AUC) between Japanese and Western participants.[11]

Therefore, detailed post-marketing safety evaluations of drugs developed through MCTs in Japanese patients are essential. Moreover, post-marketing revisions of package inserts are crucial. These revisions reflect the occurrence of adverse events in Japanese patients that could not be fully identified during clinical trials, as well as changes in the safety profile with long-term use.

The package insert serves as a primary source of information for healthcare professionals to ensure appropriate drug use. Revisions are directly linked to risk management and the promotion of proper drug use. These revisions, based on the accumulation and analysis of real-world data (RWD), reflect information that matches actual drug use. They also help address differences in drug responses due to ethnic factors.[12,13]

This study focused on the frequency of package insert revisions. We aimed to elucidate the differences between drugs developed using MCTs and those developed otherwise (non-MCTs). This approach allowed us to examine the impact of MCTs on post-marketing safety evaluations in Japanese patients.

MATERIALS AND METHODS

Data Source For Japanese drugs, the application materials and interview forms were obtained from the database available on the Pharmaceuticals and Medical Devices Agency (PMDA) website (http://www.pmda.go.jp/). Data on package insert revisions, indications, review categories, and other relevant details were extracted for the drugs approved in Japan between 2012 and 2021.

For drugs approved in the U.S., package inserts were obtained from the U.S. Food and Drug Administration (FDA) website (http://www.fda.gov/Drugs/default.html). Data regarding package insert revisions and other relevant details were also extracted.

The Anatomical Therapeutic Chemical (ATC) classification system was employed as the reference (https://www.kegg.jp/brite/br08303).

Exclusion Criteria Drugs were excluded from the analysis if they were not approved as new active ingredients in Japan, if dosage comparisons between Japan and the United States were difficult—such as in the case of topical drugs, vaccines, contrast media, pediatric drugs, or products with differing routes of administration, indications, or treatment regimens—and if sufficient information was unavailable. The latter included drugs lacking publicly available data on the FDA website (e.g., blood products), those approved under emergency conditions such as for COVID-19, and those for which package insert information at the time of first approval could not be obtained.

Package Insert Revisions In Japan, we focused on safety revisions based on individual drug reports from the PMDA website (http://www.pmda.go.jp/), whereas in the U.S., we examined additions to the "Warnings & Precautions" sections that include drug usage information. The observation period was 5 years after drug approval. This period was set on the basis of a previous report indicating a maximum of 44 months for the emergence of previously unknown adverse drug reactions in the U.S.,[14] and it also took into account the one-year prescription restriction period imposed after approval in Japan.

Analytical Factors Factors previously reported as candidate factors that could influence approved dosage in Japan and the U.S. were analyzed.[15] In Japan's review report, drugs for which pivotal trials were conducted through international collaborative trials were defined as MCTs. Drug classification was based on the ATC classification from the KEGG BRITE website (https://www.kegg.jp/brite/jp08303). Review type was based on the review process in Japan. Polymorphisms in major metabolic pathways were defined as pathways involving enzymes or transporters with high frequencies of genetic polymorphisms in Japanese individuals (CYP2D6, CYP2C9, CYP2C19, and OATP), which play key roles in primary drug metabolism. The development manufacturer was defined as "domestic" if the headquarters of the manufacturer that created the drug was located in Japan. The Japanese definitions for development strategy, review type, and development manufacture were also applied to the analysis of U.S. package insert revision frequency.

Statistical Analysis The following statistical methods were applied, with all analyses conducted using JMP Pro 17.2 (SAS Institute Inc., Cary, NC, USA). The significance level (α) was set at 5% for all analyses. For comparing the proportion of drugs that underwent at least one revision, Fisher's exact test was used for comparisons involving three or fewer groups. For comparisons using the ATC classification, logistic regression models were adopted because sample sizes were small within several groups. The dependent variable was defined as "one or more revisions", and the independent variables included each group of the ATC classification. Regarding the comparison of revision counts, the Wilcoxon rank-sum test was used to compare two groups, while the Kruskal–Wallis test was employed to analyze variations among multiple groups.

Ethical Considerations This study used publicly available data that did not involve human subjects. Therefore, no ethical approval was required.

RESULTS

The median (IQR) number of package insert revisions within 5 years post-approval was 0 (0-0) and the mean number was 0.22 (95% confidence interval [CI]: 0.13, 0.31) in Japan. In the U.S., the median (IQR) number was 0 (0-1) and the mean number was 0.82 (95% CI: 0.65, 0.98). Overall, package insert revisions were not frequently observed.

Development Strategy The proportion of drugs that underwent at least one revision was compared between drugs developed through MCT and other drugs. In Japan, the propor-

tion of drugs with revision was 17.6% in the MCT group and 8.4% in the non-MCT group, with the MCT group showing a significantly higher rate (p=0.047) (Fig. 1A). Same as the proportion of drugs with revision, the median (IQR) number of revisions was 0 (0-0) and the mean number of revisions 0.28 (95% CI: 0.15, 0.41) for MCT drugs, which was significantly higher than that for non-MCT drugs at 0 (0-0) and 0.17 (95% CI: 0.04, 0.30) (p = 0.040) (Fig. 1B).

In contrast, in the U.S., the proportions were 44.4% and 43.7% for the MCT and non-MCT groups, respectively, showing no significant difference (Fig. 1A). The median (IQR) number of revisions was 0 (0–1), and the mean number was 0.74 (95% CI: 0.54–0.94) for MCT drugs. For non-MCT drugs, the median (IQR) was also 0 (0–1), and the mean was 0.90 (95% CI: 0.64–1.16), with no significant difference observed (Fig. 1B).

Drug Classifications The revisions were also analyzed using pharmacological classifications based on the ATC system. The proportion of drugs that underwent at least one revision was compared in each group, there were significant differences in each therapeutic areas for both Japan and the U.S. (JP: p = 0.018, US: p < 0.005) (Fig. 2A, B) . In the number of revisions, no significant differences were identified between the groups in Japan (p = 0.130) (Fig. 2C), whereas a significant difference was observed in the groups in the U.S. (p = 0.003) (Fig. 2D). In both regions, drugs classified in group L (antineoplastic agents and immunosuppressants) tended to exhibit a higher frequency of revisions.

Polymorphisms in Major Metabolic Pathways The proportion of drugs that underwent at least one revision, and the number of package insert revisions were compared between drugs primarily metabolized by enzymes with a high prevalence of genetic polymorphisms in the Japanese population (CYP2D6, CYP2C9, CYP2C19, and OATP) and other drugs. Only 17 such drugs were identified, and there is no significant difference in both the proportion of drugs that underwent at least one revision (JP: p = 0.138, US: p = 0.612) (Fig. 3A) and the frequency of revisions (JP: p = 0.103, US: p = 0.336) (Fig. 3B).

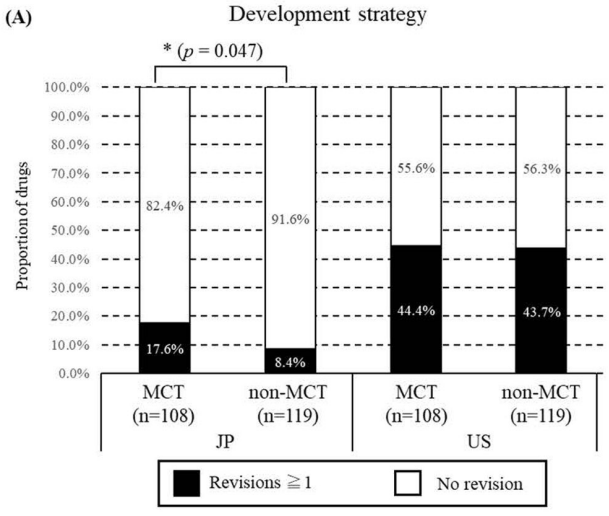
Review Process The impact of the Japanese approval process was assessed by comparing orphan, priority review, and standard review drugs. The proportion of drugs that underwent at least one revision, and the number of package insert revisions were compared in each review process. There is no significant difference in the proportion of drugs with revisions (JP: p = 0.138, US: p = 0.482) (Fig. 4A) and the revision frequency (JP: p = 0.233, US: p = 0.195) (Fig. 4B) among these categories.

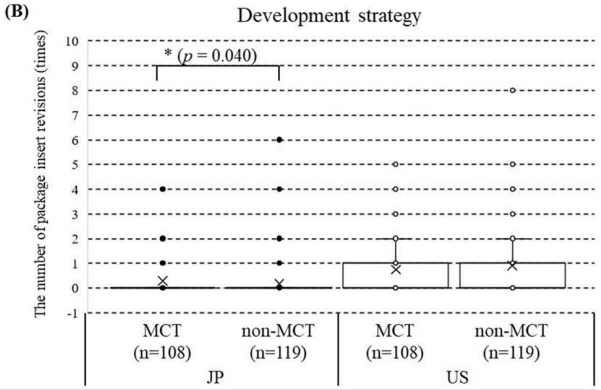
Affiliation of the Company Revisions were further compared between drugs developed by domestic and foreign companies. The number of drugs from domestic manufacturers was small, and no significant difference was observed in the proportion of drugs that underwent at least one revision (JP: p = 1.000, US: p = 0.536) (Fig. 5A), and the package insert revision frequency (JP: p = 0.896, US: p = 0.775) (Fig. 5B).

DISCUSSION

In this study, we analyzed 227 new active-ingredient drugs approved in Japan between 2012 and 2021. We focused on the frequency of package insert revisions within 5 years after approval, especially comparing drugs developed through MCTs and those developed otherwise (non-MCTs). We discovered that the number of revisions was significantly higher in the MCT group during the 5 years after approval.

The package insert revisions analyzed in Japan were based on case reports published by the Ministry of Health, Labor, and Welfare's "Pharmaceutical and Medical Device Safety Information." These revisions were limited to the safety information directly attributable to the drugs in question. Therefore, our results suggest that safety issues in Japanese patients

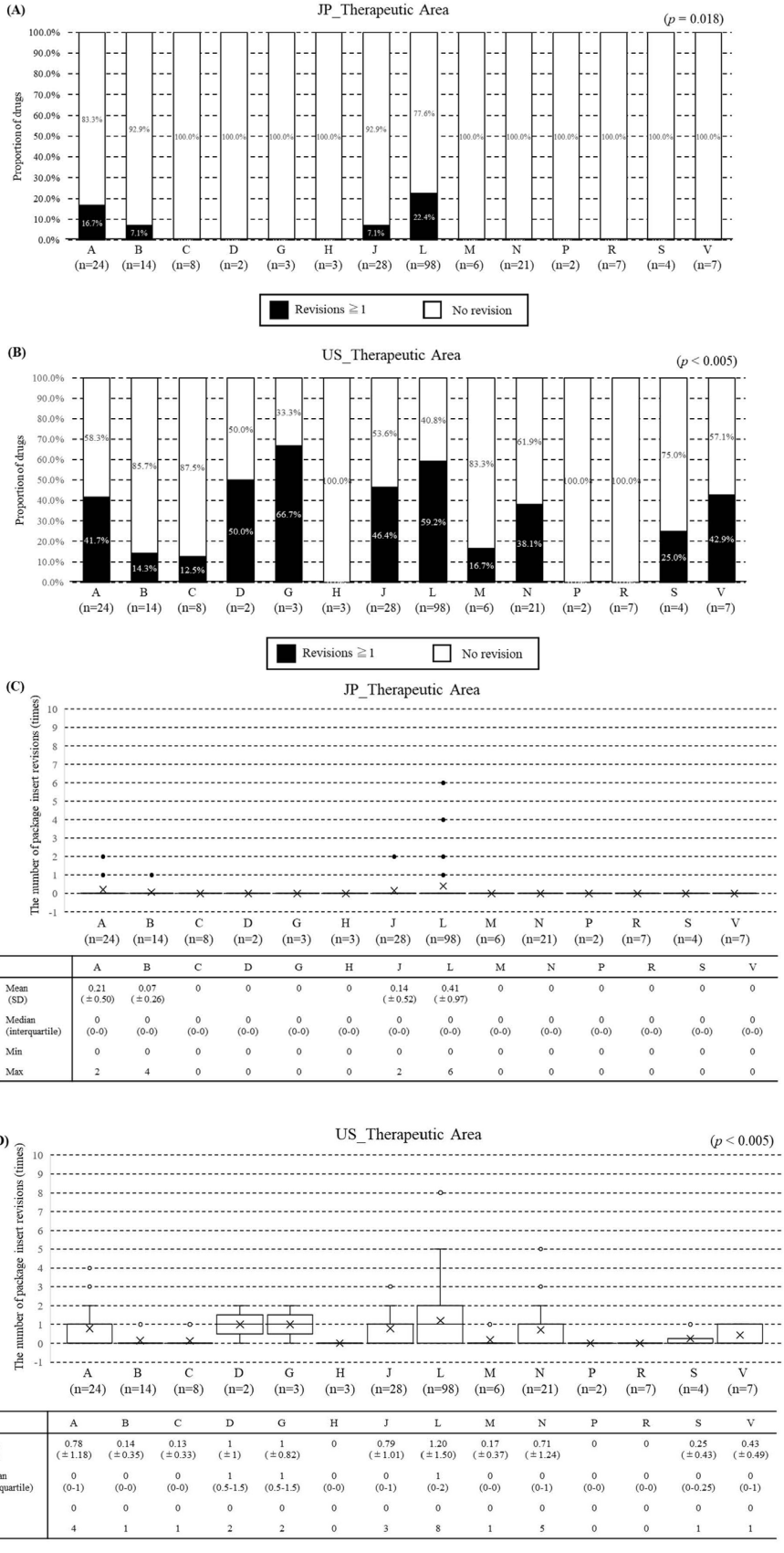




	JP		US	
	MCT	non-MCT	MCT	non-MCT
Mean (SD)	0.28 (±0.68)	0.17 (±0.73)	0.74 (±1.04)	0.90 (±1.43)
Median (interquartile)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-1)
Min	0	0	0	0
Max	4	6	5	8

Fig. 1. Analysis of the Package Insert Revisions by Development Strategy

The proportion of drugs that underwent at least one revision (A), and the number of package insert revisions (B). Statistical analysis: The Fisher's exact test was used for the analysis of the population, and the Wilcoxon rank-sum test was used for the analysis of the number of revisions. *MCT, multinational clinical trial; U.S., United States of America; JP, Japan

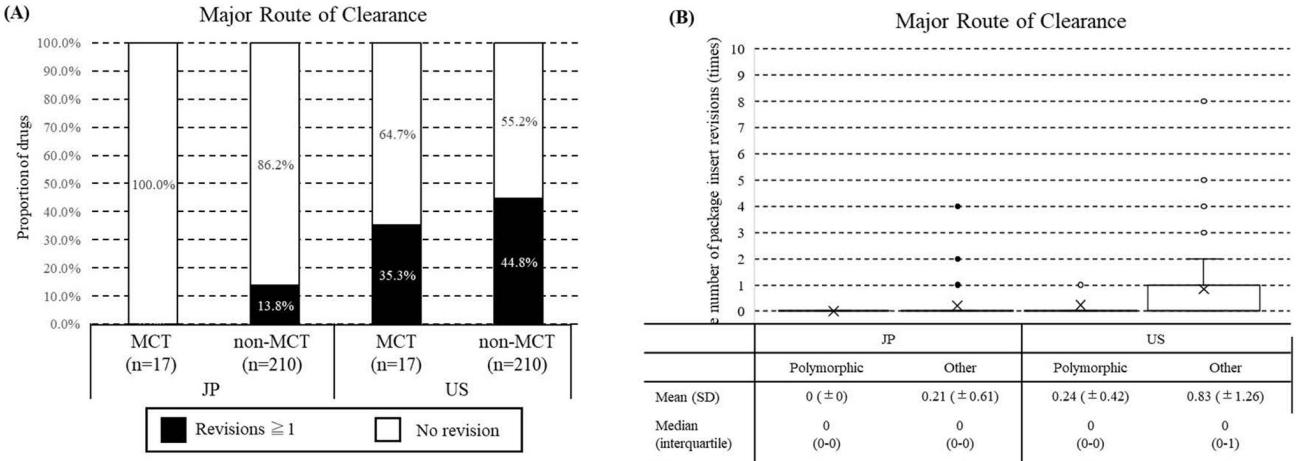


	A	B	C	D	G	H	J	L	M	N	P	R	S	V
Mean (SD)	0.21 (± 0.50)	0.07 (± 0.26)	0	0	0	0	0.14 (± 0.52)	0.41 (± 0.97)	0	0	0	0	0	0
Median (interquartile)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Min	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Max	2	4	0	0	0	0	2	6	0	0	0	0	0	0

	A	B	C	D	G	H	J	L	M	N	P	R	S	V
Mean (SD)	0.78 (± 1.18)	0.14 (± 0.35)	0.13 (± 0.33)	1 (± 1)	1 (± 0.82)	0	0.79 (± 1.01)	1.20 (± 1.50)	0.17 (± 0.37)	0.71 (± 1.24)	0	0	0.25 (± 0.43)	0.43 (± 0.49)
Median (interquartile)	0 (0-1)	0 (0-0)	0 (0-0)	1 (0.5-1.5)	1 (0.5-1.5)	0 (0-0)	0 (0-1)	1 (0-2)	0 (0-0)	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0.25)	0 (0-1)
Min	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Max	4	1	1	2	2	0	3	8	1	5	0	0	1	1

Fig. 2. Analysis of the Package Insert Revisions by Anatomical Therapeutic Chemical (ATC) Classification

The proportion of drugs that underwent at least one revision in Japan (A) and the U.S. (B). The number of package insert revisions in Japan (C) and the U.S. (D). Statistical analysis: The logistic regression models were adopted for the analysis of the population, and the Wilcoxon rank-sum test was used for the analysis of the number of revisions. *A, Alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; D, dermatologicals; G, genito-urinary system and sex hormones; H, systemic hormonal preparations, except sex hormones and insulins; J, anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculoskeletal system; N, nervous system; P, antiparasitic products, insecticides, and repellents; R, respiratory system; S, sensory organs; V, various



	JP		US	
	Polymorphic	Other	Polymorphic	Other
Mean (SD)	0 (±0)	0.21 (±0.61)	0.24 (±0.42)	0.83 (±1.26)
Median (interquartile)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)
Min	0	0	0	0
Max	0	4	1	8

Fig. 3. Analysis of the Package Insert Revisions Based on Genetic Polymorphisms in the Major Clearance Routes

The proportion of drugs that underwent at least one revision (A), and the number of package insert revisions (B). Statistical analysis: The Fisher's exact test was used for the analysis of the population, and the Wilcoxon rank-sum test was used for the analysis of the number of revisions.

may emerge post-marketing for drugs developed via MCTs. In these trials, global development efficiency is often prioritized, limiting the number of Japanese participants and potentially leading to insufficient safety evaluation based on ethnic factors.

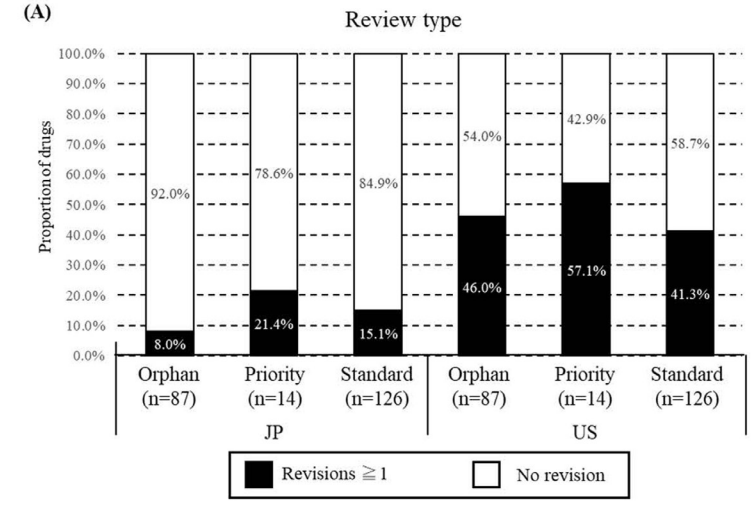
One ethnic factor is that Japanese individuals exhibit different genetic polymorphisms in drug-metabolizing enzymes compared to Western populations. These differences are known to affect pharmacokinetics and the occurrence of adverse drug reactions.[16] In this study, we examined drugs primarily metabolized by enzymes with high-frequency genetic polymorphisms in Japanese individuals. However, no significant differences were observed in either region, and no revisions occurred in Japan. Of the 227 drugs analyzed, only 17 were metabolized by these enzymes. The small sample size may have limited the ability to identify differences. Future studies should expand the number of target drugs and more thoroughly assess the impact of genetic polymorphisms.

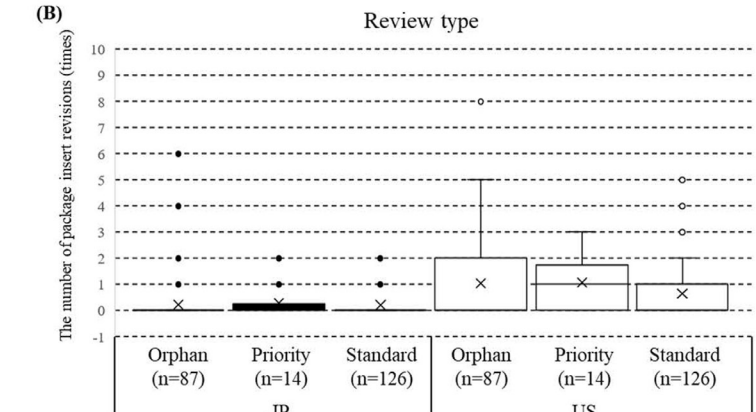
Analysis of the number of revisions by pharmacological classification based on the ATC system demonstrated no significant differences between the groups in Japan. In the U.S., however, significant differences were noted. In both regions, the drugs in group L (antineoplastic agents and immunosuppressants) exhibited higher revision frequencies. These drugs have a narrow therapeutic range and a high incidence of adverse events, allowing safety signals to be detected even with a small number of cases.[17,18] In oncology, development is advancing rapidly, and approvals often involve a relatively small number of Japanese cases.[19] In addition, the rapid introduction of new oncology drugs often limits clinical experience. Consequently, collecting safety information based on RWD is becoming increasingly important. These factors may have contributed to the higher frequency of package insert revisions for group L drugs.[20]

To analyze the approval process, we compared orphan drugs, priority reviews, and standard reviews. No significant differences in the revision frequency were observed between Japan and the U.S. This suggests that differences in the approval process do not necessarily affect the frequency of post-marketing safety information updates. In particular, orphan drugs involve a small patient population, limiting post-marketing experience and making it difficult to detect safety signals over a short period.

In the analysis of company affiliation, we compared drugs developed by domestic and foreign companies. No significant differences were observed between the groups. The proportion of drugs developed through MCTs has been reported to be lower for domestic companies.[9] However, the number of drugs developed by domestic companies was small (n = 26), potentially limiting statistical power. In the future, a more detailed analysis of development strategies and post-marketing surveillance systems by company affiliation may help clarify the factors behind revision frequency.

Additionally, this study demonstrated that the overall frequency of package insert revisions in the U.S. (mean 0.82 times) was significantly higher than that in Japan (mean 0.22 times). This difference may reflect variations in drug safety systems and post-marketing information collection between the two countries. In the U.S., the FDA actively imposes post-marketing requirements (PMRs) and post-marketing commitments (PMCs) at the time of drug approval. These systems were designed to collect additional data on safety and efficacy following marketing. A systematic review published in 2022 reported that the FDA imposes PMRs or PMCs on most new drugs, with over half providing clinically useful information and prompting regulatory actions such as package insert revisions.[21] The widespread use of electronic labeling (eLabeling) in the U.S. may also contribute to the immediacy and flexibility of revisions. In contrast, paper-based information provision remained standard in Japan. This may have limited the frequency and timing of revisions. Moreover, Japan has a re-examination system that requires re-evaluation of safety and efficacy after a certain period following new drug approval. This period is typically 8–10 years. During the re-examination period, companies are required to conduct extensive post-marketing surveillance. The PMDA tends to make revision deci-





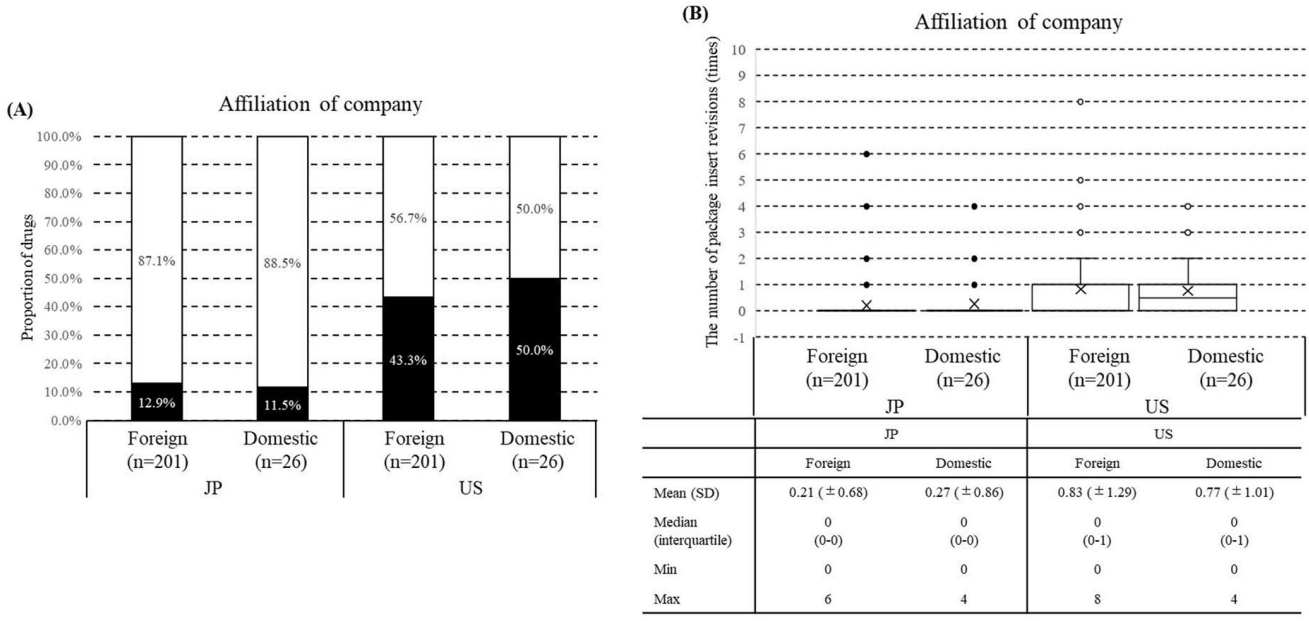
	JP			US		
	Orphan	Priority	Standard	Orphan	Priority	Standard
Mean (SD)	0.22 (±0.90)	0.29 (±0.59)	0.21 (±0.54)	1.05 (±1.55)	1.07 (±1.16)	0.64 (±0.99)
Median (interquartile)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-2)	0 (0-1.75)	0 (0-1)
Min	0	0	0	0	0	0
Max	6	2	2	8	3	5

Fig. 4. Analysis of Package Insert Revisions by Approval Review Type in Japan

The proportion of drugs that underwent at least one revision (A), and the number of package insert revisions (B). Statistical analysis: The Fisher's exact test was used for the analysis of the population, and the Wilcoxon rank-sum test was used for the analysis of the number of revisions.

sions with caution during this period. Kondo and Masamune[22] reported that for many drugs under the post-marketing surveillance, revisions are often postponed until survey results are available, especially when Japanese experience with the drug is limited. In this study, the 5-year post-approval observation period may have contributed to the lower frequency of revisions in Japan.

This study had several limitations. First, the analyzed package insert revisions were limited to safety information derived from case reports published on "Pharmaceutical and Medical Device Safety Information," ensuring their reliability and clinical significance. On the other hand, because the overall event occurrence rate was low, sufficient analysis could not be performed in groups with small sample sizes. And the mild adverse events commonly encountered in clinical practice may not be reflected. Such mild events can also impact the patients' quality of life. In the future, comprehensive safety evaluations using RWD are required. Second, in clinical practice, drugs may be prescribed at doses lower than approved doses. It has been reported that prescribing the approved dosage is common for certain ATC classifications and for drugs with a discrepancy between the starting and maintenance doses.[23] And in older patients or those on multiple medications, physicians often adjust doses at their discretion, considering changes in pharmacokinetics and the risk of adverse events. Hayashi *et al*.[24] reported that older patients are at an elevated risk of adverse reactions to renally excreted drugs and that the approved doses are often not followed in clinical practice. Such prescription practices may affect the frequency of adverse events and lead to an underestimation of post-marketing safety information. To reflect actual prescription practices, analyses considering dose adjustment trends and patient backgrounds are needed. Third, although the observation period was 5 years after approval, the number of patients and indications varied among the drugs. For drugs targeting rare diseases or specific cancers, post-marketing experience during the observation period may have been insufficient to detect safety signals, suggesting that the period may have been inadequate for all drugs.



	JP		US	
	Foreign	Domestic	Foreign	Domestic
Mean (SD)	0.21 (±0.68)	0.27 (±0.86)	0.83 (±1.29)	0.77 (±1.01)
Median (interquartile)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-1)
Min	0	0	0	0
Max	6	4	8	4

Fig. 5. Analysis of the Package Insert Revisions by Company Affiliation

The proportion of drugs that underwent at least one revision (A), and the number of package insert revisions (B). Statistical analysis: The Fisher's exact test was used for the analysis of the population, and the Wilcoxon rank-sum test was used for the analysis of the number of revisions.

The strength of this study is that we limited the analysis to revisions "related to safety" and "attributable to the drug in question." This enabled a more clinically meaningful comparison. However, the frequency of revisions was also influenced by factors such as drug usage, dose adjustments, and monitoring systems. Future analyses should account for patient numbers and actual prescribed doses.

Conflict of interest The authors declare no conflict of interest.

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