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ARTICLE

# Exploratory Analysis of Associations Between Postmarketing Safety Events and Approved Doses of New Drugs in Japan

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**While efficient and less onerous for the industry, the globalization of clinical drug development may lead to limited efforts to optimize drugs for regional conditions. We examined the association between clinical development pathways, approved doses, and postmarketing safety risks in Japan for 135 new molecular entities approved between 2004 and 2011. The risk of drug-related deaths seemed higher when pharmaceutical companies chose exactly the same dose as in the United States, even after conducting Japanese dose-ranging studies. We also found a positive association with drug-related deaths when the review process was expedited and when Japanese dose-ranging studies were not conducted for nonexpedited drugs. Our findings suggest that the decisions on regional dose settings and the choice of global clinical development pathways are associated in ways that may influence the postmarketing outcomes in the target populations.**

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**Study Highlights**

**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**
✔ Approved doses of new drugs in Japan were lower than those in the United States before the 1990s but have increasingly become the same since 2000. An association between the global nature of the drug-development process and dose setting has been found, but the implication to safety risks has not been investigated.

**WHAT QUESTION DID THIS STUDY ADDRESS?**
✔ We examined how differences in drug development pathways are associated with postmarketing safety risks of drugs in Japan.

**WHAT THIS STUDY ADDS TO OUR KNOWLEDGE?**
✔ The risk of drug-related deaths in Japan seemed higher when pharmaceutical companies chose the same recommended dose as in the United States, even after conducting Japanese dose-ranging studies.

**HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE**
✔ The global nature of the current drug-development process may be leading to a conflict between overall efficiency in research and development and the level of local optimization. With further substantial evidence, a need to propose new guidelines for global development to strike a better balance may be warranted.

Since the implementation of several key internationally harmonized guidelines in the late 1990s, pharmaceutical companies have set a goal to obtain approval of new drugs in all the major countries and regions across the world. This change had a significant impact in Japan.[1] Before the mid-1990s, the Japanese health authority used to require pharmaceutical companies to conduct dose-ranging and pivotal studies on Japanese patients, even when similar foreign data were already available, with the belief that ethnic differences may impact safety and efficacy of the tested drugs. In 1998, the International Conference on Harmonization E5 guideline was implemented.[2] This guideline enabled pharmaceutical companies to extrapolate clinical data obtained in foreign countries into the local new drug application (NDA) data package. Under the guideline, pharmaceutical companies are no longer required to replicate pivotal studies if successful bridging studies are achieved. As a result, as early as 2001–2002, one-third of NDAs in Japan included bridging studies and foreign clinical data.[3]

Subsequently, drug development has become more globalized, and multiregional studies are routinely conducted to improve the efficiency of the process. In 2007, a new guidance was issued by the Japanese health authority[4] that promoted participation of Japanese patients in global studies. With these regulatory changes toward a lenient acceptability of foreign clinical data, the number of global studies for Japanese NDA data packages has been increasing.

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A recent report showed that one-fifth of drugs approved in 2014 included data from global studies.[5]

Globalization in drug development has benefits not only to pharmaceutical companies through accelerated recruitment of patients at lower costs but also to patients by allowing earlier access to new drugs. However, the globalization of drug development may have its costs because such a globalized process may not be leading to optimal results for each local region.

There are growing concerns regarding dosages for each region.[6,7] Due to the nature of global drug development, the recommended dose is frequently optimized for use in the United States, the largest market and where the majority of clinical development is either conducted and/or planned. From the standpoints of pharmacokinetics (PK) and pharmacodynamics, however, the appropriate dosage of drugs may vary depending on intrinsic ethnic factors (e.g., polymorphism of cytochrome P450 and body weight) and extrinsic ethnic factors (e.g., dietary habit and medical practice).[8–11] For example, Japanese patients tend to have lower body weights and applying the same dose may potentially result in a higher level of exposure and consequently a higher incidence of side effects.[10] A recent example of drugs drawing attention to approved doses was paliperidone palmitate, which was approved in 2013 based on a global NDA data package with the recommended dose established for the global markets. After multiple risk events, the Pharmaceutical and Medical Devices Agency (PMDA), the Japanese regulatory agency, issued a Blue Letter to warn of the possible risks.[12] Subsequently, precautions regarding dosage and administration in its prescribing information were revised to add "caution should be exercised in dosage and administration to avoid overdose when switching from risperidone sustained-release suspension for injection to this drug."[12]

A previous study found that the approved dose in Japan was considerably lower than that in the United States for about half of the drugs approved until the 1990s when clinical studies were conducted separately in the United States and Japan.[10] However, another study found that the recommended doses for new molecular entities (NMEs) approved after 2000 have gradually become identical between the United States and Japan and that the drug development pathways are associated with dose setting.[13]

Furthermore, employing the recommended dose determined in the United States for use in Japan could involve additional risks when the drug has only recently been developed. Some reports suggest possible systemic flaws in premarketing dose evaluation, including possibilities that the maximum tolerated dose established in phase I or small phase II studies would be applied in some phase III studies.[6,7] Due to inadequate dose optimization in clinical studies, the initially approved dose level is often found to be excessive in the United States postmarketing surveys and is later adjusted downward.[6] In these cases, the dosage of drugs could also be excessive for Japanese patients. Exacerbating the problem is the fact that once a drug is approved in Japan, there is no officially established process to adjust the recommended dose.

The aim of this study is to determine whether the clinical development pathways, decisions of dose setting, and options adopted in drug-development strategies are associated with the number of drug-related deaths as postmarketing safety events.

## METHODS

Dependent variable. The number of drug-related deaths in the first 3 years after the commercial launch of the drug was the dependent variable as in a previous study.[14] Drug-related deaths are the most serious adverse drug reactions and hence least likely to be underreported. The number of NME-related deaths for 2004–2011 was obtained from the Japanese Adverse Drug Event Report database maintained by the PMDA.[15] The Pharmaceutical Affairs Law in Japan mandates that pharmaceutical companies and medical practitioners report serious adverse drug reactions to the PMDA. The full data set of this analysis is provided in **Supplementary Table S1**.

**Explanatory variables**. Information on the approved dose as well as on the indication, review type, clinical studies data, and other characteristics was extracted from the review reports posted on the PMDA website (http://www.pmda.go.jp/PmdaSearch/iyakuSearch/). Data on the US-approved dose were collected from the respective prescribing information posted on the US Food and Drug Administration (FDA) website Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/daf/).

We used dummy variables for drug classes with higher risk; central nervous system, anticoagulants, antitumor agents, and anti-HIV agents were tagged based on the Japan Standard Commodity Classification. We adopted these classes based on ancillary regression analysis, the number of reported drug-related deaths in each class, and similar analyses in previous reports.[16] As orphan drugs were automatically given priority review status in Japan, the dummy variable for orphan drugs indicated they were given both orphan and priority review status. The priority review dummy variables were assigned to nonorphan drugs that were granted priority review status based on potentially improved efficacy/safety profiles.

Dummy variables that indicate whether the all-case surveillance was imposed, the nationality of pharmaceutical companies (categorized based on the headquarter location for each company), and the total number of Japanese patients enrolled in clinical studies were also incorporated into the models. We used the peak annual sales divided by the price of drugs as a proxy for the peak patient number and included it as the offset variable.

**Regression models**. We chose the negative binomial model since the count of drug-related deaths was overdispersed. We established four models with different sets of explanatory variables.

In Model 1, we examined the relationship between the Japan/United States dose ratio and risk of drug-related deaths. We hypothesized that the same dose in Japan and the United States could result in inappropriate drug exposure to Japanese patients and may lead to a higher number of drug-related deaths. In Model 2, we added a

dummy variable, "same dose," to indicate when minimum and maximum doses are the same in Japan and in the United States. The recommended dose is usually determined from the results of dose-ranging phase II studies. For expedited drugs, such as priority and orphan drugs, implementing a dose-ranging study is not always feasible. Furthermore, we found that Japanese dose-ranging studies were not implemented even for some nonexpedited drugs. Therefore, we added the interaction terms of "review type" and "no Japanese dose-ranging study" into Model 3 to examine how the presence or absence of a Japanese dose-ranging study was associated with the safety of a drug. Model 4 includes all the variables used in Model 2 and Model 3. In all four models, therapeutic categories of drugs were controlled as fixed-effect terms and peak patient numbers in the market were incorporated as the offset term.

We used the terms "positive association" and "negative association" to indicate that regression coefficients obtained from regression analysis had statistically significant positive and negative values, respectively.

Statistical analyses were performed using Stata/SE13.

## RESULTS

In our analysis, NMEs approved between 2004 and 2011 in Japan were included. NMEs for external use and prophylaxes were excluded as well as cases in which dosage form, route of administration, and indication were different between Japan and the United States. The descriptive statistics of the 135 NMEs eligible for this study are shown in **Table 1**. The median dose ratio (MDR) was calculated as the ratio of the median maintenance dose in Japan to the one in the United States. The mean MDR was 1.0, and the dosages of 63% of NMEs were the same as in the United States.

Although most of the drugs had MDRs close to 1.0, some drugs had MDRs much higher or less than 1.0 during the observed period (**Figure 1a**). MDRs also varied according to therapeutic categories of drugs (**Figure 1b**). Antitumor agents were likely to have the same approved dose between the United States and Japan, and drugs for the central nervous system and anticoagulants were likely to have different approved doses. Drugs of Japanese companies tended to have Japanese doses that were different from the US doses (**Figure 1c**). Interestingly, most of the drugs given priority or orphan drug status at the time of development and/or approval had an MDR of 1.0, while MDRs of nonexpedited drugs were distributed somewhat widely (**Figure 1d**). These findings suggested that various background profiles of drugs, including therapeutic categories and needs, regulatory status in clinical development and approval stages, and license holders' attributes, might be associated with final dose setting and thus efficacy and safety profiles of drugs in the United States and Japan.

The results of the regression analysis are shown in **Table 2**. In Model 1, we examined the relationship between the MDR and the risk of drug-related deaths. The MDR alone did not have any association with drug-related deaths; however, when we added the square of the MDR in Model 1, the MDR had a positive coefficient and the square of the MDR had a negative coefficient, which indicated that the overall relationship between the MDR and drug-related deaths was not simply linear when we adjusted other conditions. For other explanatory variables, prioritized and orphan drugs were associated with a higher number of drug-related deaths. Other things being equal, prioritized and orphan drugs would have a higher drug-related death rate by a factor of 3.25 and 3.04, respectively, compared with nonexpedited drugs. The number of Japanese study subjects was negatively associated with drug-related deaths. All-case surveillance was also associated with a higher number of drug-related deaths. The variables that described clinical development pathways (i.e., the presence of dose-ranging, phase III, and bridging studies in Japan) did not show any significance.

In Model 2, we examined the hypothesis that applying the same dose as in the United States may result in a higher number of drug-related deaths. We added a dummy variable, "same dose," to indicate when minimum and maximum doses are the same in Japan and in the United States. We found that the "same dose" dummy variable was negatively associated with the risk of drug-related deaths; however, the interaction term of "same dose" and "Japanese dose-ranging study" displayed a positive relationship with the risk of drug-related deaths. This indicated that drug-related deaths would increase by a factor of 4.02 with other conditions remaining the same when the dose approved in the United States was selected following a Japanese dose-ranging study. We also observed in the regression results that when the interaction term of "same dose" and "Japanese dose-ranging study" was included in the model, conducting a dose-ranging study in Japan had a negative statistical association with the risk of drug-related deaths. In other words, the combination of a different dose and a dose-ranging study was negatively associated with the risk of drug-related deaths.

In Model 3, we examined if the presence of a dose-ranging study has any relationship with the drug's safety in different review types by introducing the interaction term "review types" and "dose-ranging study in Japan." The results showed that among nonexpedited drugs, the absence of dose-ranging studies in Japan was positively associated with the risk of drug-related deaths; however, for expedited drugs, the absence of dose-ranging studies in Japan did not show any statistical association with drug-related deaths.

Results similar to Model 2 and Model 3 were obtained when we added both interaction terms to Model 4. Across Models 2–4, non-Japanese pharmaceutical companies were positively associated with drug-related deaths.

## DISCUSSION

Regarding the approved dose of drugs, our initial hypothesis was that the higher approved dose compared with that in the United States might increase the risk of drug-related deaths. When we applied the simplest model (Model 1), a positive association between MDR and drug-related deaths was observed. However, our results also indicated that when various factors in clinical development and drug attributes were controlled, the higher dosage in Japan was not necessarily associated with an increased risk of drug-related deaths (Models 2–4). The quadratic association between MDR and

**Table 1** Descriptive statistics

| Variables | Mean | [Range] | SD |
|---|---|---|---|
| Dependent variables | | | |
| Number of drug-related deaths for the first 3 years | 43.7 | [0–515] | 79.5 |
| Explanatory variables (continuous) | | | |
| Median dose ratio (JPN/US) | 1.0 | [0.1–3.0] | 0.3 |
| Number of Japanese patients in clinical trials | 521.9 | [0–4,198] | 695.6 |
| Peak patient number (×1000) | 221.5 | [0.005–4,410] | 511.6 |
| **Explanatory variables (dichotomous)** | **Value** | **Frequency** | **%** |
| Same dose | No | 50 | 37.0 |
| | Yes | 85 | 63.0 |
| Japanese dose-ranging study | No | 81 | 60.0 |
| | Yes | 54 | 40.0 |
| Japanese phase III study | No | 74 | 54.8 |
| | Yes | 61 | 45.2 |
| Bridging study | No | 114 | 84.4 |
| | Yes | 21 | 15.6 |
| Review type | Standard (nonexpedited) | 76 | 56.3 |
| | Priority | 19 | 14.1 |
| | Orphan | 40 | 29.6 |
| Drug class | Other | 92 | 68.2 |
| | CNS | 6 | 4.4 |
| | Anticoagulants | 4 | 3.0 |
| | Antitumor agents | 25 | 18.5 |
| | Anti HIV agents | 8 | 5.9 |
| All case surveillance | No | 74 | 54.8 |
| | Yes | 61 | 45.2 |
| Firm nationality | Japanese | 42 | 31.1 |
| | Foreign | 79 | 58.5 |
| | Japanese & Foreign | 14 | 10.4 |

CNS, central nervous system; SD, standard deviation.

the risk of drug-related death observed in Model 1 also suggests that their relationship is somewhat complicated. As shown in **Supplementary Table S1**, the majority of drugs (85/135) had an MDR equal to 1, and some of them apparently had a high incidence of drug-related deaths. The numbers of deaths were not high for NMEs with an MDR more than 1, although there was only a limited number of NMEs in the MDR range. The presence of possibly "high-risk" drugs with an MDR equal to 1 may have led to these observations.

The results of regression Models 2 and 4 provide an important clue how to further investigate the association above. The drugs with the same dose in both countries showed lower risks of drug-related deaths as a whole; however, the drugs for which a dose-ranging study in Japan was conducted and the same dose was set based on the study results showed higher risk. These results suggest that heterogeneity in terms of dose-related risks exists in drugs having the same dose in the United States and Japan. For some drugs, the same dose is chosen and justified based on similarities in PK profiles for Japanese and Western populations; Japanese dose-ranging phase II studies are not necessarily implemented for these drugs, but similarities in PK profiles *per se* may result in lower safety risks in different markets. For other drugs that have different PK profiles, however, companies have to investigate the optimal dose for Japanese patients by conducting a dose-ranging study in this population.

It is interesting to note that choices of the same dose after conducting a dose-ranging study in Japan are associated with a higher risk of drug-related deaths. This association seems to reflect profiles of some drugs with high numbers of drug-related deaths in the sample (see **Supplementary Table S1**). For example, 32 drug-related deaths were reported for teriparatide, which was approved in 2010 to treat osteoporosis. The recommended dose for the drug was determined the same as in the United States despite the concerns for differences in PK profiles (i.e., higher area under the curve (AUC) in Japanese patients than in Western patients) and/or body weights between the two populations, an issue that was explicitly discussed in the review report from the PMDA. Another example that fell into this category is fondaparinux sodium, which was approved in 2007 as a prophylaxis for deep vein thrombosis in patients undergoing surgery and for which 18 drug-related deaths were reported. The PK profile showed that clearance decreases with decreasing body weight and that the AUC is slightly higher in Japanese patients. A possible explanation of these cases is that pharmaceutical companies tend to choose the same recommended dose as in the United States even when they suspect that the PK is somewhat different between

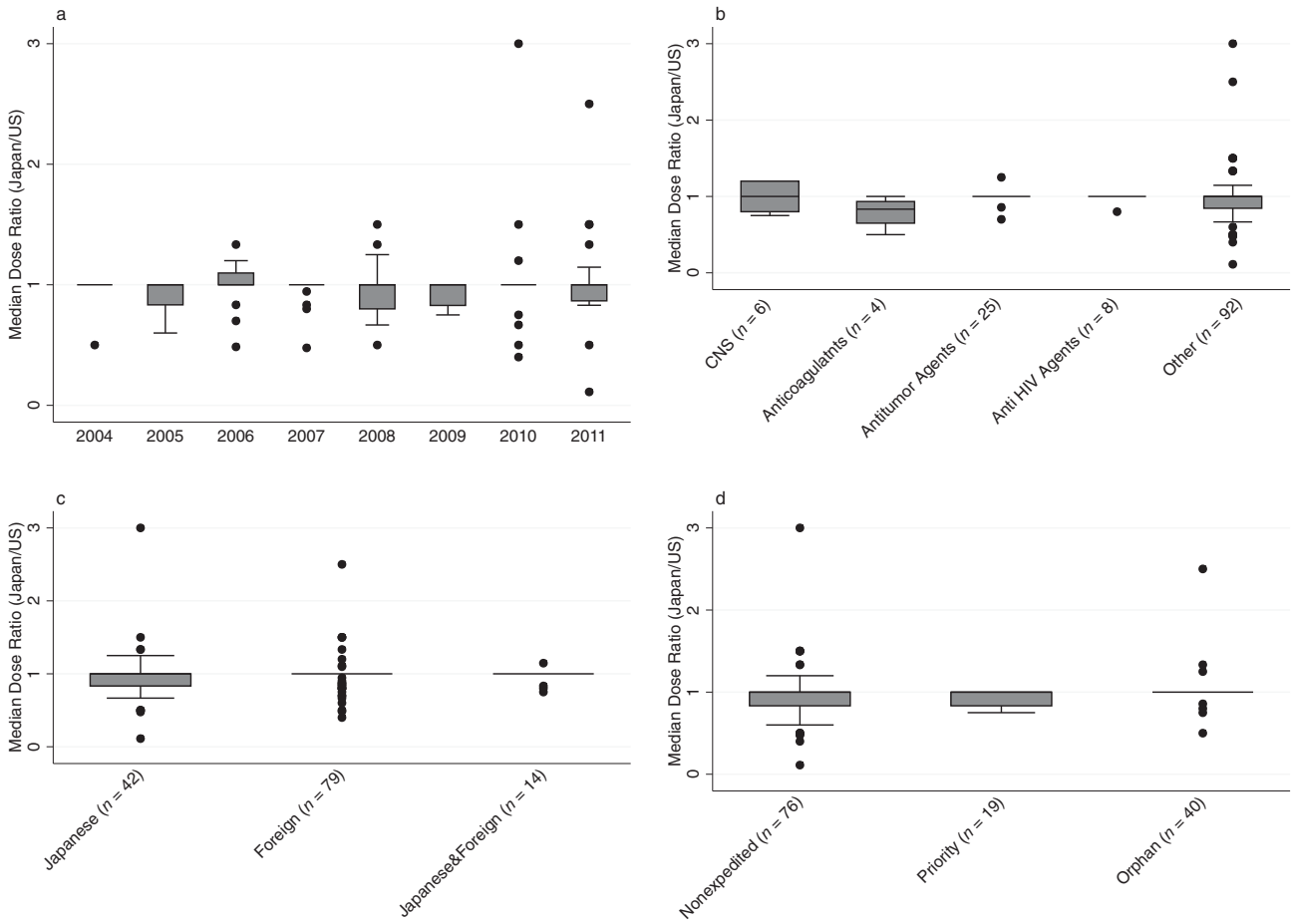


**Figure 1** Distribution of median dose ratios (MDRs) (Japanese dose/United States dose). Boxplot with whiskers with maximum 1.5 interquartile range. Any data not included between whiskers are plotted as an outlier with a dot. (**a**) MDR by approval year. (**b**) MDR by therapeutic category. (**c**) MDR by nationality of license holders. (**d**) MDR by regulatory status. CNS, central nervous system.

Japanese and Western populations, although this speculation has not be substantiated by solid evidence.

In general, pharmaceutical companies have an incentive to choose the same recommended dose evaluated in the global studies so that they can use foreign data and skip phase III studies in Japan. If they decide to set a different dose for Japanese patients, they need to conduct a separate phase III study with Japanese patients. Even when local dose-ranging studies are implemented and results are scrutinized, final decisions on the choice of recommended doses could be affected by various considerations. We need to continue to examine whether these incentives and decisions would have a substantial impact on postmarketing safety.

The nonexpedited drugs for which companies did not conduct dose-ranging studies had a positive association with the risk of drug-related deaths (Models 3 and 4), which may suggest the value of information from implementing local dose-ranging studies. However, it is difficult to ascribe this association to some specific components. It is possible for drug companies to make decisions on dose setting and labeling based on PK data and results of foreign clinical trials, but the criteria to determine the similarity of PK is somewhat ambiguous. Recent trends toward new approaches, such as exposure-matched dosing, would reduce the uncertainty in evaluating PK profiles and dose ranging in different populations based on global development strategies.[17]

Expedited drugs have a higher risk than nonexpedited drugs. This is unsurprising because most indications for orphan and priority drugs are for sicker and riskier patients than those for standard drugs. In addition to the inevitable higher risks in patients' backgrounds, several other factors peculiar to orphan and priority status may play a role. Requirements for the NDA data package, including dose-ranging and phase III studies in Japan, are eased for expedited drugs, which can lead to a higher risk of drug-related deaths. The number of patients enrolled in clinical studies tends to be smaller. It is also possible that the dosage is decided based on its efficacy rather than its safety for serious indications, which could lead to a higher dosage being preferably selected. Previous studies showed that the recommended dose of anticancer drugs is systematically set at the maximum tolerated dose.[18–20] Despite insufficient clinical information and possibly a different dose-setting philosophy, all the players face pressure on early approval for these expedited drugs due to high medical needs. The benefit of earlier

**Table 2** Negative binomial model results on the determinants of drug-related deaths (shown as incident risk ratio)

| | Model_1 | | | Model_2 | | | Model_3 | | | Model_4 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **IRR** | **SE** | ***P*-value** | **IRR** | **SE** | ***P*-value** | **IRR** | **SE** | ***P*-value** | **IRR** | **SE** | ***P*-value** |
| Median dose ratio (JPN/US) | 8.15 | 8.61 | 0.047** | 0.76 | 0.32 | 0.507 | 0.9 | 0.37 | 0.788 | 0.77 | 0.32 | 0.527 |
| Square of median dose ratio (JPN/US) | 0.47 | 0.17 | 0.04** | | | | | | | | | |
| Same dose† | | | | 0.36 | 0.13 | 0.004*** | | | | 0.41 | 0.14 | 0.011** |
| Same dose & Japanese dose-ranging study | | | | 4.02 | 1.94 | 0.004*** | | | | 2.58 | 1.32 | 0.065* |
| **Clinical development path†** | | | | | | | | | | | | |
| Japanese dose-ranging study | 0.72 | 0.18 | 0.179 | 0.31 | 0.12 | 0.002*** | 2.46 | 1.56 | 0.155 | 1.17 | 0.91 | 0.84 |
| Japanese phase III study | 0.95 | 0.38 | 0.906 | 0.77 | 0.32 | 0.541 | 0.73 | 0.32 | 0.48 | 0.6 | 0.27 | 0.248 |
| Bridging study | 0.53 | 0.22 | 0.133 | 0.47 | 0.2 | 0.073* | 0.42 | 0.19 | 0.049** | 0.41 | 0.17 | 0.035** |
| **Review type (base = nonexpedited drugs)** | | | | | | | | | | | | |
| Priority | 3.25 | 1.25 | 0.002*** | 3.23 | 1.28 | 0.003*** | 12.15 | 11.35 | 0.007*** | 9.8 | 9.56 | 0.019** |
| Orphan | 3.04 | 1.18 | 0.004*** | 3.05 | 1.19 | 0.004*** | 13.04 | 9.08 | <0.001*** | 10.24 | 7.54 | 0.002*** |
| **Review type & no Japanese dose-ranging study (base = drugs with the presence of Japanese dose-ranging studies)** | | | | | | | | | | | | |
| Standard & no Japanese dose-ranging study | | | | | | | 5.53 | 3.83 | 0.014** | 4.24 | 3.05 | 0.044** |
| Priority & no Japanese dose-ranging study | | | | | | | 0.96 | 1.09 | 0.974 | 1.07 | 1.2 | 0.956 |
| Orphan & no Japanese dose-ranging study | | | | | | | (omitted) | | | (omitted) | | |
| **Risky drug class (base = other drugs)** | | | | | | | | | | | | |
| CNS | 0.92 | 0.45 | 0.871 | 1.84 | 0.95 | 0.241 | 1.72 | 0.87 | 0.283 | 1.85 | 0.96 | 0.237 |
| Anticoagulants | 71.9 | 55.77 | <0.001*** | 50.14 | 41.29 | <0.001*** | 17.49 | 19.38 | 0.01** | 17.64 | 19.77 | 0.01** |
| Antitumor agents | 2.48 | 0.92 | 0.014** | 2.69 | 1.02 | 0.009*** | 3.4 | 1.27 | 0.001*** | 3.12 | 1.17 | 0.002*** |
| Anti-HIV agents | 0.15 | 0.07 | <0.001*** | 0.22 | 0.11 | 0.003*** | 0.26 | 0.13 | 0.009*** | 0.28 | 0.14 | 0.013** |
| All case surveillance† | 11.02 | 4.16 | <0.001*** | 13.03 | 5.08 | <0.001*** | 7.19 | 2.95 | <0.001*** | 9.05 | 3.85 | <0.001*** |
| Number of Japanese subjects (/100 subjects) | 0.92 | 0.02 | <0.001*** | 0.93 | 0.02 | <0.001*** | 0.93 | 0.02 | <0.001*** | 0.93 | 0.02 | <0.001*** |
| **Firm nationality (base = Japanese)** | | | | | | | | | | | | |
| Foreign | | | | 1.63 | 0.4 | 0.046** | 1.76 | 0.45 | 0.026** | 1.79 | 0.45 | 0.021** |
| Japanese & foreign | | | | 1.68 | 0.59 | 0.136 | 1.5 | 0.54 | 0.261 | 1.55 | 0.54 | 0.214 |
| _cons | 0.21 | 0.18 | 0.074* | 1.38 | 0.98 | 0.652 | 0.16 | 0.13 | 0.022** | 0.41 | 0.38 | 0.333 |
| ln(peak patient number) | 1 (exposure) | | | 1 (exposure) | | | 1 (exposure) | | | 1 (exposure) | | |

CNS, central nervous system; IRR, incidence rate ratio; SE, standard error.
*$P < 0.1$; **$P < 0.05$; ***$P < 0.01$
†Dichotomous variable; equals 1 for the presence of Japanese dose-ranging studies, Japanese phase III studies, bridging studies, all-case surveillance, and drugs with same dose.

access to these drugs and the need to ensure appropriate drug safety have to be carefully balanced.

The risk of drug-related deaths had a positive association when drugs were developed by foreign companies (Models 2–4). This association was observed in all the models with implementation of the Japanese dose-ranging study as an explanatory variable, indicating that there exist unobserved confounders related to the nationality of companies. In general, the foreign pharmaceutical branches in Japan have incentives to make effective use of foreign data but not to conduct Japanese-specific studies. Such incentives lead foreign companies to conduct fewer Japanese-specific studies compared with Japanese pharmaceutical companies. If observed safety risks are related to low numbers of Japanese study subjects, one possible remedy to neutralize these incentives would be to encourage earlier and wider participation of Japanese patients into global clinical studies so that a larger sample of Japanese patients can be obtained and incorporated into the global drug development process.

In terms of optimizing the approved dose, there should be more flexibility to adjust downward the approved dose when it is found to be excessive in postmarketing surveillance. Currently, there are few examples in Japan where the approved dose was changed in the postmarketing phase. In the United States, in contrast, the FDA can order pharmaceutical companies to modify the dose based on reports of drug-related adverse events to the FDA.[6] Our results suggest that more flexible doses, especially for expedited drugs for which not enough data were available at the time of approval, should be allowed after their commercial launch as more abundant data, including dose, efficacy, and safety, will become available from postmarketing surveillance and real-world usage in the clinical setting.

Our exploratory analysis has limitations. This is an exploratory study intended to detect possible association(s).

It is highly possible that unobserved confounders exist and were not properly controlled with the current set of explanatory variables. Due to the small sample size, it was also difficult to apply complicated regression models to control for unobserved effects and confounders. Furthermore, our observed statistical association between the different risk factors and the risk of drug-related death does not necessarily lead us to infer a strict causal relationship.

In conclusion, our findings suggest that postmarketing safety risks in the Japanese market may depend on critical decisions regarding dose settings and clinical development pathways. There are various incentives that underlie the decisions on regional dose settings and the choice of development pathways, which is likely to influence health outcomes. Pharmaceutical companies and regulatory authorities need to achieve the right balance between the efficiency of the drug development process and the level of dose optimization in each local population.

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**Author Contributions.** S.O. and T.K.O. wrote the manuscript, designed the research, performed the research, analyzed the data, and contributed new reagents/analytical tools.

**Conflict of Interest.** T.K.O. is an employee of Pfizer Japan, Tokyo, Japan. S.O. declared no conflict of interest.

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