

ARTICLE

Analysis of Global Drug Development Pathways and Postmarketing Safety in Japan: Local Studies May Reduce Drug-Related Deaths

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Recent International Conference on Harmonization (ICH) guidelines provide pharmaceutical companies with regulatory justifications to pursue various global drug-development pathways, in some of which “local” dose-ranging and/or pivotal phase III studies are skipped. We examined the association between the clinical development pathway and postmarketing safety in Japan for 177 new molecular entities approved between 2004 and 2013 focusing on dose setting histories for each drug. The risk of drug-related deaths was higher when companies did not conduct local (i.e., Japanese) dose-ranging studies and/or pivotal studies. Even when local dose-ranging studies were conducted, the risk remained higher in some drugs for which the approved dose in Japan was set equal to that in the United States. Drugs developed under a bridging strategy tended to show lower risks. These results suggested that local clinical studies may play a substantial role in achieving optimization of post-marketing drug use in each local target population.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Before the mid-1990s, the Japanese health authority required pharmaceutical companies to conduct dose-ranging and pivotal studies on Japanese patients. In 1998, the International Conference on Harmonization-E5 and related guidelines provided companies with strategic options to extrapolate foreign clinical data into the local new drug application data package. However, the implication of these changes to local postmarketing safety risks has not been well investigated.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We examined in what ways the drug-development pathway, including dose setting processes is associated

with postmarketing safety risks of new drugs in Japan.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Drugs for which dose-ranging or pivotal phase III studies using local populations were conducted tend to show lower safety risks in those local populations.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Pharmaceutical companies and regulatory authorities may need to re-examine if they are striking a right balance between the efficiency of drug development and the level of optimization of drug use in each local population.

Simultaneous global development programs of new drugs have become the norm not the exception in the current pharmaceutical regulations and markets. Pharmaceutical companies develop new drugs making the most of their opportunities and resources, aiming at all possible markets around the globe. In response, public health authorities worldwide have been adjusting their stance on drug approval to benefit from the competitive environment in the pharmaceutical industry.

Since the implementation of the International Conference on Harmonization (ICH)-E5 guideline in 1998, the Japanese authority started to accept foreign clinical data for marketing approval much more leniently.¹ A development strategy called “bridging” has led to more than 50 drugs being

approved in Japan since then. The strategy allows companies to use clinical data obtained in one region/country in another region/country for a new drug application (NDA) data package. Pharmaceutical companies are no longer required to replicate pivotal studies if bridging studies have yielded satisfactory results.

In tandem with the trend above, data obtained in multi-regional clinical trials (MRCTs) have become an important component of the clinical data package.² New guidelines were issued by the Japanese authority to promote participation in global studies in 2007.³ With these regulatory changes toward expanding acceptability of foreign clinical data, the number of global studies in Japanese NDA data packages has been increasing. A recent report showed that

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111 drugs were approved between 2005 and 2015 based on data from global studies,⁴ and another report showed that of 121 drugs approved between 2007 and 2015 based on data from global studies, 31 were based on Asian studies.⁵

Pharmaceutical companies globalize drug-development activities to establish clinical evidence of new drugs for global markets in the most efficient way. As mentioned above, implementing bridging and MRCTs are typical components of globalized development. Global development is efficient for companies in that they can accelerate recruitment of patients as a whole while keeping predetermined numbers of patients in several regions/countries. It usually enables companies not to repeat “local” phase III studies in each country as long as certain conditions are met. Consequently, all regions/countries seem to benefit from earlier access to new drugs due to the accelerated NDA submission and approval.

However, as observed in several recent serious postmarketing safety events in Japan, there are growing concerns regarding the appropriateness of approved doses in general as well as doses for each region.⁶⁻⁹ Due to strategic reasons, the recommended dose is commonly optimized for use in the United States, the world’s largest market where the majority of clinical development projects are conducted.^{10,11} 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 and that most of the clinical studies for these drugs were conducted separately in the United States and Japan.¹² 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 drugs lacking local studies in Japan tended to have the same doses in both countries.¹³

We found that the risk of drug-related deaths seemed higher when pharmaceutical companies chose the same dose as in the United States, even after conducting dose-ranging studies in Japan.¹⁴ Pharmaceutical companies have an incentive to choose the dose evaluated in global studies as the “universal recommended dose.” In this way, they can use foreign data and skip additional local phase III studies in Japan in a strategically consistent way. When they set a dose solely for Japanese patients, they generally conduct a separate phase III study in Japan. Even when local dose-ranging studies are implemented and their results are well-scrutinized, the final choice of the recommended dose could be affected by various considerations. From the standpoint of public health, it is necessary to examine whether such strategic choices could exert a substantial impact on health outcomes.

This study aims to determine if clinical development pathways, including options for local optimization, phase II dose-ranging studies, pivotal phase III studies, and choices of recommended doses are associated with the number of drug-related deaths, a critical marker for postmarketing drug safety in a local population.

METHODS

We chose the drugs approved as NMEs between 2004 and 2013 in Japan, with the exception of those used externally and for prophylaxis (e.g., vaccines). The drugs for which marketing approval were not given in the United States or

dosage form, route of administration, and indication were different between Japan and the United States were excluded from the study sample.

Dependent variable

The dependent variable was the number of drug-related deaths in the first 3 years after the commercial launch of the drug, as seen in previous studies.^{14,15} Drug-related deaths are the most serious adverse drug reaction and, hence, the least likely to be under-reported. The number of drug-related deaths between 2004 and 2016 was obtained from the Japanese Adverse Drug Event Report database maintained by the Pharmaceuticals and Medical Devices Agency (PMDA).¹⁶ The Pharmaceutical Affairs Law in Japan mandates the pharmaceutical companies and medical practitioners report serious adverse drug reactions, for which causal relationship was judged by physicians.

Explanatory variables

Information on the approved dose, indication, review type, data of clinical studies, and other drug characteristics were extracted from review reports posted on the PMDA website. The approved doses in the United States were collected from the Drugs@FDA website.

The clinical development pathway of a drug was classified according to the implementation of a Japanese dose-ranging study, a Japanese phase III study, a bridging study, and a global study in which Japan participated as well as combinations thereof.

Based on the results of a previous study and preliminary analysis, we used dummy variables for high-risk drug classes: central nervous system drugs, anticoagulants, antitumor agents, and anti-HIV agents.¹⁴ As orphan drugs are automatically given priority review status in Japan, the dummy variable for orphan drugs indicated they were given both orphan and priority review statuses. The priority review dummy variables were assigned to nonorphan drugs that were granted priority review status based on potentially improved efficacy/safety profiles.

We used dummy variables that indicate whether all-case surveillance was imposed, whether the nationality of pharmaceutical companies was Japanese or not, based on the headquarters’ location for each company and whether the drug is metabolized by cytochrome P450 (CYP)2D6, CYP2C9, CYP2C19, or CYP3A5, for which differences in polymorphism are reported between Japanese and white populations.¹⁷ The area under the concentration-time curve (AUC) ratio was calculated as the ratio of AUC (or peak plasma concentration (C_{max}) in cases where AUC is unavailable) in Japanese populations to the one in white populations. The total number of Japanese patients enrolled in clinical studies was also incorporated into the models. We used the ratio of peak annual sales divided by the daily 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 because the count of drug-related deaths was overdispersed. We established four models with different sets of explanatory variables.

In model 1, we examined the linear relationship between Japan/United States dose ratio and risk of drug-related deaths to see whether excessive drug exposure to Japanese patients could lead to a higher number of drug-related deaths. In model 2, we added a dummy variable, “same dose,” which indicated the drugs whose minimum and maximum doses in Japan and the United States are identical. In model 3 we used the variables showing the patterns of strategic combination in terms of “Japanese dose-ranging study” and “pivotal phase III study in Japan.” We excluded five drugs for which two pivotal studies were conducted. In model 4, we applied the same regression model as in model 3, excluding orphan drugs because dose-ranging studies and pivotal phase III studies are usually not feasible for orphan drugs. In all four models, therapeutic categories of drugs were controlled as the fixed-effect terms, and peak patient numbers in the market were incorporated as the offset term. We tested a classification using therapeutic subcategory for antineoplastics, a dummy variable showing if an anticancer drug was a monoclonal antibody drug and confirmed that our conclusions were not affected by these adjustments of background.

Analysis using propensity scores

In addition to regression analysis, we tested whether local dose-ranging studies and pivotal studies would lead to fewer drug-related deaths in Japan applying propensity score matching to adjust the imbalance in each drug’s background. We used the logistic model for predicting each drug’s propensity score. The covariates used in the model were review type; firm nationality; drug classes with higher risk, such as central nervous system drugs, anticoagulants, and antitumor agents; peak patient number; AUC ratio; CYP; and the presence of dose-ranging studies. Average treatment effects were obtained by matching each drug to a single drug with the opposite treatment whose propensity score is the closest. We also performed regression adjustment and augmented inverse probability weighting that has double-robust property. As the postestimation, we confirmed that the matched cohort was well-balanced by checking for covariate balance over treatment groups, drawing the estimated densities of the probability of getting each treatment level, and overidentification tests.

In this analysis, 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. The statistical analyses were performed using Stata/SE14 (Stata, College Station, TX, USA).

RESULTS

The descriptive statistics of the 177 drugs (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.

Most of the drugs that had no local dose-ranging study had MDRs close to 1.0, and drugs with local dose-ranging studies had varied MDRs centered at 1.0 (**Figure 1a**). Drugs with bridging studies in Japan were likely to have the same

Table 1 Descriptive statistics

Variables	Mean	Range	SD
Dependent variables			
Number of drug-related deaths for the first 3 years	38.7	0–515	72.5
Explanatory variables (continuous)			
Median dose ratio (JPN/US)	1.0	0.1–3.0	0.3
Number of Japanese patients in clinical trials	450.6	0–4,198	634.4
Peak patient number (×1,000)	204.6	0.005–4,410	473.1
Explanatory variables (Dichotomous)			
	Value	Frequency	%
Same dose	No	62	35.0
	Yes	115	65.0
Japanese dose-ranging study	No	113	63.8
	Yes	64	36.2
Japanese phase III study	No	107	60.5
	Yes	70	39.6
Bridging study	No	150	84.8
	Yes	27	15.3
Global study	No	158	89.3
	Yes	19	10.7
Review type	Standard (nonexpedited)	100	56.5
	Priority	25	14.1
	Orphan	52	29.4
Drug class	Other	121	68.4
	CNS	7	4.0
	Anticoagulants	6	3.4
	Antitumor agents	33	18.6
All case surveillance	Anti-HIV agents	10	5.7
	No	101	57.1
	Yes	76	42.9
Firm nationality	Japanese	60	33.9
	Foreign	99	55.9
	Japanese and foreign	18	10.2
Foreign first	No	8	4.5
	Yes	169	95.5
AUC ratio (JPN/US)	< 0.8	85	48.0
	≥ 0.8 and ≤ 1.2	18	10.2
	> 1.2	58	32.8
	Unavailable	16	9.0
CYP2D6, 2C9, 2C19, 3A5	No	156	88.1
	Yes	21	11.9

AUC, area under the concentration-time curve; CNS, central nervous system; CYP, cytochrome P450; JPN, Japan, US, United States.

approved dose in both the United States and Japan, and drugs that underwent a Japanese phase III study were likely to have differences in the approved dose between Japan and the United States (**Figure 1b**).

The results of the regression analysis are shown in **Table 2**. The MDR did not have a statistically significant association with drug-related deaths in any of the models. Prioritized and orphan drugs tended to have a higher number of drug-related deaths. For example, with other conditions being equal, prioritized and orphan drugs would have

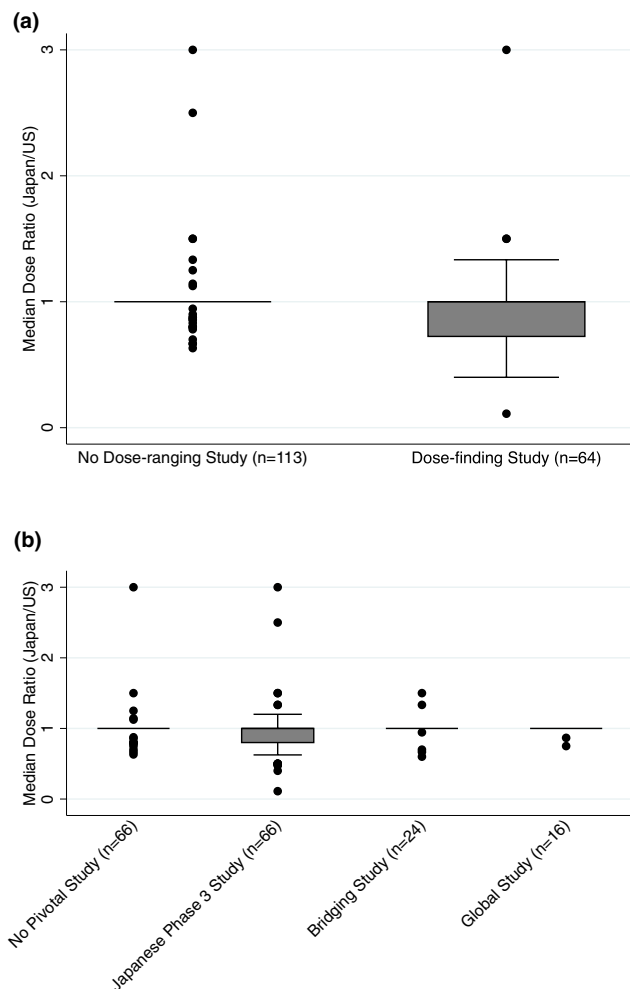


Figure 1 Distribution of median dose ratios (Japanese dose/United States dose). **(a)** Median dose ratio (MDR) by Japanese dose-ranging study. **(b)** MDR by pivotal study. Box and whisker plots were shown. Because 90 of 113 drugs of no dose-ranging study in **(a)** and 51 of 66 drugs of no pivotal study, 18 of 24 drugs of bridging study, and 14 of 16 drugs of global study in **(b)** have an MDR of 1, there are few observations visible. Outliers of MDR were palonosetron and miglustat (MDR = 3), canakinumab (MDR = 2.5), ropinirole and cinacalcet (MDR = 0.47), liraglutide (MDR = 0.4), and repaglinide (MDR = 0.11) (see **Table S1**).

a higher drug-related death rate by a factor of 3.39 and 4.02, respectively, compared with nonexpedited drugs in model 1. The number of Japanese study subjects was negatively associated with drug-related deaths in all models. All-case surveillance was associated with a higher number of drug-related deaths in all models.

The presence of local dose ranging in models 1 and 2 or phase III studies in Japan in model 1 was negatively associated with drug-related deaths. Drugs with bridging studies in Japan were also likely to have fewer drug-related deaths. The coefficients for global studies were not significant in any model.

In model 3, with the variables showing the patterns of combination of “Japanese dose-ranging study” and “pivotal

phase III study in Japan,” drugs for which global studies were conducted showed impressively different results depending on the implementation of local dose-ranging studies. In cases where a local dose-ranging study was not done, drugs with a global study showed a much higher risk compared with the baseline. To the contrary, drugs showed a lower risk in cases where a local dose-ranging study was done. In our preliminary analysis, we checked the impact of trend using “approval year” as an explanatory variable and found that “no dose-ranging study and Japanese phase III study” was not statistically significant. This suggests that there may be some unobserved historical factors associated with both choice of drug-development pathway and drug safety.

The dummy variable indicating the “same dose” in Japan and the United States showed a negative association with drug-related deaths in models 2, 3, and 4, as we reported in a previous paper.¹⁴ Interestingly, however, the interaction term of “same dose” and “Japanese dose-ranging study” displayed a positive relationship with the risk of drug-related deaths. This implies that drugs for which local dose-ranging studies were done and the same dose was subsequently chosen might have higher risks, whereas other conditions remained the same. In our preliminary analysis, we tested a dummy variable indicating if a drug had a fixed dose or dose per body weight/body surface and found that this interaction term was not statistically significant.

The regression analysis, excluding orphan drugs, yielded similar coefficients (model 4). Drugs for which clinical trials had already started in countries other than Japan were associated with higher numbers of drug-related deaths.

Drugs with low AUC ratios (Japanese AUC/white AUC) tended to show higher risks in one model (model 2), and drugs metabolized by cytochrome P450 showed lower risks, other conditions being the same.

The analysis using propensity score matching showed that drugs for which local dose-ranging studies or local phase III studies were conducted tend to correlate with fewer drug-related deaths (**Table 3**). Drugs having Japanese phase III studies showed fewer drug-related deaths consistently in all three models. Drugs for which global studies were conducted were not safer or riskier.

DISCUSSION

We found that global clinical development pathways of new drugs, local development histories, in particular, are associated with postmarketing safety risks in the Japanese market. Implementing local dose-ranging studies and/or local pivotal phase III studies in the development pathway was associated with significant reduction of drug-related deaths not only in the regression analysis (**Table 2**) but also in the analysis done using propensity scores (**Table 3**). Considering that local studies are required for drugs whose pharmacokinetic (PK) and/or pharmacodynamic profiles are sensitive to local factors (e.g., ethnicity, race, and other demographic and environmental factors), such local clinical studies seem to play a substantial role in the promotion of drug safety in local target populations.

Table 2 Negative binomial model results on the determinants of drug-related deaths (shown as incidence rate ratio)

	Model 1 (N = 177)			Model 2 (N = 177)			Model 3 (N = 172)			Model 4 (N = 120)		
	IRR	SE	P value	IRR	SE	P value	IRR	SE	P value	IRR	SE	P value
Natural log of median dose ratio (JPN/US)	1.54	0.55	0.228	1.34	0.56	0.482	1.51	0.62	0.315	1.49	0.71	0.399
Same dose				0.47	0.14	0.011**	0.47	0.11	0.002***	0.32	0.09	< 0.001***
Same dose and Japanese dose-ranging study				2.18	0.98	0.083*						
Clinical development path (I)												
Japanese dose-ranging study	0.62	0.15	0.053*	0.39	0.14	0.01**						
Japanese phase III study	0.64	0.18	0.107	0.62	0.17	0.085*						
Bridging study	0.42	0.13	0.005***	0.50	0.16	0.03**						
Global study	0.92	0.31	0.796	1.09	0.37	0.806						
Clinical development path (II) (base = dose-ranging study × Japanese phase III study)												
No dose-ranging study × global study							7.07	3.35	< 0.001***	10.13	5.91	< 0.001***
No dose-ranging study × bridging study							1.19	0.44	0.641	1.89	0.79	0.128
No dose-ranging study × Japanese phase III study							2.16	0.74	0.024**	3.87	1.48	< 0.001***
Dose-ranging study × global study							0.04	0.03	0.001***	0.06	0.06	0.003***
Dose-ranging study × bridging study							2.41	1.69	0.208	3.98	2.84	0.053*
Others							3.50	1.16	< 0.001***	6.52	2.78	< 0.001***
Review type (base = nonexpedited drugs)												
Priority	3.39	1.16	< 0.001***	3.75	1.32	< 0.001***	3.09	1.03	0.001***	3.08	1.12	0.002***
Orphan	4.02	1.49	< 0.001***	4.47	1.65	< 0.001***	3.56	1.34	0.001***			
Risky drug class (base = other drugs)												
CNS	1.85	0.91	0.208	2.00	1.00	0.166	1.37	0.68	0.53	2.65	1.57	0.098*
Anticoagulants	24.78	16.93	< 0.001***	23.31	16.20	< 0.001***	56.90	41.00	< 0.001***	35.99	26.02	< 0.001***
Antitumor agents	3.37	1.02	< 0.001***	3.85	1.18	< 0.001***	2.97	0.93	0.001***	4.50	2.13	0.002***
Anti-HIV agents	0.16	0.09	0.001***	0.16	0.09	0.001***	0.16	0.09	0.001***			
All case surveillance	6.22	1.94	< 0.001***	6.23	1.94	< 0.001***	9.55	3.20	< 0.001***	7.73	2.91	< 0.001***
Number of Japanese subjects (/100 subjects)	0.94	0.02	< 0.001***	0.94	0.02	0.001***	0.96	0.02	0.013**	0.99	0.02	0.705
Firm nationality (base = Japanese)												
Foreign	1.48	0.32	0.068*	1.55	0.33	0.042**	1.30	0.29	0.235	1.30	0.37	0.354
Japanese and Foreign	1.50	0.48	0.204	1.60	0.51	0.14	1.53	0.49	0.181	1.68	0.67	0.195
Foreign first	1.13	0.54	0.802	1.23	0.59	0.671	1.36	0.65	0.528	4.90	2.66	0.003***
AUC ratio (JPN/US) (base = 0.8–1.2)												
< 0.8	1.49	0.47	0.2	1.78	0.57	0.069*	1.63	0.52	0.123	1.22	0.46	0.605
> 1.2	1.06	0.23	0.775	1.09	0.23	0.674	1.12	0.24	0.614	1.10	0.28	0.696
Unavailable	0.95	0.47	0.922	1.28	0.64	0.627	1.07	0.53	0.898	0.91	0.75	0.909
CYP	0.50	0.17	0.036**	0.53	0.18	0.055*	0.49	0.17	0.037**	0.16	0.07	< 0.001***
_cons	0.74	0.42	0.601	0.93	0.54	0.905	0.24	0.13	0.006***	0.05	0.03	< 0.001***
ln (peak patient number)	1 (exposure)			1 (exposure)			1 (exposure)			1 (exposure)		

AUC, area under the concentration-time curve; CNS, central nervous system; CYP, cytochrome P450; IRR, incidence rate ratio; JPN, Japan; US, United States.

*P < 0.1; **P < 0.05; ***P < 0.01.

Plausible explanations for these results would be that there is still room for a higher level of optimization of drug use at a local level in this age of global development and that

local studies, once implemented, could make up for the deficiencies in evidence and help achieve optimization of drug use in the local population and clinical environment.

Table 3 Possible effects of development pathway on drug-related deaths

	Propensity score matching			Regression adjustment			Augmented inverse-probability weighting		
	ATE	SE	<i>P</i> > <i>z</i>	ATE	SE	<i>P</i> > <i>z</i>	ATE	SE	<i>P</i> > <i>z</i>
Dose-ranging study vs. no dose-ranging study	-17.57	8.50	0.039**	-4.72	15.84	0.766	-4.25	15.04	0.777
Japanese phase III study vs. no Japanese phase III study	-12.85	7.65	0.093*	-14.53	8.33	0.081*	-14.92	6.40	0.02**
Global study vs. no global study	-5.31	6.31	0.4	-1.27	10.98	0.908	-22.11	52.80	0.675

ATE, average treatment effect.
P* < 0.1; *P* < 0.05; ****P* < 0.01.

It is important to identify which aspects and/or components of local studies actually generate these observations. Needless to say, all local studies produce some information and experience for local medical professionals and health authorities, which may forestall serious safety events after marketing. In addition, local dose-ranging studies aim to find the best dose for the target population. Our results suggest that local dose-ranging studies contribute to the improvement in making decisions on dose setting. They are probably worthwhile, not redundant, as long as they achieve their intended objectives. However, our results suggested that there might be cases where implementing dose-ranging studies may not necessarily be a signal for safer profiles, as explained below.

First, regarding the dose itself, Japanese approved doses with reference to the ones in the United States (i.e., MDR) were not linearly associated with safety risks in our analysis. Prior papers reported that approved doses in Japan used to be lower than ones in Western countries,^{12,18} implying a safety concern about excessive doses for the Japanese population. However, our result did not support a general belief that “Japanese doses should be set lower than US doses.” Second, we found that drugs having the same approved dose in Japan and the United States generally showed a safer profile regarding drug-related deaths. It is interesting, however, that some of these “same dose” drugs showed significantly higher risks (model 2 in **Table 2**); drugs for which local dose-ranging studies were done, and the same dose was chosen based on the results showed higher risks. These findings seem to present a complicated role of local dose-ranging studies in global clinical development.

The finding that drugs having the same Japan–United States approval dose are likely to be safer on average is not surprising, because they are expected to have a PK profile in which race, ethnicity, or other regional factors do not make a substantial difference. Due to the preferable profile, they tend to have the same dose and show advantages in safety. Most of the “same dose” drugs in our sample actually showed the same or similar PK profiles in different populations, which support this finding. On top of this, companies may have an incentive to set the same recommended dose in all regions. Setting a different dose traditionally necessitates a separate phase III study with Japanese patients, although innovative approaches including exposure-matched regional dosing have been proposed to provide scientifically

solid rationale for choosing a bridging strategy study or a global phase III study with a different dose.¹⁹ This would sometimes incur additional dosage forms and marketing materials only for the Japanese market. Choosing the same “global dose” allows companies to use foreign data and skip the phase III study in Japan and, thus, possibly elude some local costs.

The use of a bridging strategy was associated with lower risks. By definition, bridging studies are conducted in the target country (i.e., Japan). Companies usually establish a “bridge” by showing similarities in efficacy/safety profiles including the dose-response relationship and also by investigating PK profiles in each population. For all the drugs developed and approved under a bridging strategy, PK/pharmacodynamic profiles in local populations are, thus, scrutinized, and doses for the target population are carefully optimized, which may result in preferable post-marketing outcomes. The bridging strategy is commonly applied to drugs that have already been marketed in preceding countries (e.g., the United States), which may also explain why such drugs look safer in the Japanese market.^{20–22}

Our analysis did not show that drugs with pivotal global studies in their data package had significant safety risks, but they were heterogeneous in terms of drug safety; drugs without local dose-ranging studies tended to be riskier than ones with local dose-ranging studies (model 3, **Table 2**), whereas other conditions remained the same. Again, local dose-ranging studies seem to add useful information to the local optimization.

In this regard, it is interesting to note that some drugs for which efficacy/safety was established in global studies were given special attention and guidance during the NDA review by the PMDA. (Dabigatran etexilate mesylate/dabigatran etexilate methanesulfonate and tofacitinib citrate are examples of cases in which Japanese dose-ranging studies were conducted and then followed by global studies. Global studies for both drugs were conducted at the same dose as in the United States, and their recommended doses in the first submission dossier were also the same as those in the United States. However, the PMDA instructed the applicants to lower their doses during the review process. In the case of tofacitinib citrate, the US Food and Drug Administration (FDA) instructed to lower the dose, and this might have impacted the PMDA’s decision to decrease Japan’s approval dose. These examples show how local dose-ranging studies

help to optimize local doses not only at the developmental stages but even after NDA submission. Without data from a Japanese dose-ranging study, the PMDA could not have judged whether lowering the dose was appropriate, even if some safety concerns were detected in global studies or after marketing.

The profile of global studies should also be considered. For peramivir and edoxaban tosilate hydrate, the pivotal global phase III studies used for both drugs' approval applications were Asian studies in which Japan, Taiwan, and/or Korea participated because the sponsors were concerned about ethnic differences in safety profiles. They were not "typical" global studies that were conducted worldwide mainly led by sponsors in the United States or the European Union. Balancing local optimization under a global development pathway can be achieved in that way.

Regarding the nationality of pharmaceutical companies, drugs developed by Japanese companies were less likely to have drug-related deaths in Japan. Because the nationality of companies is founded on many unobservable characteristics and behaviors, it is difficult to specify what caused this finding. We suppose that there is some advantage that accrues to local companies to achieve optimization, as has been reported in the context of launching success.^{23,24} Our finding that drugs that were developed outside Japan first tended to have a higher risk of drug-related deaths in Japan, suggests the importance of considering local concerns at early developmental stages. For global companies, it is common that critical components of drug usage, including the dosing regimen, are proposed by the headquarters, and it is practically impossible for local branches to modify the established global development plans.

There are growing concerns regarding how to choose an optimal dosage for each region.^{25,26} A recent example of drugs drawing attention to approved doses was paliperidone palmitate, which was approved in 2013 in Japan based on a global NDA data package with the recommended dose established for the global markets. After multiple safety events in markets, the PMDA issued a warning letter on the possible risks and recommended users consider lower doses.²⁷ Ceritinib is another example where side effects became a problem in the postmarketing phase. Ceritinib was approved for the dosage of 750 mg/day, but an application to reduce the dosage to 450 mg/day was made to manage gastrointestinal toxicity.

In the era of global drug development, the implementation of MRCTs has become a standard option. The first guideline on MRCTs (ICH-E17 guideline) was adopted in 2018.²⁸ It describes general principles for the planning and design of MRCTs with the aim of increasing the acceptability of MRCTs in regulatory submissions. MRCTs can facilitate the simultaneous global development of a drug, reducing the number of clinical studies conducted separately in each region and thereby minimizing the "unnecessary" duplication of studies. The guideline suggests a few recommended practices, such as implementing PK studies of applicable parameters across the regions at an early phase or adding further exploratory studies if clinically relevant differences among regions are observed.

Although the scientific principles of the guideline are seen as acceptable by all the stakeholders, our results seem to present possible concerns that regional variabilities might be overlooked and the values of local dose-ranging studies and local pivotal studies might be underestimated in cases where MRCTs are the default option for global development.

Our analysis suggests that local dose-ranging studies and local phase III studies seem to contribute to postmarketing drug safety, probably through optimization of drug use for local populations. Local studies can provide substantial evidence on decisions not only during clinical development but also during the regulatory review process. Mechanisms of safety improvement may include optimal dose setting, accumulating information, and know-how among all the players (i.e., physicians, pharmaceutical companies, and regulatory authorities) through local trial implementation and improvement in Japanese package inserts, especially in adverse drug reaction sections. If these relationships were causal, current stakeholders would seem to have a rationale to insist that pharmaceutical companies and regulators worldwide need to more seriously consider the balance and tradeoffs between the efficiency in industrial drug development and the accruing costs to achieve optimization for local or subdivided populations.

Our analysis has certain limitations. This is an exploratory study intended to detect possible associations. It is highly possible that unobserved confounders exist and were not fully controlled within the set of explanatory variables. We did not apply variables that may directly reflect potential safety risks of drugs (e.g., therapeutic index), although risks due to ethnic differences were partly adjusted by variables related to AUC and metabolic enzymes. In the context of drug development, it is inevitably difficult to draw a clear line between what can be intervened and what cannot, which makes discussions on causality somewhat complicated. The results give a possible explanation or mechanism on how imbalance (or heterogeneity) in drug safety occurred solely in Japan, but they do not necessarily support an assertion that "local phase II/III studies are a must." Such an assertion should be supported by rigorous benefit and risk considerations in terms of public health, which is apparently beyond our scope. With emerging markets in Asian countries, for example, the "local" concept itself has been changing. It may be necessary to apply broader frameworks and methodologies in clinical evaluation to respond to these global trends. We cannot elude all the issues stemming from "under-reporting" of safety events.

In conclusion, our findings suggest that global and local clinical development pathways are associated with postmarketing drug safety in local target populations. Drugs for which dose-ranging studies or pivotal phase III studies using a local population were conducted tend to show lower safety risks in the local population. Drugs resulting in the same United States–Japan dose may not be homogeneous in terms of drug safety. Pharmaceutical companies and regulatory authorities may need to re-examine if they are striking a right balance between the efficiency of drug development and the level of optimization of drug use in each local population.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Table S1. Data set for the analysis.

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