Assessment of the impact of Japanese-specific long-term safety data on new drug approval

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Abstract
Under the International Council for Harmonization (ICH)-E1 guideline for drugs intended for chronic or repeated intermittent use in non-life-threatening diseases, data from 100 patients exposed for a minimum of 1 year are required to be included in the safety data base of a new drug application. In response to the recent globalization of drug development, the Ministry of Health, Labour, and Welfare of Japan requires that the data according to the ICH-E1 guideline should be collected from 100 Japanese patients by the administrative notice of Basic Principles on Global Clinical Trials (reference cases) by considering ethnic differences in safety between Japanese and foreigners. In this study, we assessed Pharmaceuticals and Medical Devices Agency (PMDA) review reports of new drugs from 2016 to 2020 that include safety data for 100 Japanese patients exposed to these drugs for a minimum of 1 year to see if the study data led to the detection of Japanese-specific safety issues. The result showed that the safety data from these patients provided only marginal value to identify Japanese-specific safety issues, and no drugs were subjected to regulatory measures. Based on these studies and the fact that Japanese-specific safety differences detected for a few drugs did not lead to adaptations of drug regulatory measures, we would like to propose not to make it a rule to collect safety data from 100 Japanese patients exposed at least 1 year, while keeping the ICH-E1 guideline.

Study Highlights
WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
Given long-term repeated administration of drug/s for non-life-threatening diseases, a safety study on 100 or more patients with 1-year administration is required by the ICH-E1 guidelines. The administrative notice by the Ministry of Health, Labour, and Welfare (MHLW) requires that the long-term safety data should be collected from Japanese patients. The usefulness of this requirement has not been confirmed by systematic examination of the results.

WHAT QUESTION DID THIS STUDY ADDRESS?
To what extent do the long-term safety data on at least 100 Japanese patients required by the administrative notice contribute to the identification of new safety signals that result in package insert adaptation?
INTRODUCTION

Prior to the approval of new drugs, their efficacy and safety are investigated in clinical studies, wherein it must be confirmed that the benefits outweigh the risks. In terms of safety, drugs administered for a long period are needed to determine whether there are adverse reactions that occur during long-term administration and whether the incidence of adverse reactions increases during administration. The International Council for Harmonization (ICH)-E1 guideline “The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions” stated that if drugs are intended for long-term treatment (chronic or repeated intermittent use for longer than 6 months) of non-life-threatening diseases, data from 100 patients exposed to these drugs for a minimum of 1 year is required to be included in the part of the safety data base of a new drug application.1

Multiregional development of drugs has recently been increasing. Because ethnic differences may affect the efficacy and safety of drugs, the ICH-E5 guideline “Ethnic Factors in the Acceptability of Foreign Clinical Data” describes regulatory strategies that minimize duplication of clinical data and facilitate acceptance of foreign clinical data.2 In response to the ICH-E5 guideline, the Ministry of Health, Labour, and Welfare (MHLW) of Japan announced two requirements regarding the number of the Japanese population in the multiregional clinical trials; one is the notification “Basic Principles on Global Clinical Trials” in September 2007 and the other is the administrative notice “Basic Principles on Global Clinical Trials (reference cases)” in September 2012. The notification in 2007 demonstrates the requirement of the Japanese sample size generally by calculating from the point of efficacy in order to evaluate the consistency across regions. The administrative notice in 2012 requires safety data from at least 100 Japanese patients exposed for a minimum of 1 year has been discussed controversially. Ohta et al. compared Japanese and US package inserts of new drugs approved between September 1999 and June 2012 and reported that there was no case in which the safety information differed between the Japanese and US package inserts.5 They expressed their doubts about the necessity of additional data collection on top of the number of long-term administrations with regard to Japanese patients.

In this study, we focused on the requirement of a minimum of 100 Japanese patients for long-term safety in the administrative notice of 2012 and evaluated the extent to which long-term safety studies in Japanese patients have a regulatory impact based on the review reports prepared by the Pharmaceuticals and Medical Devices Agency (PMDA). First, review reports of the last 5 years (from 2016 to 2020) were examined, and new drugs that could be compared between long-term studies in Japan and overseas were selected. Then, we evaluated the drug development strategy that each company implemented in order to satisfy the 100 Japanese patients rule in terms of long-term safety (e.g., conducting a domestic study to add Japanese patients) in the administrative notice, “Basic Principles on Global Clinical Trials (reference cases).” Finally, we evaluated ethnic differences in long-term safety for each new drug and investigated whether the differences, if any, led to a regulatory action.

METHODS

Review reports of new drugs prepared by the PMDA from September 2016 to August 2020 were examined. The term was set by considering the date of September 2012 in which
the administrative notice was published, the time to prepare and conduct long-term safety studies, and the time to review drugs. The definition of new drugs in this study is a drug containing a new active substance, a new indication and/or new dosage, and administration. We selected new drugs for which safety in long-term administration could be compared between Japan and overseas, such as new drugs for which studies were conducted to collect data from 100 Japanese patients exposed for at least 1 year according to the administrative notice in Japan, and those for which confirmatory studies included the safety data of 100 Japanese patients. The following drugs were excluded from our investigation:

1. Drugs for which long-term safety studies were waived in Japan, such as biosimilars or drugs designed for off-label use.
2. Anticancer drugs or drugs not requiring long-term safety data according to the ICH-E1 guideline and therefore having no information of at least 1 year administration data in their clinical package.
3. New drugs for which phase III and long-term safety studies were conducted only in Japan.
4. New drugs for which the data from 100 Japanese patients for at least 1 year administration is exempted because the data could not be collected due to rare diseases or because the data of already approved indications were used in the application of new additional indications.

In the selected review reports, we investigated the drug development strategy of the applicants on how to satisfy the necessity of examining 100 Japanese patients for long-term safety. Furthermore, we investigated whether there are ethnic differences in long-term safety based on the description of PMDA’s opinion in the review reports and whether the differences led to new precautions or addition of new safety information in the package inserts. The analysis of review reports and package inserts was conducted according to the following four steps:

Step 1. Whether PMDA pointed out ethnic differences in safety by comparing the long-term safety data of 100 Japanese patients exposed for a minimum of 1 year with that in foreign populations.
Step 2. Whether PMDA pointed out ethnic differences in the results of the integrated analysis of various studies with less than 1 year administration to the patients.
Step 3. Whether the precautions in the Japanese and US package inserts were described or not by reflecting ethnic differences that were pointed out in the review reports.
Step 4. Whether the precautions in the Japanese and US package inserts were described or not for a drug for which PMDA did not comment any ethnic differences in the review reports.

The United States-Japan comparison of package inserts was based on the Japanese package insert at the time the Japanese review report was finalized and the most recent version of the US package insert before the Japanese review report was finalized. The contents of “Contraindications,” “Careful Administration,” and “Important Precautions” in the Japanese package inserts were checked to see if they were included in corresponding parts of the US package insert.

The PMDA review reports and Japanese package inserts were obtained from the PMDA homepage. US package inserts were from the US Food and Drug Administration (FDA) homepage.

RESULTS

Figure 1 shows which new drugs were selected for this investigation. There were a total of 423 PMDA review reports from September 2016 to August 2020. Based on the selection criteria steps (1) to (4) as described in the METHODS section, we selected 38 review reports for this analysis.

Among the new drugs subject to long-term safety studies according to the ICH-E1 guideline, 115 could not be included in the analysis because only domestic long-term safety studies were included in clinical data packages. Of the remaining 112 cases, 74 had to be excluded due to the fact that less than 100 Japanese patients were included in long-term administration studies.

Drug development strategies to obtain data sets from 100 Japanese patients

Table 1 shows the drug names and target diseases for each drug development strategy. The new drugs with additional studies or additional cohorts of Japanese patients accounted for 63% (24/38), and the new drugs for which 100 Japanese patients exposed for a minimum of 1 year were accumulated in the multinational clinical trials accounted for 37% (14/38). Both strategies were used regardless of the disease.

Ethnic differences in long-term safety

Table 1 shows the presence or absence of ethnic differences in long-term safety based on the description of PMDA’s opinion regarding the comparison of safety between Japan and overseas in the review reports of selected new drugs. Ethnic differences pointed out in the review reports and the differences in their package insert descriptions are shown in Table 2. None of the drugs of the PMDA reviewed data from 100 Japanese patients exposed for at least 1 year showed ethnic differences with regard to safety. Based on the integrated
analysis by including studies with an administration period of less than 1 year, the new drugs that were concluded to show similar safety profiles or no differences in them accounted for 76% (29/38), and the new drugs that had ethnic differences in safety between the Japanese population and foreign or overall population accounted for 16% (6/38). For two drugs, namely sarilumab and certolizumab pegol, the PMDA did not comment at all on ethnic differences in 3 of 38 review reports, although the applicants clearly stated that there were no ethnic differences. For the remaining drug, namely sodium zirconium cyclosilicate hydrate, ethnic differences were not commented on at all in the respective PMDA review report.

We then looked in more detail into the six cases (6/38) considered to show ethnic differences. In four of the six cases, the ethnic differences were identified in the exposure duration of less than 1 year. For blonanserin, adverse events at the dermal application site, which were considered to be frequent in Japanese patients, tended to be observed within 6 weeks after administration. For upadacitinib hydrate, infections and cytopenia, which were also frequent in Japanese patients, tended to be observed within 12 or 14 weeks. For sacubitril valsartan sodium hydrate, hypotension, which was observed frequently in Japanese patients, occurred with a high incidence immediately after the beginning of the administration and at the time the dosage was increased. The PMDA also recognized that the incidence of pneumonia was higher in Japanese patients with the use of fluticasone, umeclidinium, and vilanterol. The incidence in the 24-week administration study was 10% (4/40 patients) in the Japanese population and 2.7% (14/527) in the overall populations, and the incidence in the 52-week administration study was 18.1% (27/149) in the Japanese population and 7.6% (317/4151) in the overall populations. Thus, a higher incidence in Japanese patients as compared to all patients was already observed in the 24-week treatment study. In the other two drugs, namely rasagiline mesylate and baricitinib, it was not concluded in the review reports whether the differences in the incidence of Japanese as compared to all patients were similar or not between 1 year or shorter periods of administration.

To investigate whether a regulatory response occurred regarding the ethnic differences described in the review report, the relevant descriptions were compared between Japanese and US package inserts at the time of approval in Japan (Table 2). Among the six cases that were evaluated to have some ethnic differences in the integrated analysis, blonanserin, which had not been approved in the United States, was excluded from investigation. As for the remaining five cases, the safety information described in Japanese and US package inserts were similar, except for baricitinib for which the incidence of adverse reactions in Japanese patients was additionally described, and sacubitril valsartan sodium hydrate for which attention was called by considering other criteria apart from clinical study results.

Although ethnic differences were not discussed by the PMDA review reports on sarilumab, there were differences in the descriptions in the package inserts between Japan and the

![FIGURE 1](image-url)
### TABLE 1  Drug development strategies to elucidate possible ethnic differences in long-term drug safety: (a) additional Japanese studies / cohorts, (b) multiregional trials including 100 ethnic Japanese exposed for 1 year to the mentioned drugs

| Development strategy | Fix date of review report | Drug name | Main target disease | Difference of safety |
|----------------------|---------------------------|-----------|---------------------|---------------------|
| (a)                  | 1610                      | Vilanterol Trifenatate/fluticasone furoate | COPD | × |
|                     | 1611                      | Eplerenone | Chronic cardiac failure | × |
|                     | 1611                      | Apremilast | Psoriasis vulgaris | × |
|                     | 1702                      | Guanfacine hydrochloride | ADHD | × |
|                     | 1702                      | Golimumab | Ulcerative colitis | × |
|                     | 1702                      | Fluticasone furoate | Asthma | × |
|                     | 1707                      | Sarilumab | Rheumatoid arthritis | - |
|                     | 1711                      | Semaglutide (subcutaneous injection) | Type 2 diabetes mellitus | × |
|                     | 1802                      | Rasagiline mesylate | Parkinson’s disease | 〇 |
|                     | 1805                      | Vedolizumab | Ulcerative colitis | × |
|                     | 1901                      | Dapagliflozin propylene glycolate hydrate | Type 1 diabetes mellitus | × |
|                     | 1902                      | Risankizumab | Psoriasis | × |
|                     | 1902                      | Peficitinib hydrobromide | Rheumatoid arthritis | × |
|                     | 1904                      | Vedolizumab | Crohn’s disease | × |
|                     | 1905                      | Blonanserin (dermal administration) | Schizophrenia | 〇 |
|                     | 1905                      | Glycopyrronium bromide/formoterol fumarate | COPD | × |
|                     | 1905                      | Budesonide/ glycopyrronium bromide/ formoterol fumarate | COPD | × |
|                     | 1908                      | Safinamide mesylate | Parkinson’s disease | × |
|                     | 2002                      | Sodium zirconium cyclosilicate hydrate | Hyperkalemia | - |
|                     | 2002                      | Lurasidone hydrochloride | Schizophrenia | × |
|                     | 2005                      | Semaglutide (tablets) | Type 2 diabetes mellitus | × |
|                     | 2005                      | Opicapone | Parkinson’s disease | × |
|                     | 2005                      | Indacaterol acetate/ mometasone furoate | Asthma | × |
|                     | 2005                      | Indacaterol acetate/ glycopyrronium bromide/ mometasone furoate | Asthma | × |
| (b)                  | 1705                      | Baricitinib | Rheumatoid arthritis | 〇 |
|                     | 1710                      | Dupilumab | Atopic dermatitis | × |
|                     | 1811                      | Romosozumab | Osteoporosis | × |
|                     | 1902                      | Dupilumab | Asthma | × |
|                     | 1902                      | Fluticasone furoate/ umeclidinium bromide/ vilanterol trifenate | COPD | 〇 |
|                     | 1908                      | Ivabradine hydrochloride | Chronic cardiac failure | × |
|                     | 1911                      | Lemborexant | Insomnia | × |
|                     | 1911                      | Upadacitinib hydrate | Rheumatoid arthritis | 〇 |
|                     | 1911                      | Certolizumab pegol | Psoriasis vulgaris | - |
|                     | 2001                      | Abatacept | Rheumatoid arthritis | × |
|                     | 2002                      | Insulin lispro | Type 1 and 2 diabetes mellitus | × |
|                     | 2004                      | Sacubitril valsartan sodium hydrate | Chronic cardiac failure | 〇 |
|                     | 2005                      | Tildrakizumab | Psoriasis vulgaris | × |
|                     | 2008                      | Filgotinib maleate | Rheumatoid arthritis | × |

“〇” means that differences in safety were found, “×” means no differences and “–” means no description related to differences in the review reports. Abbreviations: ADHD, attention deficit hyperactivity disorder; COPD, chronic obstructive pulmonary disease.
United States. The precaution for interstitial pneumonia was described only in the Japanese package insert of sarilumab, but there were no differences in other contents of the package inserts between Japan and the United States. According to the review report of sarilumab, interstitial pneumonia was reported in one patient in the Japanese studies, and 12 patients in the pooled population of overseas clinical studies. PMDA instructed that the precaution in the Japanese package insert of sarilumab should be included because there is a possibility of concomitant use with other rheumatoid drugs.

**DISCUSSION**

In this study, we selected and investigated 38 review reports of new drugs that are intended for chronic or repeated intermittent use of non-life-threatening diseases. These reports were made after September 2016, following the administrative notice of “Basic Principles on Global Clinical Trials (reference cases)” published in 2012. The new drugs with newly obtained clinical data from 100 Japanese patients exposed for a minimum of 1 year accounted for 63% of review reports (24/38). This means that applicants took approaches specific to Japan for more than half of new drug applications to meet the administrative notice in Japan. The remaining new drug review reports (14/38) presented data of 100 Japanese patients exposed for a minimum of 1 year in multiregional clinical trials. Thus, it appeared that safety information specific to Japanese patients, which follows the administrative notice, could be obtained within the framework of multiregional clinical trials.

We then investigated the presence or absence of ethnic differences in long-term safety and differences in descriptions in the package inserts, which were made based on PMDA's opinion on the comparison of safety between the Japanese population and foreign or overall populations in the review reports. As a result, we found that the studies with 100 Japanese patients exposed at least 1 year did not contribute to the detection of ethnic differences in safety. Even with the integrated analysis of various studies, including studies with an administration period of less than 1 year, PMDA evaluated that there was no difference in safety between Japanese and foreign or overall populations in 76% (29/38) of the review reports. Among the new drugs (6/38) that had ethnic differences in safety between Japanese population and foreign or overall populations, we compared the descriptions in the package inserts in Japan and the United States for five cases, excluding one case that had not been approved in the United States, and found that precautions were similar except that a little reference information was added to the Japanese package inserts. Based on these investigations, it can be concluded that the contribution of the results from the clinical studies with 100 Japanese patients exposed at least 1 year toward the regulatory response in the package inserts can be considered as marginal.

The ICH-E1 guideline requires the results of the clinical studies with 100 patients exposed at least 1 year to evaluate long-term safety of new drugs for their approval. The Japanese administrative notice requires that the data based on the ICH-E1 guideline should be collected from the Japanese population in general by considering that adverse events can be overlooked by ethnic differences in safety between Japanese population and foreign populations related to the ICH-E5 guideline. The statistical rationale for the requirement of the ICH-E1 guideline appears to be based on the Rule of Three.15 For example, when the incidence of adverse events is 1%, the probability to detect at least one adverse reaction is 63% for 100 patients, but it will be 95% for 300 patients, based on the Rule of Three as follows:

$$Pr (X \geq 1|p, n) = 1 - \exp(-np),$$

where $Pr$ is the probability to detect adverse reactions, $X$ is the number of adverse reactions, $p$ is the proportion of adverse reactions, and $n$ is the sample size of the overall populations. The purpose of the requirement for safety data in the ICH-E1 guideline is to detect adverse events of 3% incidence in new drug review. The point of the Japanese regulatory rationale to collect data from 100 Japanese patients is whether adverse events of 3% incidence can be detected by the data from less than 100 Japanese patients. We examined the probability of detection with less than 100 Japanese patients. Figure 2 shows the probability of detection affected by the sample size of Japanese patients with a 3% incidence of adverse reactions. The probability of detection is 95% when the number of Japanese patients is 100, and it decreases only slightly when the number of Japanese patients is not much less than 100. We also examined the probability of detection of total 100 patients consisting various number of Japanese population and foreign population when there are ethnic differences in safety between Japanese population and foreign populations. The effect of sample size of Japanese population as compared to overall populations on the probability of adverse reactions is as follows. The incidence proportion of adverse reactions in the entire clinical data package can be expressed as a sum of the incidence proportion of adverse reactions in Japanese and foreign populations weighted by the proportion of each population as follows:

$$p_{\text{Overall}} = \left(\frac{n_{\text{Japan}}}{n_{\text{Japan}} + n_{\text{Foreign}}}\right) p_{\text{Japan}} + \left(\frac{n_{\text{Foreign}}}{n_{\text{Japan}} + n_{\text{Foreign}}}\right) p_{\text{Foreign}},$$

where $p_{\text{Overall}}$ is the proportion of adverse reactions for overall population, $p_{\text{Japan}}$ is the proportion of adverse reactions for the Japanese population, $n_{\text{Japan}}$ is the number of Japanese patients, $p_{\text{Foreign}}$ is the proportion of the adverse reactions for foreign populations, and $n_{\text{Foreign}}$ is the number of foreign patients.
### Table 2: Difference in safety between the Japanese and overall population in the review reports and difference in precautions between US and Japanese package inserts

| Drug name                        | Main target disease | Differences in safety according to PMDA review reports                                                                 | Differences in package inserts content                                                                 |
|----------------------------------|---------------------|------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Sarilumab                        | Rheumatoid arthritis | Interstitial pneumonia was reported in one patient in the Japanese studies, and 12 patients in the pooled population of overseas studies | No difference except for information of interstitial pneumonia: Japanese package insert has precaution for interstitial pneumonia in “Careful Administration.” US package insert has no information about interstitial pneumonia. |
| Blonanserin (dermal administration) | Insomnia            | Incidence of adverse events on administration site, 42.7% (44/103) in the Japanese long-term study, is higher than that, 18.6% (97/521), in overall population in the multiregional study. However, the same trend was seen in the 6 weeks administration of the multiregional clinical trial. For example, incidence of erythema is 14.0% (8/57) in Japanese population and 9.3% (18/194) in overall population. | Not approved in the United States                                                                 |
| Baricitinib                       | Rheumatoid arthritis | Incidence of adverse events, 87.8% (448/510) in Japanese population is higher than that, 76.7% (2,617/3,411), in overall population. There was no clear difference in safety profile between the Japanese population and overall population that could affect tolerability. | No difference except for adding information of Japanese patients Both Japanese and US package inserts have the precaution for viral reactivation including herpes virus reactivation (e.g., herpes zoster). The information that many cases of serious infections in Japanese patients were herpes zoster was added in the Japanese precaution. |
| Fluticasone furoate/umeclidinium bromide/vilanterol trifenatate | COPD | Incidence of pneumonia, 18.1% (27/149), in Japanese population is higher than that, 7.6% (317/4,151), in overall population in the multi-regional clinical trial. | No difference                                                                                                                                                  |
| Upadacitinib hydrate             | Rheumatoid arthritis | Incidence of infection and cyopenia, 81.4% (302/371) and 5.7% (21/371) as neutropenia, in Japanese population is higher than that, 56.2% (2,606/4,638) and 3.9% (182/4,638), in overall population. The same trend was seen at 12 and 14 weeks’ administration. Incidence of infection and cyopenia in Japanese population is 38.4% (38/99) and 4.0% (4/99) as neutropenia, and that in overall population 28.7% (276/963) and 2.9% (29/963). | No difference                                                                                                                                                  |
| Sacubitril valsartan sodium hydrate | Chronic heart failure | Incidence of hypotension, 37.84% (42/111), in the Japanese study is higher than that, 24.43 (1,027/4,203), in the overseas study. Highest incidence of hypotension was observed within 1 month after the start of administration in both Japanese and overseas study. | No difference except for precautions at the start of administration and when increasing the dose. No information for onset time of hypotension is found in US package insert. |
| Certolizumab pegol               | Psoriasis vulgaris  | Not commented by PMDA                                                                                                    | No difference                                                                                                                                                  |
| Rasagiline mesylate              | Parkinson’s disease | Although incidence of adverse events is different between 62.4% (73/117) in the Japanese study and 94.6% (141/149) in the overseas study, adverse events are similar between the two studies. | No difference                                                                                                                                                  |
| Sodium zirconium cyclosilicate hydrate | Hyperkalemia       | Not commented by PMDA                                                                                                    | No difference                                                                                                                                                  |

Abbreviations: COPD, chronic obstructive pulmonary disease; PMDA, Pharmaceuticals and Medical Devices Agency.
evaluated the incidence proportion of adverse reactions of overall population when the incidence proportion of adverse reactions in the Japanese population is 4% and that in foreign populations is 0%, 1%, 2%, or 3% and the number of patients in overall populations is 100, as required by the ICH-E1 guideline. The results of incidence proportion of adverse reactions in overall populations are shown in Figure 3. If the incidence of adverse reactions in foreign populations is 2% and the number of Japanese patients is more than 50, the incidence of adverse reactions in overall populations is higher than 3%, which matches the ICH-E1 guideline. Thus, the data from overall 100 patients, including foreign populations, can be enough to detect the adverse reactions even with less than 100 Japanese patients in multiregional clinical development. In many of the recent global drug developments, the number of overall patients greatly exceeds 100. Under this circumstance, the adverse reactions related to the ICH-E1 guideline are expected to be detected even if the incidence proportion is lower than 3%. For example, when the incidence proportion of an adverse reaction in the Japanese population and foreign populations is 4% and 1%, respectively, and the number of Japanese and foreign patients is 50 and 150, respectively, the incidence proportion for the overall population is 1.75% according to Equation 2, but the probability to detect at least one adverse reaction is 97% in overall population according to Equation 1. From these theoretical considerations the following can be concluded. (1) The probability to detect an adverse reaction decreases only slightly when the number of Japanese patients is not much less than 100. (2) The purpose of the Japanese-specific long-term safety study can be achieved by using the data from the overall population, depending on the number of patients and the incidence proportion of adverse reactions in Japanese and foreign populations.

We found in our investigation on the PMDA’s review reports that there were no new drugs for which adverse reactions specific to Japanese patients were detected in the long-term safety data of Japanese patients. Some cases showed differences in the incidence of adverse reactions between the Japanese population and foreign or overall population in the integrated analysis, but these differences did not lead to regulatory response in the package inserts. Thus, the above theoretical considerations and the analysis of the review reports may lead to the conclusion that the implementation of a long-term safety study on 100 Japanese patients exposed 1 year has only marginal impact for the reviews. Obviously, when a strong concern on long-term safety in Japanese people is obtained from information other than clinical studies, such as safety information on other indications of the same drug, or safety information of drugs of the same category, studies on Japanese patients might be recommended.

Drugs are approved based on the results of clinical studies while considering the balance between efficacy and safety. However, safety information obtained at the time of approval is generally limited, and adverse reactions may be found through the use of drugs in a great number of patients in the postmarketing phase. In the case of the antirheumatic drug leflunomide, interstitial pneumonia as an adverse reaction was not detected in the drug review for the data neither from the Japanese long-term study in which 110 Japanese patients were administered the drug for greater than or equal to 52 weeks nor from the overseas
long-term study in which 182 non-Japanese received the drug for greater than or equal to 52 weeks. However, the adverse reaction mentioned above was found in the postmarket phase in Japan. Azuma et al. reported a 100-fold higher incidence rate of an adverse reaction, namely interstitial pneumonia, in Japan as compared to overseas. Thus, it is obviously important to examine local safety information not only before approval but also throughout the drug life cycle, including the postmarketing phase. In Japan, pharmacovigilance, which has been enhanced by ICH, is well-implemented and the risk management plan have been institutionalized and improved. Risk minimization activities and pharmacovigilance activities are now conducted based on identified risks, potential risks, and lack of information, in addition to ordinal pharmacovigilance, such as individual case reports of adverse events. Moreover, safety measures, such as precautions in the package inserts, are generally based on the comprehensive evaluation of not only the clinical studies used for application but also various other information, such as the mechanism of drug action, nonclinical study data, results of other clinical studies related to the drug, and the information on drugs of the same category.

In conclusion, based on this study and the recently strengthened comprehensive safety management throughout drug life cycles, we would like to propose that it is acceptable to delete the requirement for the data from 100 Japanese patients exposed to the drug in focus for at least 1 year while following the ICH-E1 guideline.

CONFLICT OF INTEREST
The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
S.U., S.S., J.A., and M.I. wrote the manuscript. S.U. designed the research. S.U. and J.A. performed the research. S.U. and J.A. analyzed the data.

DISCLAIMER
The views expressed in this article are those of the authors and do not necessarily reflect the official views of the Pharmaceuticals and Medical Devices Agency.

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