

Points to Consider for Implementation of the ICH E17 Guideline: Learning from Past Multiregional Clinical Trials in Japan

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We identified the major points that are described in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E17 guideline but have not been considered in the past multiregional clinical trials (MRCTs) used for drug approval in Japan to elucidate potential challenges in the implementation of the ICH E17 guideline in Japan. Based on the analysis of 167 MRCTs of 130 drugs, several points, such as the same dose setting and consistency between the overall and Japanese populations, in addition to good clinical practice compliance, have been well considered in $\geq 75\%$ of MRCTs. In contrast, the use of relevant guidelines for disease and primary end point definitions, standardization of efficacy/safety information, sample size allocation, as well as training/validation on subject selection and primary end point, have been addressed less adequately and may need to be considered when planning future MRCTs. This study provides useful information for the implementation of the ICH E17 guideline in Japan.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E17 guideline is expected to promote international harmonization in application of multiregional clinical trials (MRCTs); however, the implementation of the ICH E17 guideline for drug approval in Japan still presents challenges.

WHAT QUESTION DID THIS STUDY ADDRESS?

What are the major points described in the ICH E17 guideline that have not been considered in past MRCTs?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The use of relevant guidelines for disease definitions and primary end points, standardization of efficacy/safety

information, sample size allocation, as well as training/validation on subject selection and primary end points were identified as less-considered key principles in the past MRCTs, including Japan.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study provides useful information for implementing the ICH E17 guideline in Japan. In planning future MRCTs for drug approval in Japan, more attention may be needed on the less-considered key principles.

Multiregional clinical trials (MRCTs) are frequently used in drug development to promote rapid patient access to new drugs simultaneously in various regions.¹⁻³ To increase the acceptability of MRCTs in global regulatory submissions, the E17 guideline entitled “General principles for planning and design of multi-regional clinical trials” was published by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in November 2017⁴ and was followed by regulatory implementation in June 2018 in Japan and the

European Union and in July 2018 in the United States. Prior to the publication of the ICH E17 guideline, a Japanese guideline on MRCTs entitled “Basic principles on global clinical trials” was published in 2007,⁵ followed by the publication of a related guideline in 2012.⁶ These Japanese guidelines resulted in a marked increase in Japanese participation in MRCTs.^{3,7}

The ICH E17 guideline is expected to promote international harmonization of the application of MRCTs, although challenges remain for its implementation in all regions. In this study, we have

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identified the major points that are described in the ICH E17 guideline but have not been considered in the past MRCTs used for drug approval in Japan to elucidate potential challenges in the implementation of the ICH E17 guideline in Japan.

METHODS

Data sources and target MRCTs for this study

In this study, we used information on MRCTs that were submitted for approval in Japan, because those MRCTs included not only Japan but also many other regions.^{3,8} Data from them had been usually submitted to various regulatory agencies, including those in Japan, the United States, and the European Union. Another reason for using the information on those MRCTs was that modules 1 and 2 of the common technical document (CTD) submitted by marketing authorization holders (i.e., pharmaceutical companies) and the Pharmaceuticals and Medical Devices Agency (PMDA; Japanese regulatory agency) review reports for a specific product, including information on MRCTs, are publicly available in Japan.⁹ Thus, detailed information was available for analysis in this study. For example, information from the CTD was used to confirm the details of the MRCT design and analysis, as well as to evaluate the process of training for handling data and efficacy/safety assessment.

In detail, we collected data from a list of approved products on the website of the PMDA¹⁰ and identified drugs that were approved between April 2007 and March 2018 based on MRCTs as a pivotal clinical study in Japan; note that the data collected are before the implementation of ICH E17 in Japan. “Pivotal clinical study” was defined as an important clinical study for efficacy evaluation among submitted studies categorized as “major sources for evaluation” (“HYOUKA SIRYO” in Japanese), as described in the PMDA review reports. If a clinical study was mentioned as a “reference” (“SANKO SIRYO” in Japanese) in a review report, the study was not classified as a pivotal clinical study. Furthermore, we selected “studies for which approval application materials are disclosed” and “confirmatory studies” out of “pivotal clinical studies.” Therefore, “studies such as nondisclosure of approval application materials,” “nonconfirmatory studies,” and “long-term treatment studies” were excluded. For “studies such as nondisclosure of approval application materials,” the PMDA website⁹ does not have application materials related to drugs with a new indication or new dosage or combination prescription drug with similar formulations.

Process to identify the key principles of the ICH E17 guideline used for analysis

The process used to identify the key principles of the ICH E17 guideline for analysis in this study is shown in **Figure S1**. The contents of the ICH E17 guideline were carefully and independently reviewed by two persons, including a member of the ICH E17 expert working group. Important principles described in the ICH E17 guideline were selected for each section in section 2 (general recommendations in the planning and design of MRCTs). We only focused on the major principles, which meant we focused on recommendations that described an ideal situation and were usually stated in an initial or early paragraph of each section of the ICH E17 guideline, because our focus in this study was to identify the major points that have been considered when conducting MRCTs and that will be necessary to consider in future MRCTs. Therefore, our analysis did not cover other recommendations, although the ICH E17 guideline describes many optional cases, reflecting practical situations. For example, in section 2.2.3, “Selection of Doses for Use in Confirmatory MRCTs,” we picked “The dose regimens in confirmatory MRCTs should in principle be the same in all participating ethnic population” as the major principle, but the ICH E17 guideline provides other options to use a different dosing regimen if appropriate. If a consensus on the major principle could not be reached between two persons, a third person, who was a member of the ICH E17 expert working group, was included in the discussion to help achieve a consensus.

Next, the key principles used for analysis were created based on the major principles selected. In this step, we recognized the limitations of the application of the ICH E17 guideline principles in MRCTs that had been initiated before implementation of the ICH E17 guideline. Therefore, we modified the major principles selected in a simple way so that the principles can be applied to the past MRCTs and its assessments could be performed more objectively. For example, in section 2.2.5, “Sample Size Planning,” the ICH E17 guideline describes sample size allocation to regions (including pooled population), but not to individual countries. However, the key principle was set as “the sample size allocation to Japanese population,” because the previous Japanese guideline⁶ only referred to the sample size allocation in the Japanese population, and the broader concept described in the ICH E17 guideline was not recognized at the planning stage of the past MRCTs targeted in this study.

Based on these processes, the consensus was reached on the final major principles and 18 key principles that are shown in **Table 1**.

Analysis and term definitions

For analysis, we collected relevant information on the 18 key principles in as much detail as possible for each MRCT from the official documents (CTD and PMDA review reports) that described the target MRCTs (see above “Data sources and target MRCTs for this study”). Then we checked whether explanations of the key principles were included in the official documents. To make the assessment as objective as possible, we defined terms as follows: an “MRCT” : a clinical trial conducted in more than one region (including Japan) under a single protocol; “General MRCTs” : clinical trials conducted in multiple countries and regions (Asia, America, Europe, Oceania, and Africa); “Asian MRCTs” : clinical trials conducted in Asian countries and regions (East Asia, Southeast Asia, and South Asia); “an objective indicator” : for inclusion criteria and the primary end point: a lack of evaluator intervention and no variation in evaluation parameters (e.g., biochemical testing, genetic testing, bacteriological examination, and overall survival); “a subjective indicator” : an evaluation that varied by the evaluators and changed even when the same evaluator was involved (e.g., imaging assessments, psychometric scales, pain scales, and subject diary); note that if the primary end point included both objective and subjective indicators, we classified it as “subjective primary end point” : “Standardized collection and handling of efficacy and safety information” : measures taken for a uniform evaluation, such as central independent data monitoring committee, centralized assessment by a single adjudication committee (e.g., centralized laboratory and centralized adjudication of imaging), and training/validation; “Essential concomitant medications” : drugs used concomitantly with the investigational drug at all times in the treatment of a disease (e.g., antidiabetic drugs, anti-epileptic drugs, anticancer drugs, respiratory disease drugs, and inflammatory disease drugs).

RESULTS

Considerations regarding the key principles of the ICH E17 guideline in past MRCTs

We identified drugs newly approved in Japan based on data from MRCTs according to the criteria in the comprehensive survey shown in **Figure 1**, which excluded bridging development, single-country (Japan) development, nondisclosure of approval application materials, nonconfirmatory studies, and long-term treatment studies. Between April 2007 and March 2018, 10.5% (130/1,235) of new drugs were approved based on MRCTs, as the pivotal clinical trials. In total, 167 MRCTs of 130 drugs (Asian MRCTs: 29 studies; general MRCTs: 138 studies) were included, with some drugs tested in two or more MRCTs (**Supplementary Data Table S1**).

The considerations for the 18 key principles (**Table 1**) described in the 167 MRCTs are shown in **Figure 2**. For many MRCTs

Table 1 Each aspect of the ICH E17 guideline and corresponding investigation object

ICH E17 Guideline General recommendations in the planning and design of MRCTS			
	Section	Major principles as an ideal situation	Key principles used for analysis in this study
Strategy-related issues	2.1.2 GCP requirements and MRCTS	MRCTS should be conducted in compliance with ICH E6 GCP standards in all regions and sites	Compliance with GCP standards [1]
	2.1.3 Scientific consultation meetings with regulatory authorities	Sponsors of MRCTS are encouraged to have scientific consultation meetings with relevant regulatory authorities	Conducting scientific consultation meetings related to MRCT with the PMDA [2]
Clinical trial design and protocol-related issues	2.2.1 Preconsideration of regional variability and its potential impact on efficacy and safety	The intrinsic and extrinsic factors important to the drug development program, should be identified during the planning stage of an MRCT, and information about them should be collected during the confirmatory trial for later evaluation of their impact on treatment effects	Considerations of ethnic differences based on pharmacokinetic data between Japanese and non-Japanese populations [3]
	2.2.2 Subject selection	To harmonize subject selection, uniform classification and criteria for diagnosis of the disease or definition of the at-risk population should be implemented, such as the use of relevant guidelines for disease definitions	The use of relevant guidelines for disease definitions in the inclusion and exclusion criteria [4]
		In particular, when subject selection is based on subjective criteria, the same methods should be used uniformly across regions. This aspect should be considered in the planning stage, in order to implement training requirements and other strategies for potential mitigation of the impact.	Conducting training/validation on the subjective criteria [5]
	2.2.3 Selection of doses for use in confirmatory MRCTS	The dose regimens in confirmatory MRCTS should in principle be the same in all participating ethnic populations.	The setting of the same doses in confirmatory MRCTS [6]
		Dose-response studies should cover a broad range of doses and generally include the populations to be enrolled in confirmatory MRCTS.	Conducting dose-response studies for the selection of dose regimens in confirmatory MRCTS [7]
	2.2.4 Choice of end points	An ideal clinical trial end point is one that is clinically relevant, accepted in medical practice (e.g., by regulatory guidance or professional society guidelines) and sufficiently sensitive and specific to detect the anticipated effect of the treatment	The use of relevant guidelines for clinical evaluation at the primary end point [8]
Of specific concern in MRCTS are those end points that could be understood and/or measured differently across regions. Examples are hospitalization, psychometric scales, assessment of quality of life, and pain scales. To guarantee that such scales can be properly interpreted, the scales should be validated and their applicability to all relevant regions justified before starting the MRCT.		Conducting training/validation on the subjective primary end point [9]	
2.2.5 Sample size planning	Regional allocation should have a scientific basis (rather than arbitrary targets), should support the evaluation of consistency, and should provide the information needed to support regulatory decisions	The sample size allocation to Japanese population [10]	
2.2.6 Collecting and handling of efficacy and safety information	Methods of collecting and handling efficacy and safety information should be standardized across participating regions	The setting of standardized collection and handling of efficacy information [11]	
		The setting of standardized collection and handling of safety information [12]	

Continues

Table 1 Continued

ICH E17 Guideline General recommendations in the planning and design of MRCTs		
Section	Major principles as an ideal situation	Key principles used for analysis in this study
2.2.7 Statistical analysis planning	The standard is to specify a single primary analysis approach in the statistical section of the study protocol to be agreed upon with the authorities in advance of initiating the trial	Conducting a single primary analysis [13]
	The statistical analysis strategy should include the evaluation of the consistency of treatment effects across regions and subpopulations.	Conducting the evaluation of consistency in treatment effects between the overall population and Japanese population [14] Conducting the evaluation of consistency in treatment effects across regions, race, or variant frequencies [15]
	Subgroup analyses will usually also be of interest, just as they are for any clinical trial (e.g., analyses to investigate differential treatment effects by sex and age) and should be planned.	Conducting subgroup analyses (e.g., analyses to investigate differential treatment effects by sex and age) [16]
2.2.8 Selection of comparators	Comparators in MRCTs should in principle be the same in all participating regions	The uniform placebo or active ingredient of active comparator [17]
2.2.9 Handling concomitant medications	In general, drugs used concomitantly with the investigational drug should be the same throughout the regions to the extent possible	The uniform dose of concomitant medications [18]

GCP, good clinical practice; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; MRCT, multiregional clinical trial; PMDA, Pharmaceuticals and Medical Devices Agency.

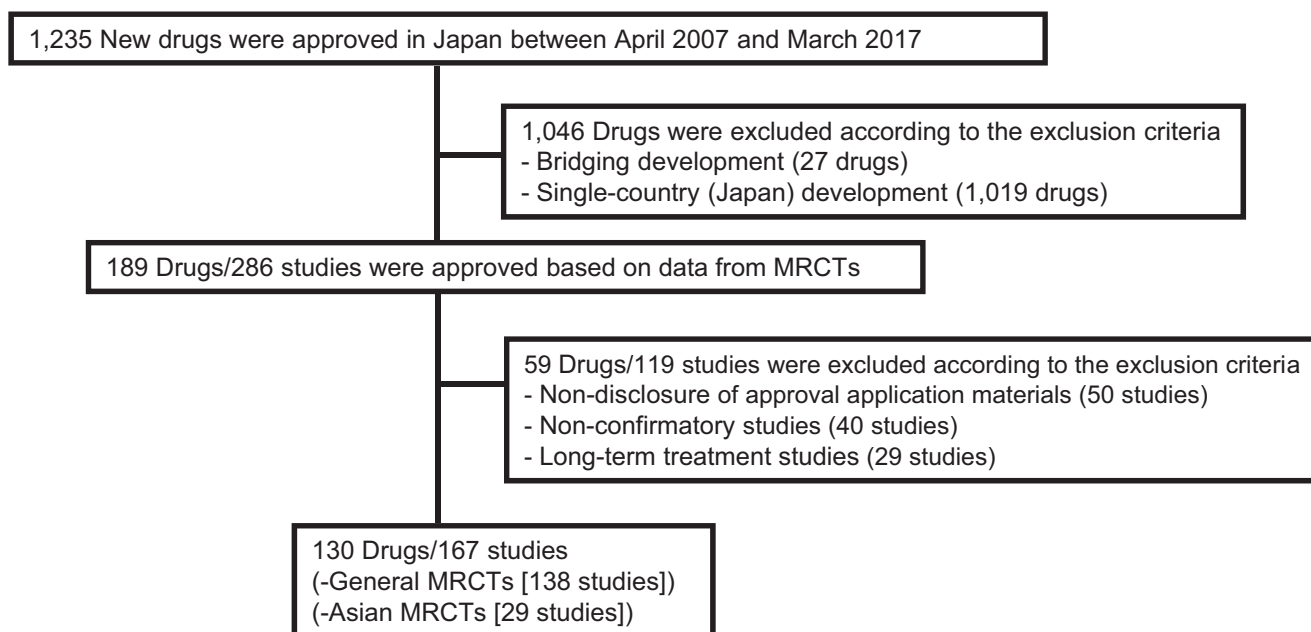


Figure 1 Identification of drugs newly approved in Japan based on data from MRCTs. We collected data of newly approved drugs from the website of the Pharmaceuticals and Medical Devices Agency and identified drugs that were approved between April 2007 and March 2018 based on MRCTs, as the pivotal clinical trial type in Japan. MRCTs, multiregional clinical trials.

(≥ 75%), explanations by the marketing authorization holders of the following principles were included in the official documents: [1] good clinical practice (GCP; 100%, 167/167 studies), [17] comparators (100%, 151/151 studies), [6] same doses (98.8%, 165/167 studies), [14] consistency with Japanese population (98.8%, 165/167 studies), [13] single primary analysis (94.6%,

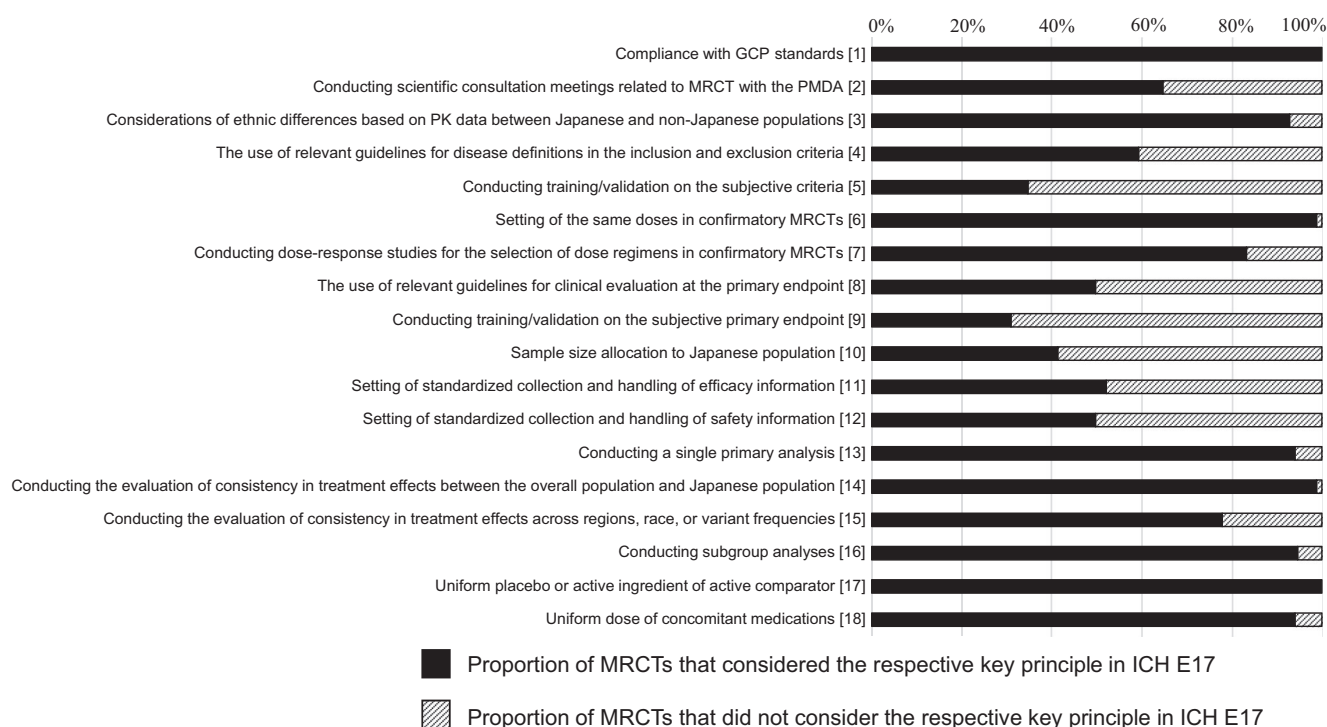


Figure 2 Considerations of 18 key principles of the ICH E17 guideline in past MRCTs. GCP, good clinical practice; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; MRCTs, multiregional clinical trials; PK, pharmacokinetic; PMDA, Pharmaceuticals and Medical Devices Agency.

158/167 studies), [16] subgroup analysis (94.6%, 158/167 studies), [18] concomitant medications (94.0%, 47/50 studies), [3] ethnic pharmacokinetic (PK) differences (92.8%, 155/167 studies), [7] dose response study (83.2%, 139/167 studies), and [15] consistency in other aspects (77.8%, 130/167 studies). In contrast, the other key principles were less well-described in the studied MRCTs (< 75%): [2] scientific consultation meetings (64.7%, 108/167 studies), [4] use of guidelines for disease definitions (59.3%, 99/167 studies), [11] standardized efficacy information (52.1%, 87/167 studies), [8] use of guidelines for primary endpoint (49.7%, 83/167 studies), [12] standardized safety information (49.7%, 83/167 studies), [10] sample size allocation (41.3%, 69/167 studies), [5] training/validation on the subject selection (34.7%, 34/98 studies), and [9] training/validation on primary end point (30.9%, 30/97 studies).

Characteristics of the well-considered key principles ($\geq 75\%$ of MRCTs)

We further characterized the key principles that were usually explained in the official documents. With regard to [3] ethnic PK differences, considerations were actually based on data for interethnic PK comparisons between Japanese and non-Japanese populations, which were derived from two sources: early-phase PK studies (e.g., maximum concentration and area under the curve values) and late-phase studies, such as MRCTs (e.g., trough level; **Figure 3**). Among the 167 studies, the PK data were obtained from both early-phase PK studies and late-phase studies in 84 studies (50.3%, 84/167 studies), from only late-phase studies in 42 studies (25.1%, 42/167

studies), and from only early-phase PK studies in 29 studies (17.4%, 29/167 studies). Among 42 studies from which PK data were obtained in the late phase, such as MRCTs, 21 studies were conducted on topically applied drugs and intravenously administered drugs, for which the treatment effect was known to be relatively insensitive to ethnic factors, as they did not undergo first-pass metabolism.¹¹ Another 10 studies were Asian MRCTs in which the participating regions were thought to be similar from the perspective of intrinsic ethnic factors¹²; seven studies were on rare diseases. Among the 12 studies that did not evaluate ethnic difference based on PK data, in 6 studies, the ethnic difference was considered based on data and information other than cross-ethnic PK comparisons. Specifically, four studies of topically applied drugs explained the ethnic difference based on the mechanism of action and/or PK profile. One Asian MRCT explained the ethnic difference between Japanese and other Asian populations based on the lack of significant PK differences between Japanese and Caucasian populations, and one study explained the ethnic difference using efficacy data obtained from domestic and foreign phase II or phase III studies. The other six studies were unable to confirm the status of explanations regarding ethnic difference in the official documents.

For [6] same dose, 165 studies used the same dose in confirmatory MRCTs, but 2 studies, on eliglustat and benralizumab, used different dose regimens among populations. In the eliglustat study, 50 mg twice daily was orally administered from day 0 to day 28 in non-Japanese subjects and 50 mg once daily on day 1 and 50 mg twice daily from day 2 to day 28 were orally administered in Japanese subjects. In the benralizumab study, the dose regimens

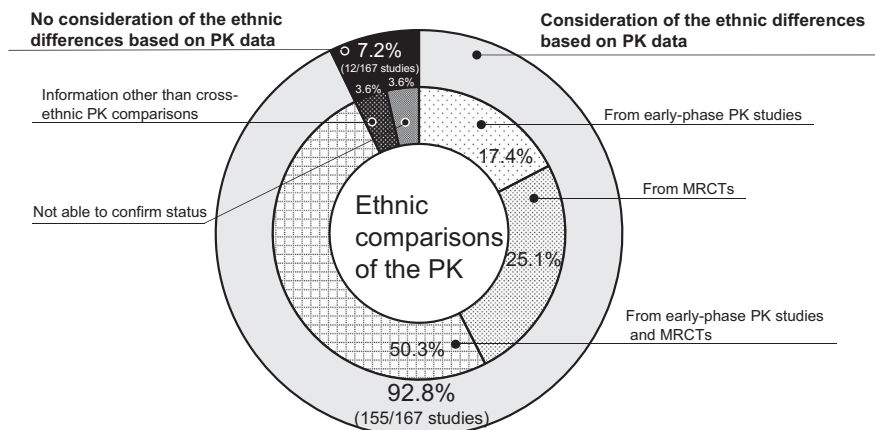


Figure 3 Considerations of ethnic differences based on PK data between Japanese and non-Japanese populations. The outer circle shows the ratios of studies that considered ethnic differences based on PK data, and the inner circle shows a detailed breakdown. MRCTs, multiregional clinical trials; PK, pharmacokinetic.

for adults and adolescents with asthma were 30 mg every 4 weeks or every 8 weeks in all regions, but the dose in adolescents in the European Union was limited to 30 mg every 8 weeks. Different dose regimens in different populations may have been based on safety considerations, although PK data showed no clear differences among ethnic populations.

In terms of [7] dose response study, we checked the status of performing dose-response studies to select dose regimens for confirmatory MRCTs (Figure 4). Dose regimens in 139 confirmatory MRCTs were selected based on dose-response studies. Japanese and non-Japanese subjects were included in 33.5% (56/167 studies) and 49.1% (82/167 studies) MRCTs, respectively (this could not be confirmed in one study). Dose-response studies were not conducted in 28 studies (16.8%, 28/167 studies). Of those 28 studies, dose regimens in 18 studies were selected based on data of the same active ingredient (e.g., data for other indications or other formulations; 10.8%, 18/167 studies; adalimumab (2 studies); pasireotide, everolimus (Indication: the inhibition of rejection in liver transplantation); ticagrelor, tadalafil (Indication: pulmonary arterial hypertension); sildenafil, pramipexole, perampanel, and aripiprazole (Indication: schizophrenia); paliperidone, olanzapine, pregabalin, and ranibizumab

(Indication: macular edema following retinal vein occlusion and choroidal neovascularization in pathologic myopia); aflibercept (Indication: macular edema following central retinal vein occlusion); aflibercept (Indication: choroidal neovascularization in pathologic myopia); belimumab, and gefitinib); eight studies were selected based on comparison of PK/pharmacodynamic data between the investigational drug and similar drugs (4.8%, 8/167 studies; insulin-glargine (2 studies); insulin-glulisine, turoctocog alfa, nonacog gamma, ruriococog alfa pegol, lonococog alfa, and idarucizumab; most of these were for insulin preparations in which the dosages were adjusted according to patient condition and intravenously administered drugs, of which treatment effect was known to be relatively insensitive to ethnic factors as the drugs do not undergo first-pass metabolism¹¹); and two studies were determined based on nonclinical data and clinical experience (1.2%, 2/167 studies; asfotase alfa and canakinumab; **Supplementary Data Table S1**).

With respect to [13] single primary analysis, 158 studies were conducted with a single primary analysis for a primary end point. The other nine studies included eight studies in which the analysis approach (e.g., closed testing procedure, hypothesis testing and estimation, and analysis dataset) differed among regulatory

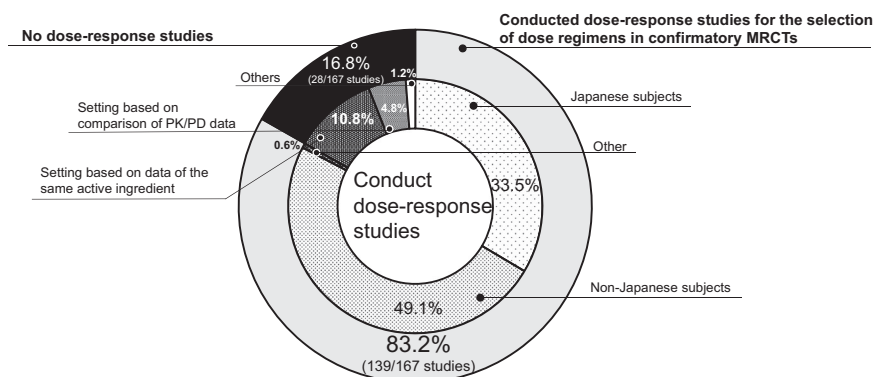


Figure 4 Conducting dose-response studies for the selection of dose regimens in confirmatory MRCTs. The outer circle shows the ratios of conducting dose-response studies, and the inner circle shows a detailed breakdown. MRCTs, multiregional clinical trials; PK/PD, pharmacokinetic/pharmacodynamic.

authorities (umeclidinium/vilanterol (two studies), tiotropium/olodaterol (two studies), dupilumab (two studies), adalimumab (two studies)) and one study (perampanel) in which the primary end point differed among regulatory authorities.

As for [14] consistency with Japanese population, 165 studies were conducted, with the evaluation of consistency in treatment effects between the overall population and the Japanese population. The other two studies included one (bosutinib) in which there were fewer Japanese subjects than expected and one (panitumumab) in which the efficacy could not be confirmed in the overall population.

Regarding [15] consistency in other aspects, 130 studies were conducted, with the evaluation of consistency in treatment effects across regions, race, or variant frequencies. Of these, the evaluation of consistency was actually considered for regions in 82 studies, race in 117 studies, and variant frequencies (included duplicated measures) in 5 studies. The other 37 studies did not include an evaluation of consistency or did not confirm this in the official documents; most of these studies were on rare diseases (16 studies) and topically applied drugs and intravenously administered drugs, for which treatment effect was known to be relatively insensitive to ethnic factors, as the drugs do not undergo first-pass metabolism¹¹ (10 studies) and Asian MRCTs in which the participating regions were thought to be similar from the perspective of intrinsic ethnic factors¹² (3 studies).

For [16] subgroup analyses, 158 studies were conducted with subgroup analyses (e.g., analyses to investigate differential treatment effects by sex and age); the other 9 studies were on rare diseases (7 studies), topically applied drugs (1 study), and intravenously administered blood coagulation factors (1 study).

Characteristics of the less-considered key principles (< 75% of MRCTs)

As compared with the well-considered key principles, some of key principles were less adequately described in the official

documents, such as [8] use of guidelines for primary end point and [9] training/validation on primary end point. Specifically, primary end points in 83 studies (49.7%) were selected based on relevant guidelines for clinical evaluation. In contrast, 84 studies (50.3%) did not use guidelines for the selection of primary end points or did not confirm the use of guidelines in the official documents. Similarly, 70 studies (41.9%) adopted objective primary end points, but 97 studies (58.1%) adopted subjective primary end points that consisted of only subjective scales or subjective and objective scales. It should be noted that 30 of 97 studies (30.9%) were conducted with training/validation for these end points, and most of the drugs in these studies were for the central nervous system. The remaining 67 of the 97 studies (69.1%) with subjective primary end points were either not conducted with training/validation or did not confirm the conduct of training/validation in the official documents. Although 42 of the 67 studies included objective scales in addition to subjective scales for primary end points, the other 25 studies adopted only a subjective primary end point, mostly for intravenously administered blood coagulation factors, respiratory tract drugs, and antiviral agents against influenza (**Supplementary Data Table S1**).

Two other less-considered principles, [11] standardized efficacy information and [12] standardized safety information, are shown in **Figure 5**. Of the 167 studies, a standardized method for collecting and handling information was only adopted in 87 studies (52.1%) for efficacy information and 83 studies for safety information (49.7%). Standardization for collecting and handling efficacy information was usually ensured by conducting training/validation (39/87 studies) or centralized assessment by a single adjudication committee, such as central laboratory data and central imaging assessments (36/87 studies). Similar methods, such as the use of central laboratory data, electrocardiogram results, and an adjudication

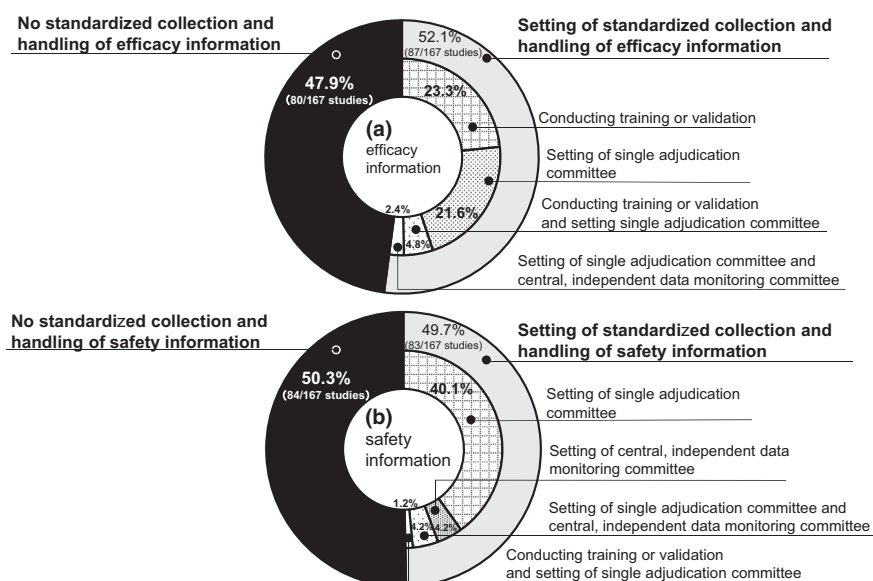


Figure 5 Setting of standardized collection and handling of efficacy and safety information. The outer circle shows the ratios of the setting of standardized collection and handling of efficacy and safety information, and the inner circle shows a detailed breakdown. (a) Setting of standardized collection and handling of efficacy information and (b) setting of standardized collection and handling of safety information.

committee for specific adverse events, were introduced for safety information (67/83 studies).

Consideration of the pooling strategy

One of new concepts introduced in the ICH E17 guideline is the use of a well-justified and prespecified strategy for pooling regions in conjunction with a carefully determined sample allocation plan.⁴ Although the pooling strategy was not available at the time of planning the MRCTs targeted in this study, we performed a preliminary check of how the related analysis was considered. Among 138 general MRCTs, which excluded Asian MRCTs (29 studies), 55 studies were accompanied by the evaluation of consistency in treatment effects across regions, including Asian regions (39.9%, 55/138 studies). Of these, two studies (for pertuzumab and belimumab) included the evaluation of consistency in treatment effects between the overall population and the population from Asian regions to complement the evaluation of consistency between the overall population and Japanese population.

DISCUSSION

In this study, we examined how the key principles described in the ICH E17 guideline were considered in the past MRCTs used for drug approval in Japan. The results clearly indicated the principles that have already been taken into consideration when performing MRCTs and the principles that will need to be considered in future MRCTs. However, it should be noted that the results of this study could be biased because it only targeted the approved drugs, which generally included a clinical data package accepted by the PMDA.

Among the key principles, [1] GCP and [17] comparators were considered in all MRCTs targeted in this study, indicating that those are already well-recognized as a point for consideration. For the [3] ethnic PK differences, [6] same doses, [7] dose response study, [13] single primary analysis, [14] consistency with Japanese population, [15] consistency in other aspects, [16] subgroup analyses, and [18] concomitant medications were also categorized as well-considered principles. These findings could be a result of the previous Japanese guidelines published in 2007⁵ and 2012,⁶ because the Japanese guideline described similar points, such as compliance with the GCP; PK comparisons between Japanese and non-Japanese populations; a plan for dose-response study; primary end point acceptable to all regions; evaluation of consistency in treatment effects between the overall population and Japanese population; conducting subgroup analysis based on the relevant factors, such as race, region, and patient demographics; and setting of comparators and concomitant medications. Thus, it is not surprising that those points have been well-considered even before implementing the ICH E17 guideline.

In contrast, [2] scientific consultation meetings, [4] use of guidelines for disease definitions, [5] training/validation on the subject selection, [8] use of guidelines for primary end point, [9] training/validation on primary end point, [10] sample size allocation, [11] standardized efficacy information, and [12] standardized safety information have been less considered in the past

MRCTs. With regard to the use of the guideline (key principles [4] and [8]), training/validation (key principles [5] and [9]) and standardized information (key principles [11] and [12]), there has been little information in the previous Japanese guideline,^{5,6} whereas the ICH E17 guideline provides more details for considerations, such as the use of relevant guidelines for disease definitions and clinical evaluation, validated scales, a central independent data monitoring committee, a single adjudication committee, and conduct of training/validation. These results may suggest that the less well-described points in the previous Japanese guideline are associated with the less considered principles identified in this study. Addition of detailed descriptions in the ICH E17 guideline will facilitate further considerations on those points in the future MRCTs.

The results for [2] scientific consultation meetings and [10] sample size allocation were somewhat surprising, because the PMDA has had many scientific consultation meetings with industries to discuss the plans and designs of MRCTs,¹³ and these frequently included discussions on sample size allocation in the Japanese population. It may be a limitation of this study that we used only publicly available documents. The status of consultation meetings is sometimes undisclosed in the published material available from the marketing authorization holder. The allocation of overall sample size to the Japanese population is usually described in the protocols but not in the published documents. Thus, although the results may be partly underestimated, they suggest that clearer and more detailed explanations relating to the principles described in the ICH E17 should be included in CTD and other publicly available documents to help understand MRCTs and allow a more appropriate evaluation of MRCT data.

It should be noted that in future MRCTs, discussions on sample size allocation to regions, including pooled regions and populations, but not to particular ethnicities, will be increased. In fact, two MRCTs in this study included the evaluation of consistency in treatment effects between the overall population and Asian population to complement the evaluation of consistency between the overall population and Japanese population, although it was not clear from the publicly available materials whether the plan for the pooled Asian region was prespecified or not. The percentage of MRCTs conducted in Asia has recently increased,^{3,14} probably owing to ethnic similarities within Asian populations, such as genetic similarities of metabolic enzyme and gene profiles, as well as the large medical need and market values in Asia.^{12,14,15,16} In future MRCTs, the analysis strategy for consistency evaluation, including the use of pooled regions or subpopulations, should be prespecified, although more experience and data will be necessary on how to pool Asian countries as a single region for efficient clinical development and appropriate assessment of consistency in treatment effects.

In conclusion, in this study, we examined the well-considered and less-considered key principles of the ICH E17 guideline in previously conducted MRCTs used for drug approval in Japan. This study provides useful information for the implementation of the ICH E17 guideline in Japan. In planning future MRCTs for drug approval in Japan, more attention should be given to identified points regarding the less-considered principles.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

DISCLOSURE

The views expressed herein are the result of independent work and do not necessarily represent the views and findings of the Pharmaceuticals and Medical Devices Agency.

AUTHOR CONTRIBUTIONS

K.A., Y.U., and M.T. wrote the manuscript. K.A., Y.A., S.K., Y.U., and M.T. designed the research. K.A., Y.A., S.K., and Y.U. performed the research. K.A., Y.A., S.K., and Y.U. analyzed the data.

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