

ARTICLE

The necessary conduct: Exploratory multiregional clinical trials in East Asia

Inseung Jeon¹  | Yu Kyong Kim²  | Ildae Song^{3,4}  | Deok Yong Yoon¹  |
 Ki Young Huh¹  | Xuanyou Jin¹  | Kyung-Sang Yu¹  | SeungHwan Lee¹  |
 Yuji Kumagai⁴ | In-Jin Jang¹ 

¹Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Korea

²Department of Clinical Pharmacology and Therapeutics, Chungbuk National University College of Medicine and Hospital, Cheongju, Korea

³Department of Pharmaceutical Science and Technology, Kyungsung University, Busan, Korea

⁴Kitasato Clinical Research Center, Kitasato University School of Medicine, Kanagawa, Japan

Correspondence

In-Jin Jang, Department of Clinical Pharmacology and Therapeutics College of Medicine, Seoul National University and Seoul National University Hospital, Clinical Trials Center, SNU Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
 Email: ijjang@snu.ac.kr

Yuji Kumagai, Kitasato Clinical Research Center, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagami-hara-shi, Kanagawa 252-0375, Japan.
 Email: kuma-guy@za2.so-net.ne.jp

Funding information

No funding was received for this work.

Abstract

Various studies have highlighted the importance of ethnic differences. The consideration of ethnic differences in the field of individualized pharmacotherapy is imperative. Therefore, various organizations and networks across countries should aim to conduct multicountry and multiregional clinical trials (MRCTs). If there is solid evidence available to evaluate the existence of ethnic differences between the same regional areas, it will lead to an increase in the efficiency of drug development. The purpose of this paper was to compare the approval dosing regimen among four Asian countries (Korea, Japan, China, and Taiwan) and elucidate the readiness and current status of the implementation of the International Conference on Harmonization (ICH) E17 guidelines on MRCTs. Reducing unnecessary clinical trials via multinational clinical trials in East Asian countries is also suggested. The approved dosing regimens for some drugs in the four Asian countries were similar; however, some differences might be caused by differences in legislation, even though there were no ethnic differences. This indicates that there are several roles to be expected of the Asia Clinical Pharmacology study network for exploratory MRCTs, which would lead to the accumulation of evidence for MRCTs, ultimately accelerating the efficiency of drug development in East Asian countries. The exposure of the new treatment to the necessary patients through collaborative research coordination and simultaneous multinational subject recruitment would serve its role in providing East Asia with specific personalized medicine with a high treatment success rate.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

There is an increased need to consider ethnic differences in drug development. Simultaneously, the demand for conducting multicountry and multiregional clinical trials (MRCTs) has significantly increased.

Yuji Kumagai and In-Jin Jang equally contributed to this work and are co-corresponding authors.

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WHAT QUESTION DID THIS STUDY ADDRESS?

This study addresses the current status of ethnic sensitivity in Asia, suggesting specific therapeutic areas that require ethnic sensitivity evaluation in the early phases.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study focuses on the current status of ethnic sensitivity among four Asian countries (Korea, Japan, China, and Taiwan) based on comparisons of their approved dosing regimens. Differences in approved dosing regimens are potentially a result of differences in legislation despite having no ethnic differences.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

It proposes the establishment of an Asia Clinical Pharmacology study network comprising Asian investigators in the field of clinical pharmacology and therapeutics to support the implementation of International Conference on Harmonization (ICH) E17 guidelines. This would lead to the accumulation of evidence for the ethnic sensitivity of MRCTs ultimately accelerating the efficiency of drug development in Asian countries.

INTRODUCTION

Ethnic differences and the necessary consideration in individualized pharmacotherapy have significantly increased in the field of drug development over the past half century.^{1,2} The vast majority of global pharmaceutical industries have attained approval for New Drug Applications (NDAs) and Biologics License Applications (BLAs) in East Asian countries (especially Korea, Japan, and China) with the pre-obtained clinical trial results typically performed in Western countries within their resident population or with a rather limited number of Asian subjects living in Western countries.^{3,4} It is well known that extrinsic factors, such as environmental and cultural differences, can cause interindividual variability in drug responses.^{5,6} There are many existing drugs that require ethnic sensitivity analysis, especially those developed by global pharmaceutical companies where dose selections according to the ethnic groups are often overlooked.^{7,8} However, under the critical assumption of an absence or a clinically insignificant ethnic difference, the clinical trial results are utilized as part of the East Asian NDA packages and such assumptions lack the evidence of their validity.

Various studies have highlighted the importance of ethnic differences and the need to consider multiple regions. Therefore, various organizations and networks across different countries aim to conduct multicountry and multiregional clinical trials (MRCTs), such as the European Clinical Research Infrastructure Network (ECRIN), International Rare Diseases Research Consortium (IRDiRC), and the United Kingdom Clinical Research Network (UKCRN).^{9,10} The ECRIN is an organization that involves many European countries to support multinational clinical trials in Europe. This organization has overseen ~ 60 multinational clinical

research projects with a mean of 6.3 countries per trial with strong trial results, consequently paving the way for faster processing of drug approval.¹⁰ The IRDiRC is a consortium involving more than 40 countries that contribute to the development of new treatments for rare diseases, and can accelerate the progress in the field.⁹ These organizations and networks are accelerating drug development by simplifying drug approval as a one-time approval among multinational studies.

In the same manner, if there is solid evidence available to evaluate the existence of ethnic differences among the same regional areas (such as the East Asian population living in Asia), it will lead to an increase in the efficiency of drug development. Therefore, if there are no identified ethnic differences within the same regional area, either one or two MRCT results would be sufficient as part of the NDA package without having to conduct multiple independent clinical trials in several East Asian countries.^{11–15} Based on the International Conference on Harmonization (ICH) E5 and E17 guidelines, expanding perception of the inefficiency of conventional single-region clinical trials further supports the need to strengthen the accumulation of evidence that is required to outline the similarities and differences within East Asian countries through exploratory MRCTs.¹³ Moreover, evaluation of ethnic sensitivity facilitates the registration of drugs while expeditiously supplying drugs to patients for their benefit.

The results from a previous study suggest that genetic polymorphisms among Korean, Japanese, and Chinese populations are not pharmacogenetically distant; however, they may have critical gene differences.¹¹ For instance, the CYP2C19*2 allele frequencies in Korean, Japanese, and Chinese people are 30.5%, 23.3%, and 27.7%, respectively.¹¹ However, there are some genetic polymorphism differences

that exist among the Korean, Japanese, and Chinese populations; one of the strong risk factors being carbamazepine-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The HLA-B*1502 allele occurs at high frequency in the Han Chinese population, but not in the Japanese population.^{16–18} Therefore, it is necessary to evaluate ethnic sensitivity in the early phases.

A pioneering attempt by the China/Japan/Korea tripartite cooperation initiated hope in identifying the potential factors that may cause differences within the East Asian countries by comparing the clinical study methods and regulatory system in each country.^{4,11,12,16} In fact, accumulating evidence from studies that aimed to identify similarities and differences in the pharmacokinetic (PK) characteristics of certain drugs within East Asian countries showed not only similarities but also subtle differences.¹⁹ These subtle differences could restrict extrapolation of the results from a single country to the region. Therefore, drug development programs can benefit from exploratory MRCTs conducted through collaborative drug development programs.

For the purpose of planning and designing exploratory MRCTs, a leading collaborative organization, KoNECT Asia Clinical Pharmacology study (ACP) network was established. The ACP network is a research network comprising East Asian investigators in the field of clinical pharmacology and therapeutics and seeks to expand its role in bridging the pharmaceutical companies and government funding, investigator-initiated trial support, scientific support via sharing of technology between the Asian regions, and the support of the implementation of ICH E17 guidelines through regulatory harmonization.

The aim of this paper was to investigate and compare the dosage approval regimens among four Asian countries (Korea, Japan, China, and Taiwan) considering the dosage approval regimens as the best reflection of each country's approval process. Moreover, the purpose was to elucidate the readiness and the current status of the implementation of the ICH E17 guidelines on MRCTs and evaluate if they could be conducted as one study with one protocol in order to reduce unnecessary via multinational clinical trials among East Asian countries.^{13,20,21} In addition, the current paper also evaluates the current status of ethnicity sensitivity in various therapeutic areas and suggest specific therapeutic areas that require ethnic sensitivity evaluation from an early phase.

METHODS

Data collection and analysis

For the selection of drugs that require ethnic sensitivity analysis through to the conduct of exploratory MRCTs,

the information on the approved dosing regimen using generic names and ingredients was screened from a list of approved drugs on the official websites of the regulatory agencies of Korea (Ministry of Food and Drug Safety [MFDS]) and Japan (Pharmaceuticals and Medical Devices Agency [PMDA]) from April 2012 to March 2020.^{22,23} In this case, unlike the MFDS and the PMDA, the official websites of the regulatory agencies from China (National Medical Products Administration [NMPA]) and the Taiwan (Taiwan Food and Drug Administration [TFDA]) did not provide information regarding the list of approved drugs and their dosing regimens. Therefore, the approved dosing regimens in China and Taiwan were obtained from individual drug labels, which were found by searching several of the top search engines, such as Google (<https://www.google.com/>) and Baidu (<https://www.baidu.com/>). The list of approved drugs from the PMDA was used as a standard reference and the list of approved drugs with their dosing regimen was compared with the MFDS. The approved dosing regimen was compared on the basis of the total daily dose and each drug was classified by anatomic therapeutic chemical (ATC) criteria and molecule type, such as small molecule, monoclonal antibody, and others. Moreover, the drugs approved by both the PMDA and the MFDS were compared to those approved by the NMPA and the TFDA.

Potential regional differences and possible factors, such as genetic and safety aspects, were also compared. Information on the distribution and abundance of genetic polymorphisms in each region was gathered through a literature search using PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) and Scopus (<https://www.scopus.com/>). In this case, from the searched reports and literature, the adverse event frequencies were compared by each region for safety evaluation of the currently approved dosing regimens.^{3–7,12} An open database (<https://clinicaltrials.gov/>) was interrogated for the latest trends and the movement of MRCTs performed in East Asian countries. Moreover, the review systems of each regulatory agency were considered for possible cultural and environmental aspects in dosing regimen determination for approval.

Interview of professional clinicians and clinical pharmacology specialists

Based on the unmet medical needs of specific treatment areas found in the literature search, interviews with professional clinicians and clinical pharmacology specialists were conducted. A total of 34 professional clinicians and clinical pharmacology specialists participated in the interviews, which were used to determine the perspective of professionals for the realistic requirements to conduct

exploratory MRCTs within East Asian countries. The interviewees provided their opinion regarding the needs of clinical importance through PK/pharmacodynamic (PD) clinical trials by disease and special populations in Asian countries, and the medications of clinical importance. Moreover, they suggested drugs for diseases that require research in East Asia using data obtained from MRCT due to their low prevalence. Periodic meetings and consultations with local and regional clinical pharmacology specialists in Korea and Japan were also conducted. Furthermore, these interview results were used to compare the current status of medical treatment options by therapeutic area.

RESULTS

Based on the list of approved drugs on the official websites of the regulatory agencies from April 2012 to March 2020, 287 drugs were approved by both Korean and Japanese regulatory agencies. Among them, 183 drugs were approved with the same dosing regimen and 104 drugs were approved with different dosing regimens (Figure 1). Moreover, approximately 60% of the approved drugs had

the same dosing regimen in the four Asian countries (Korea, Japan, China, and Taiwan).

For further evaluation, each ATC criterion and molecule type was considered, regardless of the difference in dosing regimen (Figure 2). Similar dosing regimens between Korea and Japan were assigned according to the following criteria: blood and blood forming organs (73.3%), genito urinary system and sex hormones (71.4%), general anti-infectives for systemic use (72.2%), antineoplastic and immunomodulating agents (70.3%), and sensory organs (85.7%). Anti-infective drugs, such as ampicillin sodium and tazobactam/piperacillin hydrate, have been approved in the past and the dosing regimen has recently changed. Other drugs that have similar dosing regimens in other ATC classes are newly approved drugs. Anti-infective drugs have been used for decades compared to other classes of drugs.

In addition, the drugs classified as small molecules accounted for approximately 90% of the different dosing regimens of the total drugs that showed a different dosing regimen, whereas most of the monoclonal antibody drugs showed a similar dosing regimen (Figure 2).

Additional dosing regimen comparisons were conducted with the drugs that showed different dosing

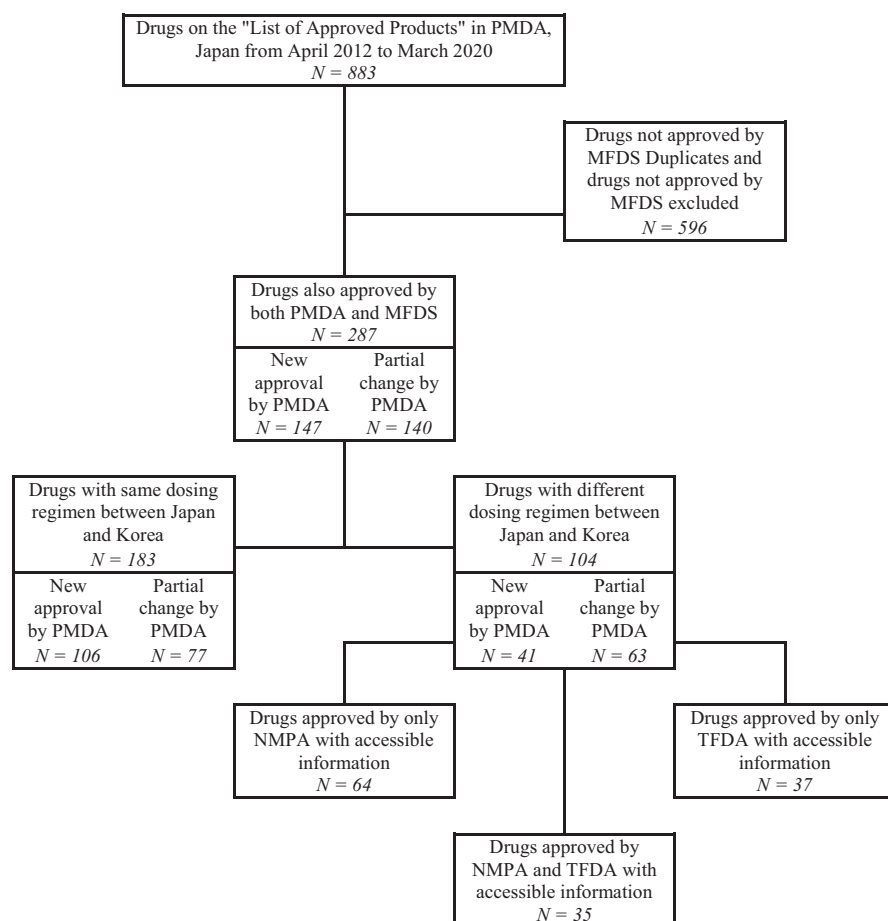


FIGURE 1 Disposition of drugs eligible for comparison among Korea, Japan, China, and Taiwan through common factor of drug approval and accessibility of information. MFDS, Ministry of Food and Drug Safety; NMPA, National Medical Products Administration; PMDA, Pharmaceuticals and Medical Devices Agency; TFDA, Taiwan Food and Drug Administration

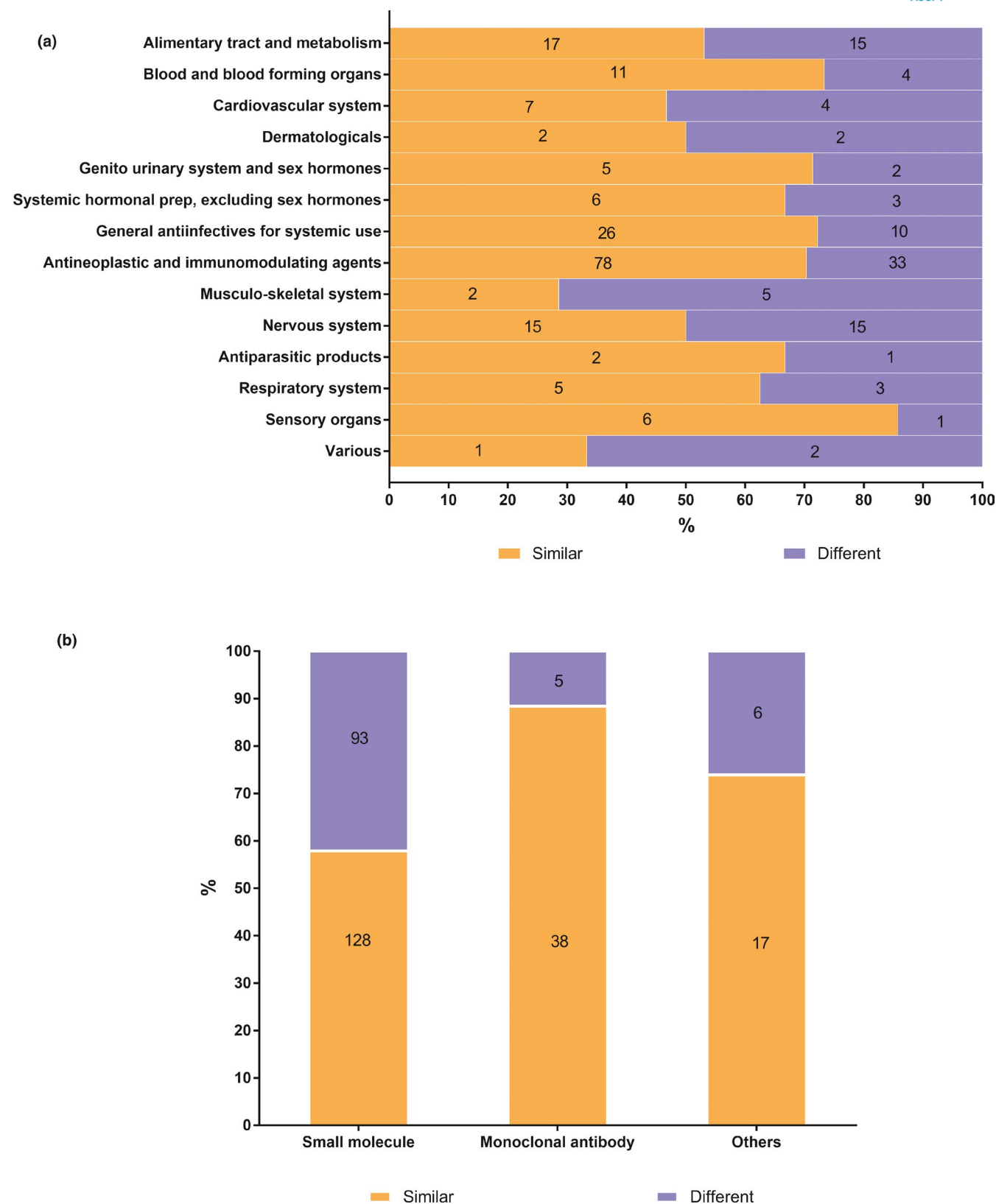


FIGURE 2 Dosing regimen comparison of the drugs approved from 2012 to 2020 in Japan to those approved in Korea on the basis of total daily dose by (a) anatomic therapeutic chemical (ATC) criteria and (b) molecular type presented as number and percentages of drugs ($N = 287$)

TABLE 1 Same dosing regimen of the drugs on the basis of total daily dose, which approved in China and Taiwan to either Korea or Japan among the drugs with different dosing regimen between Japan and Korea by ATC class

ATC class	Same dosing regimen countries			
	Korea/China (N = 19)	Korea/Taiwan (N = 18)	Japan/China (N = 10)	Japan/Taiwan (N = 4)
Alimentary tract and metabolism	6	3	1	2
Blood and blood forming organ	2	–	–	–
Cardiovascular system	–	2	–	–
General anti-infectives for systemic use	1	3	–	–
Antineoplastic and immunomodulating agents	6	5	9	–
Musculo-skeletal system	2	2	–	–
Nervous system	2	2	–	1
Various	–	1	–	1

Abbreviation: ATC, anatomic therapeutic chemical.

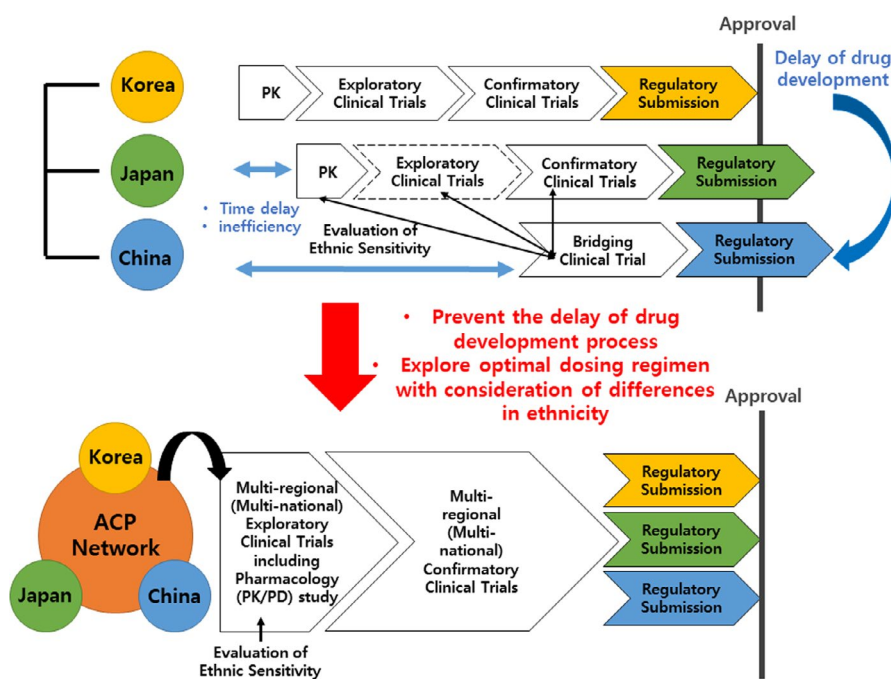


FIGURE 3 Drug development process in the East Asian countries (Korea, Japan, and China) and approval of regulatory agencies in current status and ACP network strategies in the future. ACP, Asia Clinical Pharmacology study; PD, pharmacodynamic; PK, pharmacokinetic

regimens in Korea and Japan to those approved in China and Taiwan (Figure 1). The reason for comparing Korea and Japan as the main references was due to the difficulties in finding the approved dosing regimen in China and Taiwan. The drugs approved in Korea with different dosing regimens in Japan have more of the same dosing regimen drugs as the drugs approved in either China ($N = 19$) or Taiwan ($N = 18$) compared to Japan/China ($N = 10$) and Japan/Taiwan ($N = 4$; Table 1). Moreover, many of the same dosing regimen drugs between Korea and Japan with either China or Taiwan were assigned to the alimentary tract and metabolism and antineoplastic and immunomodulating agents (Table 1).

The therapeutic areas for further interviews were selected based on the discrepancy in the approved dosing regimen. After filtering the results of the literature search, the following areas were selected for further research: neurology, pediatrics, biologics, and rare diseases. The results from the focused literature search showed that the central nervous system and cardiovascular and infectious diseases had notable discrepancies in the approved dosing regimen by regulatory agencies in East Asia. We suspect that such differences may have occurred due to the increasing number of global clinical trials with various ethnic groups participating; therefore, the doses specific to the Asian population have been disregarded.

Interviews with professional clinicians and clinical pharmacology specialists suggest that rare disease drugs and drugs targeting pediatrics are the drugs of clinical importance. Moreover, the results of the interviews with professional clinicians and clinical pharmacology specialists suggest that PK and PD clinical trials of nervous system targeting drugs are especially needed in East Asian countries for clinical importance. This is also consistent with the results of dosing regimen comparison that the drugs assigned to nervous systems have different dosing regimens among East Asian countries.

Regarding these results, the ACP network is needed to create solid evidence to evaluate the existence of ethnic differences among the same regional areas. Moreover, the ACP network would help to activate and improve MRCTs based on the implementation of the ICH E17 guideline.

DISCUSSION

This paper indicates that the approved dosing regimens among four Asian countries (Korea, Japan, China, and Taiwan) share some commonalities, which leads some drugs to have similar dosing regimens, but also indicates some differences. Some drugs with different dosing regimens are supposed to be similar because there are no ethnic differences.

The ethnic discrepancy is associated with the mechanism of action of the drugs; for example, anti-infectives exhibit an absence of ethnic sensitivity because the target of the drug is extrinsic pathogens that do not have ethnic sensitivity. In contrast, drugs highly affected by intrinsic factors (e.g., esomeprazole) show high ethnic sensitivity. Based on the results, many of the same dosing regimen drugs between Korea and Japan with either China or Taiwan were assigned to the alimentary tract and metabolism. This was supported by the fact that the dosing regimen for drugs in the alimentary tract and metabolism in Korea is more similar to that in Japan than in China or Taiwan, where genetic predisposition is significantly different. For instance, voriconazole was one of the drugs that showed a different dosing regimen. However, genetic polymorphisms in the PKs of voriconazole and the PK characteristics of these countries are relatively similar.^{24,25} Therefore, if these studies were conducted under the same protocol, the study results would be similar. This implies that the regulatory protocols in the same regions cause some drugs to have different dosing regimens, even though they are supposed to be similar. Therefore, it is necessary to support the implementation of the ICH E17 guidelines through regulatory harmonization between Asian regions. The timelines for regulatory acceptance of new

drug investigations for these countries vary (Korea and Japan: 1–2 months, Taiwan: 3–4 months, and China: ~ 8 months), and regulatory harmonization may accelerate the drug development process. Moreover, to elucidate the readiness and the current status of the implementation of the ICH E17 guidelines on MRCTs, it is suggested that they be conducted as one study with one protocol in order to reduce unnecessary, multinational clinical trials among East Asian countries.^{13,20,21} In addition to evaluating the current status of ethnic sensitivity in various therapeutic areas, the specific therapeutic areas that require ethnic sensitivity evaluation from an early phase are suggested. Each Asian country currently requires the results of clinical trials for each nationality and the variation in timelines for regulatory acceptance leads to delays in drug development (Figure 3). The ACP network governs the conducting MRCTs to evaluate ethnic sensitivity in the early stage and aligns the regulatory submissions for each Asian country in a timely manner. Moreover, it eventually prevents delays in the drug development process and explores optimal dosing regimens with consideration of differences in ethnicity.

However, at present, it is not prepared for the integration of regulatory agencies nor activates to conduct MRCTs between the Asian regions. Therefore, we require a pre-emptive correspondence of the network mainly by investigators. The following two methodologies we suggest are the roots of the ACP network sample study.

The first methodology that we suggest is a prospective phase I study to evaluate the intrinsic and extrinsic factors. For instance, the first model we suggest is a multinational, multicenter, randomized, open-label, placebo and active control, three-way crossover phase I study to investigate the PKs and PDs of drug Z in healthy Korean, Japanese, Chinese, Taiwanese, and White volunteers. The importance of this model is to clarify the differences in ethnicities in drug Z from an early phase.

The second methodology is a retrospective study of adverse drug reactions from multicenter based on real-world data and real-world evidence. For instance, data were collected from the electronic medical records of patients who had been administered drug Z at various centers in Korea and Japan. Adverse event occurrences and possible intrinsic and extrinsic factors affecting the variabilities in the drug response can be evaluated, and these results can lead to modification of the drug labels.

As a result, the role of the ACP network in encouraging exploratory MRCTs stands out even more clearly. To be able to set the dosing regimen with consideration of ethnic differences, vitalization of the ACP network through collaborative research in Korea, Japan, and China is needed. In addition, elevating cooperative ties is crucial for strengthening the global competitiveness of

drug development in the areas of unmet medical needs. The specific roles of the ACP network would also include becoming a bridge between pharmaceutical companies and government funding, supporting investigator-initiated MRCTs and providing scientific support via sharing of technology between the regions. Moreover, the ACP network may facilitate communication between the experts and the general public (via media) to advocate subject enrolment in MRCT studies. Regulatory harmonization, such as implementation of the ICH E17 guidelines, would also be one of the important roles of the ACP network.

CONFLICT OF INTERESTS

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

I.J., Y.K.K., S.H.L., Y.K., and I.J.J. wrote the manuscript. I.S., K.S.Y., S.H.L., Y.K., and I.J.J. designed the research. I.J., Y.K.K., D.Y., K.Y.H., and X.Y.J. performed the research and analyzed the data.

ORCID

Inseung Jeon  <https://orcid.org/0000-0002-4035-1230>

Yu Kyong Kim  <https://orcid.org/0000-0002-7868-1761>

Ildae Song  <https://orcid.org/0000-0002-3904-4735>

Deok Yong Yoon  <https://orcid.org/0000-0002-5281-8811>

0000-0002-5281-8811

Ki Young Huh  <https://orcid.org/0000-0002-1872-9954>

Xuanyou Jin  <https://orcid.org/0000-0003-0559-3039>

Kyung-Sang Yu  <https://orcid.org/0000-0003-0921-7225>

SeungHwan Lee  <https://orcid.org/0000-0002-1713-9194>

In-Jin Jang  <https://orcid.org/0000-0002-8384-3139>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Jeon I, Kim YK, Song I, et al. The necessary conduct: Exploratory multiregional clinical trials in East Asia. *Clin Transl Sci.* 2021;14:2399–2407. <https://doi.org/10.1111/cts.13106>