Identification of Drug Characteristics for Implementing Multiregional Clinical Trials Including Japan

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ABSTRACT

Purpose: Multiregional clinical trials (MRCT) are a standard strategy used to improve global drug approval efficiency and the feasibility of clinical trials. Japan is the world's third largest drug market with a unique health care system, making it a key inclusion as an operational region for MRCT (MRCT-JP) for global drug development. We aimed to identify the factors required for efficient drug development by comprehensively reviewing the clinical trials of drugs approved in Japan to identify the factors associated with whether or not MRCT-JP is implemented.

Methods: We surveyed the review reports and summaries of application data published by the Pharmaceuticals and Medical Devices Agency. We identified drugs for which the clinical trial data package included MRCT-JP and selected the same number of drugs for which the clinical trial data package did not include MRCT-JP from the most recent survey period for comparison. We also examined other publication information, in addition to the review reports, as necessary. The influence of each explanatory variable was analyzed by logistic regression analysis, with whether or not MRCT-JP was implemented as the explanatory variable. Statistical significance was set at 5%.

Findings: In the survey period up to September 2017, 165 drugs developed with MRCT-JP were approved for manufacture and sale in Japan. "Respiratory system," "inhalation," "biological drug," and "under review" evaluation status for the United States, European Union, and other areas, "approved" evaluation status for the United States, "new ingredients," "priority review," "non-Japanese firm," and "Top 1–10" and "Top 11–20" drug sales rankings for pharmaceutical companies were identified as potential factors leading to the implementation of MRCT-JP. In contrast, "general anti-infectives for systemic use," "various," "external," "chemical compound," "unsubmitted" evaluation status for both the United States and European Union, and "Top 51+" drug sales rankings were potential factors for not implementing MRCT-JP.

Implications: Therapeutic classification and agent type, in addition to capital type and United States and European Union evaluation status suggested by a previous study, were associated with implementing MRCT-JP. It is important to determine the best way to utilize MRCT-JP to maximize the value of products. Our findings were based on successful cases and may therefore be helpful for designing clinical development plans. Appropriate use of MRCT-JP will improve productivity in the pharmaceutical industry. (*Clin Ther*. 2018;40:284–295)

Key words: agent type, Anatomical Therapeutic Chemical (ATC) code, clinical development, formulation, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), multi-regional clinical trial (MRCT).

INTRODUCTION

The production of pharmaceuticals has declined for many years.[1] Pharmaceutical companies have been seeking more efficient strategies for drug development to counteract the decline. As such, drug development and sales business models have dramatically changed over the last decade, such that pharmaceutical

Accepted for publication December 15, 2017.
https://doi.org/10.1016/j.clinthera.2017.12.010
0149-2918/$ - see front matter

companies now develop drugs for worldwide launch. A key issue associated with such a strategy is the difference in regulatory systems among countries or regions. Multiregional clinical trials (MRCT) are used as a standard strategy to efficiently obtain drug approval in multiple countries.

The Japanese drug market remains important to pharmaceutical companies. Japan is the world's third largest drug market after the United States and China.[2] Japanese regulatory systems and policies have also greatly influenced the sustained importance of Japan in the global pharmaceuticals market. The review period by regulatory authorities is the shortest for the United States, European Union (EU), Canada, Switzerland, and Australia.[3] The unique Japanese health insurance system ensures reimbursement within 60 days of approval for almost all approved drugs before entry into the drug price list. The reimbursement system in Japan is prompt compared with similar systems in other developed countries.[4] This allows pharmaceutical companies to plan sales without concerns about insurance reimbursements. Therefore, Japan is a key region for global drug development.

"Drug lag" is a recognized social problem in Japan.[5] New drugs were traditionally first approved in the United States, EU, and other countries or areas, and later in Japan. To address drug lag, the Pharmaceuticals and Medical Devices Agency (PMDA) published the first guidelines for MRCT including Japan as an operational region (MRCT-JP) in 2007[6] and a second MRCT-JP guideline in 2012.[7] Ueno et al[8] reported that the inclusion of MRCT-JP in the clinical development strategy was important for reducing drug lag. In addition, MRCT-JP may help to reduce clinical development costs in Japan.[9] Therefore, clinical development strategies that include MRCT-JP are considered to contribute to improving the production of pharmaceuticals. However, MRCT-JP is not suitable for the development of all drugs.

Ichimaru et al[10] reported a marked increase in both the absolute number and percentage of clinical trial notifications to the PMDA concerning MRCT-JP. From a total of 168 protocols from fiscal year (FY) 2007 to early FY2009, the major target diseases of MRCT-JP were cancer and cardiovascular disease. MRCT-JP may be more suitable for rare diseases for which it is difficult to obtain the necessary number of patients in Japan alone; diseases that require simultaneous global clinical development because of high medical needs; and diseases with clear end points and that require a large-scale outcomes study. In addition, some studies have reported differences in pharmacokinetic profiles and approved drug doses between Japanese and Western populations.[11–14] If there are only small ethnic differences in the pharmacokinetic profiles and reactivity of a drug between Japanese and non-Japanese populations, little variation and consistent results can be expected in an MRCT-JP population. We hypothesized that there are certain target diseases and characteristics of drugs that are suitable for MRCT-JP.

We reasoned that we could identify factors that make drugs or diseases suitable for MRCT-JP by analyzing the detailed data of previously approved drugs. To our knowledge, there are currently no studies examining the association between drug characteristics and agent type and MRCT-JP. We comprehensively analyzed the clinical trials of drugs approved in Japan to identify the factors contributing to whether or not MRCT-JP was implemented. Because we only examined successful cases, we believe that these factors may have played an important role in the decision to implement MRCT-JP. Based on these successful cases, we discuss the factors associated with determining whether or not MRCT-JP should be implemented.

MATERIALS AND METHODS

We surveyed the review reports and summaries of application data published by the PMDA and gathered information on each explanatory factor.[15] The review reports reveal the review and approval status (evaluation status) outside Japan at the time of drug approval in Japan. For drugs that were approved in Japan by September 2017, we identified those for which the clinical trial data package included MRCT-JP and selected the same number of drugs for which the clinical trial data package did not include MRCT-JP (non–MRCT-JP) from the most recent survey period for comparison. In addition to review reports, we also examined drug interview forms, which are comprehensive documents provided by the pharmaceutical companies to compensate for missing information in Japanese package inserts, and information published by United States and EU