The Role of the Japanese Society of Clinical Pharmacology and Therapeutics in the Transition of Clinical Studies in Japan

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The Japanese Society of Clinical Pharmacology and Therapeutics (JSCPT) was founded in 1969 as an academic society of clinical pharmacologists aiming to contribute to the establishment of scientific and rational drug therapy. In 1979, this group officially became the JSCPT, and has become an important entity in the field of clinical studies, taking a leading role in the implementation of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) in Japan. The JSCPT currently has a membership of approximately 3,200 members, consisting of medical doctors, pharmacists, researchers, regulators, and clinical research coordinators (CRCs). Promoting clinical studies is one of the most important missions of the JSCPT, which aims to resolve problems such as the delay in the development of new drugs in Japan, so-called the "Drug Lag."

Japan has been one of the few countries where the whole process of drug development, from discovery and non-clinical studies to early and late phase clinical studies and also post marketing surveillances and studies, can be carried out entirely in one country, but the regulatory acceptance of only studies conducted in Japan led to isolation from international drug development. In order to begin clinical trials, Japanese regulatory agencies required more non-clinical data compared to other countries, and flexible protocols were not accepted. Regulators were conservative with regard to safety, and exceptions were rarely made. For later phase trials with a large number of subjects, the pace was slow and the cost high. Investigators were not familiar with the GCP concept and lacked resources for conducting clinical trials. Unlike clinical studies initiated by investigators, clinical trials for registration were not considered to be scientific work, and there were no incentives for investigators to conduct them. As a result, each site was able to recruit less than ten subjects, leading to a high number of sites for one protocol, which resulted in inefficient clinical trials. Another factor that delayed the start of clinical trials in Japan was that the final formulation was expected to be provided at the start of the trial.

With the implementation of the ICH agreement, many aspects of drug development were harmonized with Western countries. Since the agreement with ICH, there is no longer a significant difference in the amount of non-clinical data required at each stage of clinical development. Regulatory agencies started to accept the use of foreign data, which enabled the "Bridging Strategy" (bridge with Phase 2 data and extrapolate non-Japanese Phase 3 data) and allowed Japan to join global trials and to use the data from these trials for registration. This lead to an increase in global trials including Japan, but the number of clinical trials conducted in Japan and the total number of Japanese patients exposed to the drug candidate at the time of New Drug Application (NDA) declined. At the same time, Asian countries became more efficient in enrolling patients in late phase clinical trials, and Japan was not able to keep up with the speed.

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To improve the situation, the Ministry of Health, Labour and Welfare (MHLW) initiated a 5-year Activation Plan for Clinical Trials focusing on multinational confirmatory trials, and the plan was successful to some extent. The number of multinational trials in Japan increased and speed and quality improved, but the realization was that Japan is not highly competitive in large-scale clinical trials. At the end of the 5-year Activation Plan, Japanese regulatory agencies shifted their focus to early clinical studies, where Japan can contribute to global drug development by utilizing the infrastructure of and abundant experience accumulated through early clinical studies such as first-in-human (FIH) studies and dose finding studies. Under this concept, the MHLW accredited 5 core hospitals for exploratory clinical studies to promote FIH studies of original Japanese candidate compounds. Clinical pharmacology units (CPUs: clinical facilities that specialize in clinical pharmacology studies such as FIH studies) have been established in several university hospitals, and private CPUs have enhanced their facilities for FIH studies. Several university hospitals have opened PET centers, enabling them to conduct certain types of POC studies. There are sites that have specialized equipment and technologies that enable special studies, such as glucose clamp studies for glucose lowering drugs and polysomnography (PSG) studies for sleep drugs. The Pharmaceuticals and Medical Devices Agency (PMDA) now has more drug development professionals, and they are able to make appropriate judgments regarding the balance between risks and benefits. Flexible protocols have gradually been accepted and are supported by the FIH study guidelines that were issued on April 2, 2012. Primitive formulations (such as liquid formulations which are replaced by solid formulations later in the clinical development process) are now accepted for clinical pharmacology studies in Japan.

Early phase clinical studies are actually a very important and interesting part of clinical development. In the FIH single ascending dose (SAD) study, the drug candidate is tested for the first time in humans and a very wide dosage range in studied, usually at least in the range of 100 times. This study produces data to determine dosage levels and the frequency of dosing for the next study, which is typically the multiple ascending dose (MAD) study. The MAD study produces the first time-dependent data in humans for the drug candidate. With the increase in available biomarkers, we can often explore the Proof-of-Concept (POC) and sometimes the pharmacodynamic (PD) effects of the drug candidate in these Phase 1 studies as well. The POC study is designed to answer the question of whether or not the drug mechanism is working. Even with the advanced non-clinical methods that are now available, it is not possible to predict all aspects of drugs candidates when they are administered to humans, and consequently the learning curve is very steep at this early phase of clinical development. With the data from these early phase clinical studies, a huge amount of new and important information is gained. The data may confirm findings in non-clinical studies, but often surprises us as well. Sometimes the drug development strategy may need to change significantly, and sometimes the indications can completely change, as seen in the example of sildenafil, which was originally developed for hypertension and ischemic heart diseases, but the indications changed to erectile dysfunction (ED) based on findings in early clinical studies. These data often lead to decisions regarding whether or not drug development should be continued for the drug candidate and provides information on how to design the late phase studies if the decision is to proceed to late phase clinical development.

At the same time, early phase clinical studies are complicated and pose higher risks that late phase clinical studies. Therefore, it is important that experienced investigators and staff conduct these studies in facilities that are designed for such studies. For example, it is critical that there is access to emergency care for Phase 1 studies. It is also important that the study site is designed to handle the busy study schedule (frequent procedures) and the condition of the subjects is visible during the critical hours. Usually, about 8 subjects are dosed on the same day at a site, and accurate procedures produce data with less variability. CPUs in Japan have abundant experience, and many efficient processes are in place. For example, the unit usually has synchronized clocks, and many sites color code sample tubes so that there is less likelihood of mixing them up. With this experience, established systems, and attention to detail, the data that is generated by these Japanese CPUs are of high quality, and because of the low variability there is a better

chance that drug signals will be observed, even with a small number of subjects. Recruiting patients for Phase 1 studies has been challenging in any country because CPUs used to focus on healthy subjects. However, recent data shows that CPUs in Japan can recruit patients with good speed.

As discussed above, the infrastructure, experience, and current regulatory environment have made Japan an ideal place for conducting early phase clinical studies. The JSCPT is a medical society of investigators, researchers, and site staff who conduct early phase clinical studies. By promoting clinical studies, the JSCPT has aimed to resolve the "Drug Lag" in Japan. This is another opportunity for the JSCPT to play a key role in providing high quality early clinical data not only for drug development in Japan, but also for the global development of pharmaceuticals.