WHITE PAPER

Conducting Clinical Trials in Japan: A CRO Perspective

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Yasmine Chiu, M.D.
Senior Medical Director, Pharmacovigilance, PPD

INTRODUCTION

Japan is the world's second-largest single-country pharmaceutical market, accounting for approximately 10 percent of global drug sales and expanding quickly.[1,2] In 2011 the top eight foreign pharmaceutical companies operating in Japan enjoyed annual growth rates from 12 to 31 percent, rivaling the expansion observed in emerging markets.[3] This growth spurt has been largely attributed to the Japanese government's multi-year focus on transforming the way drugs are approved, regulated and reimbursed in their country.

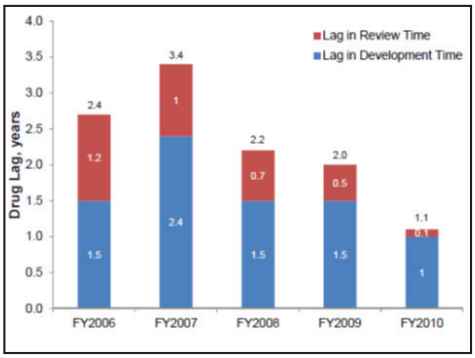

Figure 1: The drug lag between Japan and the U.S. is decreasing steadily[7] FY = fiscal year

The change is recent and ongoing. Between 1999 and 2006 several groups examined "drug lag," the term used to describe the often-sizable delay between the time a new drug is approved in the U.S. or EU compared with Japan, and consistently reported a gap of 2.5 to 3.0 years.[4-6] Data from the Pharmaceuticals and Medical Devices Agency (PMDA), part of Japan's Ministry of Health, Labour and Welfare (MHLW), indicate that drug lag peaked at 3.4 years in fiscal year (FY) 2007 and has been falling steadily ever since. For FY2010, the most recent data available, the delay had been cut to 1.1 years (Figure 1).[7]

Much of the improvement in drug lag can be attributed to a shorter regulatory review period. Between FY2008 and FY2011 the average time for standard review decreased by nearly 50 percent, dropping from 22.0 months to 11.5 months. The gain was even more impressive for priority reviews, which had an average cycle time of 15.4 months in FY2008 but only 6.5 months in FY2011. Preliminary data from FY2012 indicate that review periods continue to shorten and will easily meet the government's targets (nine months for priority review, 12 months for standard review).[8]

The two main reasons for the improvement in review time are PMDA, which was established in 2004 to consolidate services from several separate agencies,[9] and the Japanese government's ambitious and largely successful three-year (2004 to 2007) and five-year (2007 to 2012) plans (Table 1). In particular, the five-year plan contained provisions to reduce review times by hiring

Three-Year Plan (2004 to 2007)	Five-Year Plan (2007 to 2012)
Promote a clinical trial network	Provide clinical trial networks with clinical trial core hospitals and other sites
Strengthen the clinical trial mechanism at sites	Encourage, foster and ensure that clinical trial professionals have appropriate training and skill sets
Support patient participation in clinical trials	Increase the awareness of clinical trials by the general population
Reduce the cost of clinical trials	Harmonize administrative procedures and format of paperwork and electronic filing to increase efficiency and decrease the burden on clients
Promote clinical research	Address issues related to IRBs and GCP

IRB = institutional review board; GCP = Good Clinical Practice.
Table 1: Key Features of Japan's Three-Year and Five-Year Plans [12,13]

additional PMDA personnel (especially physicians) and expanding training and educational programs.[10,11]

Unfortunately, making an impact on the lag in development time is more challenging. While improving, Japan does not yet have a robust clinical trial infrastructure and, until recently, Japanese law required that all new drug applications (NDA) contain clinical data on the drug's pharmacokinetics, efficacy and safety in a sufficiently large group of Japanese citizens. As a result, the Phase I, II and III studies used to obtain marketing approval in the rest of the world had to be repeated in Japan and, in many cases, the Phase I trials didn't begin in Japan until the global Phase III trials were nearly complete.[14] New guidance released in September 2012 broadens the criteria slightly, allowing for data from well-designed and conducted global clinical trials with sites in East Asia to be included in Japanese NDAs as long as the impact of ethnic differences among East Asian populations is considered before the study begins.[15]

With a shrinking drug lag and a separate initiative to loosen pricing controls on drugs,[16] Japan has become a much more attractive market for foreign and domestic pharmaceutical companies and the contract research organizations (CRO) that support them. Challenges do remain, and this paper summarizes current PMDA processes, compares Japanese and international standards for Good Clinical Practice (GCP), examines cultural factors that may affect clinical trials, and discusses the role of CROs in the management of clinical trials in Japan.

CURRENT PMDA PROCESSES

Before initiating a clinical trial in Japan, clients must submit a clinical trial notification (CTN) to PMDA. Approval is by default; if the client does not receive any queries from PMDA in the specified time period, the trial may commence (see Figure 2 for details). Submission requirements are similar to other countries (protocol, informed consent form, names of all investigators,

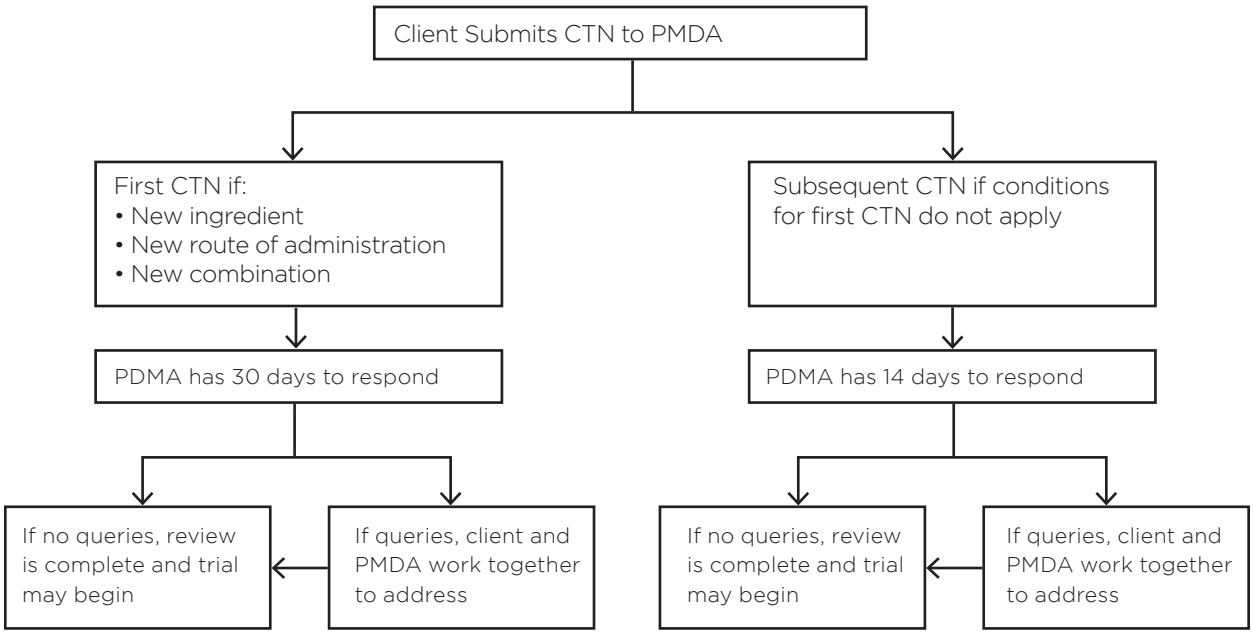

Figure 2: Flow chart of clinical trial notification (CTN) process in Japan

insurance, etc.) but, of course, all documents must be translated into Japanese.

REGULATORY CONSULTATION WITH PMDA

One service offered by PMDA is consultation on clinical trials and regulatory submissions. During clinical trial consultations, PMDA assesses whether a proposed study complies with the requirements for regulatory submission, taking into consideration the science, proposed data collection and analysis techniques, patient safety, and ethics. The reviewers also may provide suggestions on how to improve the trial.

Clients may choose whether or not to request a consultation before submitting a CTN. In cases where local trials are being conducted purely for the purpose of registering the drug in Japan, PMDA input on population, efficacy and safety endpoints, and sample size is likely to be invaluable and speed the time to approval. Clients planning multinational trials with some sites in Japan may choose to skip the pre-CTN consultation but request a session before the NDA is filed to confirm that their trial data is adequate. The time from request to consultation is approximately two months.

While often invaluable, consultations are optional and can be costly. Depending on the expected length and complexity of the consultation, PMDA charges between 140,000 and 7,000,000 yen[17] (roughly $1,400 to $70,000), and there are additional costs associated with client staff time and travel and, if needed, simultaneous interpreters and external experts. In FY2011, PMDA conducted 447 consultations.[18]

EXTERNAL INTERACTIONS

PMDA frequently consults with external experts during its reviews. In 2012 the agency established the Science Board, a high-level consultative body comprised of renowned Japanese physicians and scholars. PMDA staff also participate in academic conferences, both in Japan and overseas, and are working to build collaborative relationships with other Asian countries.

CHALLENGES OF CONDUCTING CLINICAL TRIALS IN JAPAN

While Japan's clinical trial infrastructure is growing, there are still several unique challenges to address.

STANDARDS FOR GOOD CLINICAL PRACTICE

Clinical trials in Japan are governed by country-specific standards for Good Clinical Practice (J-GCP) that, while generally harmonized with the international standard (ICH-GCP), are more comprehensive and include additional requirements that often slow the development process (Table 2). The two main differences between J-GCP and ICH-GCP are:

1. Under most circumstances, each site needs to have its own institutional review board (IRB).

2. Site heads (e.g., the chief executive officer of a hospital or clinic) must take responsibility for signing financial contracts and overseeing the conduct of the study. As the size of an institution increases, this approach quickly becomes untenable and can be demotivating both for sites and investigators.

A 2012 amendment of J-GCP introduced some flexibility regarding the use of IRBs outside the clinical trial site and reduced requirements for clinical trial contracts. While these changes are expected to shorten study start-up times, the continued need for substantial involvement by the site head is often a significant barrier to participation.

	ICH-GCP	J-GCP
Responsibilities of the site head (leader of institution)	Not mentioned	Many specific roles and responsibilities
Sign contracts	Investigator and site	Site head
Ensure site qualifications	Not mentioned (but implied to be the investigator's responsibility)	Numerous necessary conditions, including assignment of responsible person to handle the administrative process of clinical trial management
Ensure compliance with SOPs and confidentiality laws	Not mentioned	Site head
Provision of IMP	Investigator	Site head
Record keeping	Investigator	Site head (can assign duties to a responsible person)
Establishment of IRB	Not mentioned	Under most circumstances, each site must have its own IRB
Obtain IRB approval and follow guidance	Investigator	Site head

ICH-GCP = International Conference on Harmonization Good Clinical Practice; IMP = investigational medical product; IRB = institutional review board; J-GCP = Japanese Good Clinical Practice; SOP = standard operating procedures.

Table 2: Comparison of ICH-GCP and J-GCP

LIMITED RECOGNITION OF THE VALUE OF CLINICAL RESEARCH

Few medical societies, institutions or individual physicians in Japan find clinical research worthy of recognition, and an investigator does not gain professional status by having his or her name included in a lengthy list of people who were involved in a trial. Many academic centers have long traditions of excellence in basic research and, in some cases, consider clinical trials to be somewhat less scientifically sound.[19] This impression may stem from earlier standards that allowed the use of single-arm studies to support registration of drugs manufactured by local companies. Today, PMDA has more rigorous data requirements.

LIMITED AVAILABILITY OF INVESTIGATORS

A national insurance policy provides every Japanese citizen with global medical coverage and easy access to cutting-edge care. However, with increases in health care expenditures, a sluggish global economy and a rapidly aging population, the Japanese government has been forced to limit spending on health care. There is a shortage of clinicians at all levels, and few physicians have time to devote to clinical research.

Japan's three-year and five-year plans attempted to address this issue by promoting clinical trial networks, providing sites with in-house clinical trial coordinators and pharmacists to help ease workload, and adding active participation in clinical research to the mission

statements of the national university hospitals.[20] Provisions for additional staff are particularly important, as a 2009 survey of physicians at university hospitals in Japan found that most are willing to conduct clinical research if adequate trial infrastructure and administrative support are available.[21]

LIMITED INCENTIVES FOR INVESTIGATORS

Unfortunately, the issue of limited availability of Japanese investigators is exacerbated by the lack of incentives for participation. As noted earlier, clinical trials rarely bring professional recognition, as clinical research is not highly valued in Japanese society. Financial compensation for participation is also limited, as J-GCP dictates that contracts for clinical research – and the associated monetary transactions – are between the client and the head of the medical institution.[22] Little funding trickles down to the individual investigator, and some institutions even have strict regulations to prevent increases in investigator incentives. While this situation could be partially offset by choosing small clinics or individual practices as study sites, the limited patient population at each site would likely increase the total number of sites needed to meet enrollment targets and raise overall study costs.

LIMITED INCENTIVES FOR PATIENTS

Since every Japanese citizen has full medical coverage, enrollment in clinical trials does not provide a means to access a higher level of care. Some trials do offer compensation to patients, but IRBs often limit the amounts to transportation expenses and minimal stipends to discourage participation based solely on financial gain.

While drug lag is shrinking, clinical trials do offer an opportunity to gain access to drugs before they are approved by PMDA/MHLW. However, most Japanese patients are very safety conscious and prefer to wait until the government assesses a drug and declares it safe for their unique ethnic population. In addition, unapproved drugs that are available in other countries can be legally imported into Japan by physicians, although the cost can be prohibitive.

DIFFERENT WAYS OF WORKING

Many of the well-known differences in social and behavioral norms between Eastern and Western cultures can affect clinical trials. For example, the meticulous attention to detail often associated with Japanese people aids in the process of collecting high-quality data but also leads to numerous questions and lots of back-and-forth between the sites and the client or CRO. In addition, Japanese tend to value face-to-face communication, so conducting business over the phone or via email may be less productive than spending the time and money to visit the site. Foreign clients or CROs, particularly those based in Western countries, are often more successful if they employ or partner with personnel who have extensive on-the-ground experience with Japanese investigators and PMDA.

LANGUAGE BARRIER

Although most Japanese physicians are able to understand clinical trial-related documents written in English, other site-level personnel (e.g., clinical research coordinators, pharmacists and administrative assistants) may not have the same level of fluency. Language barriers often result in miscommunication and misunderstanding, and foreign clients should not underestimate the time and expense associated with translating trial documents into Japanese and then translating case report forms or other data collection instruments back into the client's native language.

HIGHER COSTS

There is nearly universal agreement that per-patient clinical trial costs in Japan are two to six times higher than anywhere else in the world.[23-25] Numerous factors contribute to this disparity, including:

- High cost of living in Japan
- Low patient density per site
- Slow patient enrollment
- Little incentive to prioritize efficiency or cost effectiveness

CROs IN JAPAN

While CROs have been legally recognized in Japan since 1997, their role in clinical research is not widely known or accepted in the medical community. Despite this limitation, use of CROs and site management organizations (SMOs) is steadily increasing as the Japanese government expands the country's capacity for – and interest in – clinical trials.

Multinational CROs looking to enter or expand their presence in Japan have found that staffing is a significant hurdle. Success hinges on recruiting and retaining experienced clinical trial personnel who are familiar with local Japanese practice and culture, able to adapt to global standards, and fluent in English (or other Western language). The talent pool is limited, and well-qualified individuals may prefer to join pharmaceutical companies or local CROs that are perceived to provide more stable employment, better benefits and a wider range of career opportunities.

A more common approach is for multinational CROs to acquire or partner with a local CRO to immediately obtain an experienced team with local knowledge. While this approach has obvious benefits, it is important to realize that in-country staff may be very familiar with Japanese practices but have limited experience with global standards. Providing up-front and ongoing training are critical if data is to be used for regulatory submissions in the United States, European Union or other markets.

Once staffing issues have been addressed, a multinational CRO can take steps to establish a favorable reputation among Japanese investigators and PMDA by:

- Providing high-quality customer service and demonstrating professionalism
- Respecting local culture and medical practices
- Offering investigators customized training on clinical research methodology, biostatistics, etc. (when possible)
- Assisting the investigators with preparation of study documents (when possible)
- Introducing global best practices (when appropriate)
- Successfully completing clinical trials in Japan or a consortium of Asian countries. PMDA has enthusiastically promoted the concept of using a pan-Asian clinical trial consortium to generate data to support regulatory approval in Japan. Potential participants include China, Indonesia, Japan, South Korea and Taiwan.

SUMMARY

Imagine it's 2003. Your multinational pharmaceutical company is finishing a successful Phase III development program in the U.S. and EU and planning to complete regulatory submissions in the next 12 months. But what about Japan? The size and strength of the market is attractive, but how much time and money will be required to repeat the development program in the country's population? If you decide to proceed, it's likely that approval in Japan will be 2 1/2 to three years after approval in other major markets.

Fast forward to 2013. Same situation: Phase III trials are almost complete and your team is busy preparing regulatory documents for the U.S., EU, and other markets. But what about Japan? Clinical trial infrastructure has improved and review times have shortened significantly, but you still need to have data on the Japanese population. Fortunately, you planned ahead, initiating Phase I studies in Japan when the drug entered Phase II elsewhere in the world. You designed your Phase III program to include Japanese and other East Asian populations, and you've met with PMDA twice to discuss regulatory strategy. You feel confident in your

Asia-based CRO staff, who have experience with global trials, an in-depth understanding of the Japanese culture and clinical trial environment, and a favorable reputation with sites, investigators and PMDA. You are on track to fulfill requirements and submit an NDA to PMDA approximately nine months after documents are filed in the U.S. and EU. The drug lag has lessened, and approval in Japan should come less than 12 months after approval in the U.S. Thanks to advanced planning, reforms from the Japanese government and a CRO with experience in Asia, your drug will be available to the world's second-largest pharmaceutical market 18 to 24 months earlier than was possible just 10 years ago.

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