How To Run Successful Clinical Trials In Japan

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There is no longer any excuse not to include Japan as an integral part of any global clinical-development program for either pharmaceuticals or medical devices. With a more receptive climate for both starting and running trials, an improved infrastructure for clinical research, and significant advances in accelerating drug approvals, Japan is now firmly on the global development map.

There have always been strong reasons to secure a foothold in Japan. It is the world's third-largest single pharmaceutical market after the US and China – or second-largest for prescription drugs – with a rapidly aging population (26.6% over 65 years old in 2016) increasing the demand for healthcare and medicines.

Other compelling reasons to always involve Japan in global drug development include: a mature local market; a renewing economy; the regulatory flexibility around Japanese data in global clinical-trial packages; an extensive, nationally-funded healthcare infrastructure with universal health insurance; a large and adherent patient population; and a strong emphasis on quality and precision in clinical research.

Japan's attractiveness for the inward investment proposition for the pharmaceutical sector has further increased in recent years as the Japanese regulatory authorities have made concerted efforts to align drug approval timelines with the US and Europe. The situation in Japan today is a far cry from before, when Japanese patients had access to new medicines five to ten years after their counterparts in the US or Europe.

More specifically, Japanese authorities have created new incentives including, but not limited to, priority- or conditional-approval programs for new medicines in areas of high unmet need such as orphan diseases. Additionally, the regulatory agency has removed some significant regulatory or bureaucratic obstacles for clinical trials, such

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as past reluctance to consider foreign study data and reliance on bridging studies over full participation in clinical development worldwide.

Nonetheless, the complexities of planning and running clinical trials in Japan can be daunting for the uninitiated. Tapping into local expertise and resources that help non-nationals to navigate the regulatory hurdles, make the right connections and home in on eligible trial participants can ease the process.

Regulatory And Operating Environment Changes

In a recent interview with Informa Pharma intelligence, Toru Fujieda, Hiroshi Yamada and Toshitaka Kawaratani, respectively President, Vice President and Head of the Consulting Division at CMIC Co., Ltd, a pioneering Tokyo-based contract research organization, highlighted how the regulatory and operating environment for clinical trials in Japan has markedly improved in the past decade.

Improvements include much shorter review times for new drug applications (NDAs). In 2007-08, for example, the average time taken to assess and approve a NDA in Japan was 1.5 to 3 years. In the US and Europe, the average drug-approval time was about two years. Now drugs are being approved in one year or less in Japan, setting a faster pace than both the FDA and the EMA, Kawaratani notes "The regulatory authority has recognized that in approval timings for product launches, we need to be competitive with other countries such as the US and European markets," he adds.

Along the way, the Japanese government and the Pharmaceutical and Medical Devices Agency (PMDA) have introduced incentives such as a 10-20% 'Japan-first' pricing premium for medicines developed locally in parallel with other major markets, or expedited approvals for rare-disease and other medically significant drugs.

Price premiums are available under the orphan drug designation, launched around three years ago and now applying to 20-25 projects annually. For truly innovative medicines, price premiums can range from 70-120%.

Special provisions were also created for the review and approval of gene and cell therapies in Japan. The *Sakigake* pathway for breakthrough and regenerative medicines includes substantial regulatory and scientific support for development plans, rolling NDA submissions and an accelerated review period.

Aggressive recruitment and training strategies were introduced at the PMDA, nearly doubling its review staff. In addition, Kawaratani points out, the agency has adopted a more consultative approach in its relations with the pharmaceutical industry. Both the frequency and quality of communications have improved in both directions, as the PMDA commits determinedly to a strategy of innovation. That includes closer communications with regulatory counterparts overseas, such as the FDA and the EMA, as well as more global alignment through the International Conference on Harmonization (ICH).

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More Flexible Conditions For Clinical Trials

The PMDA's innovative stance has created more flexible conditions for Japanese clinical trials. Rather than asking routinely for large studies in the local population, the PMDA now requires data from only a certain proportion (and sometimes a limited number) of Japanese patients to confirm drug efficacy and safety.

PMDA's increased recourse to term-restricted conditional approvals, supplemented by real-world data post-launch, for innovative medicines in areas of high unmet need is also helping to cut clinical development times.

With the liberalization throughout the drug development and registration process, "many global ventures now want to come into the market to aim for the first launch in Japan", Kawaratani says. That aligns very much with Japan's interest in promoting itself as a viable destination for global clinical trials.

Over the last 10 years there has been a growing trend for programs either to include Japanese sites in their trial protocols or to incorporate bridging studies from Asian countries such as Korea and/or Taiwan. As a result, 50-60% of clinical trials now conducted in Japan are associated with global programs.

Scheduling Clinical Trials In Japan

In parallel, clinical trial start-up times in Japan have improved significantly. "Around 10 years ago it took around five or six months for site initiation," Yamada mentions. "The current situation in Japan is that it takes three or four months on average."

More efficient study initiation reflects the availability of an extensive infrastructure for clinical trials. "Many public or university hospitals have a very good system in place for clinical trials," Fujieda points out. "It's very easy to conduct trials nowadays." Government efforts to promote a better co-ordinated clinical-trial environment through hubs and networks have further underpinned the infrastructure.

Better resourcing for local trials has also made an impact. Many investigator sites can now call on clinical research coordinators (CRCs) with a full range of capabilities to support trial initiation and implementation.

CMIC launched not only Japan's first CRO but also its first site management organisation (SMO). The group's in-house SMO, Site Support Institute, has partnerships with medical institutes and university hospitals extending from Hokkaido to Okinawa, the northernmost region to the southernmost region of Japan. This extensive geographic coverage enables local CRCs to have an important part in identifying both the right sites and the right patients for specific trials.

Joint ethics-committee reviews for smaller local trial sites are also well established. In the past, one of the hurdles to getting clinical trials up and running in Japan was the need for most sites to have their own institutional review board.

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"The time needed for selection and screening [study participants], everything is running more smoothly than 10 years ago," Kawaratani notes.

GCP Harmonization And SOPs

Touching all bases from first patient in to last patient out, the mechanisms and provisions for running clinical trials in Japan are increasingly harmonized with global standards, Kawaratani emphasizes.

That also goes for Good Clinical Practice (GCP). Despite legislation bringing the country into line with ICH GCP standards in 1997, Japan's rigorous and conservative application had traditionally been a disincentive to clinical-trial notifications. Additionally, other areas of difficulty included the obtainment of informed consent from trial participants who culturally tend to defer to medical professionals and may not welcome a full discussion of their condition with a clinical investigator; and the requirement for chief investigators at each study site to personally supervise financial arrangements and all other aspects of trial conduct. Now, information-sharing and communications with site heads are more fluid and systematic and so are speeding up clinical research approval and monitoring procedures.

Very often global CROs operating in Japan use their own SOPs when applying GCP to clinical trials. CMIC has no problem conducting trials in accordance with ICH GCP, but CMIC can also use client's SOPs.Clinical research associates (CRAs) working for CMIC are well trained in both the CRO's standard operating procedures and those of its clients.

Investigator, Patient Commitment To Clinical Trials

While 10-20 years ago hospitals were often reluctant to get involved in clinical trials owing to the perceived administrative and other burdens, with little prestige attached to clinical research among healthcare professionals and academics, and a paucity of financial or other incentives, to act as clinical investigators, that has now changed, according to Fujieda. Today, with a stream of cutting-edge therapies emerging from research and development pipelines in key areas such as oncology, physicians are more motivated to participate as a means to widen patient access to new medicines.

Despite the availability of universal healthcare coverage in Japan, a similar rationale also drives patient interest in clinical trials, particularly with non-responders to existing therapies for cancer or other critical conditions. Transportation-fee support for clinical-trial site visits, and the opportunity for detailed consultations with physicians as well as access to new treatments, may also encourage patient involvement.

Moreover, the cultural deference to healthcare professionals makes these patients more likely than their counterparts in other countries to adhere strictly to study protocols.

Managing Clinical Trial Costs

One disadvantage to running trials in Japan could be that costs tend to be higher than in other markets, a disparity blamed on various factors such as slow patient recruit-

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ment, the necessity for face-to-face communication between the investigators and CRCs, or the complexity of study payment systems.

Site costs can be high, with each trial site employing its own fee system and calculations for different trial components such as principal investigators, clinical research coordinators or indirect costs.

Fee negotiations need to be conducted with site staff, rather than principal investigators as in other markets. While some clinical-trial costs are covered by national health insurance, the sponsor is held responsible for other costs (e.g., laboratory tests, imaging, comparator drugs).

While CMIC tries to keep costs down, they can be complicated by the trend of client requirements such as 100% verification of all source data in Japan. On the upside, this attention to detail pays off in terms of the data quality, given the highly professional attitude of investigators in Japan and their patients' seriousness about following study protocols and reporting requirements to the letter.

Companies bringing clinical trials to Japan can also take advantage of the PMDA's increased openness to data from comparable Asian countries, such as South Korea, Taiwan and Singapore to recommend Asian trials including the Japanese population. They can leverage these other markets to generate an Asia data package that balances the higher costs of running trials in Japan, when US/EU trials are completed in advance.

Usually, these combined packages depend on protocol design and drug indication of interest, Yamada notes. Clinical-trial sites in other Asian countries must also be 100% GCP-compliant, as the PMDA will directly audit sites abroad where necessary.

At the same time, regulatory conditions still require some level of Phase I, II or III data to account for potential variations in the Japanese population, with pharmacokinetic data depending on the specific compound and indication. This proportion is currently around 15%, depending on the indication and protocol design.

Moreover, the PMDA no longer recommends bridging studies as a means of accessing the Japanese market. It would rather see global clinical trials that take in the Japanese population.

Overcoming Drug Lag

Most pharmaceutical multinationals start their global trial programs in either the US or Europe and will wait until Phase II studies are started in those markets before initiating Phase I development in Japan. However, some global giants and Japanese companies, developing medicines globally, do start with clinical trials in Japan. As Yamada points out, global clinical trials still tend to be slow at adding Japanese patients to the global program, due to the higher cost of running studies in Japan as well as traditional barriers such as unfamiliarity with Japanese language, culture or clinical-trial processes.

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There are exceptions, nonetheless: companies may be encouraged to start global trials in the Japanese population.in indications, such as gastric cancer, which are a high unmet need. Accelerated-approval provisions for oncology therapies may provide further leverage.

Japan's greater reliance on surrogate endpoints as a basis for drug approvals in some conditions is potentially attractive. In diabetes mellitus, for example, the primary endpoint is reduction in glucose levels or HbA1c (glycated haemoglobin) rather than broader outcomes such as death rates.

Finding The Right Patients

While patients are available and willing to enrol in clinical trials in Japan, it can be difficult making people aware of opportunities to participate and finding exactly the right patient cohort for a particular study.

As Akihisa Mitake, President of CMIC's Site Support Institute Co., Ltd., and Shinichi Keino, President of CMIC Healthcare Co., Ltd., noted in a separate interview with Informa Pharma Intelligence, in the 10 year plus the CMIC group has been involved in patient recruitment,, approaches to enrolling patients have evolved in line with the shift in the marketplace and companies' research and development pipelines from chronic diseases towards more complex conditions such as rare diseases, difficult-to-treat cancers or central nervous-system (CNS) disorders.

This shift has boosted demand for specialist patient recruitment organisations (PROs) and more targeted recruitment strategies away from traditional reliance on print media or the internet. These strategies may be hampered by the difficulty of obtaining detailed information on relevant trials from public websites such as ClinicalTrials.gov.

"Even if they find the right information, they cannot directly access the clinical-trial sites for more information," Keino comments. Moreover, participating study sites may be reluctant to disclose details such as the names of hospitals involved in a trial.

Against this backdrop, CMIC is developing new initiatives tailored to patient recruitment in the fast-growing oncology market. These include setting up an online portal for cancer trials that would act as a go-between by screening eligible patients and referring them to trial sites.

CMIC is also working with ReasonWhy Inc., an internet-based company offering second opinions on medical diagnoses through a system called Findme, on disseminating oncology-trial information to patients.

Another initiative involves partnering with life assurance companies enabling CMIC to provide information on available clinical trials to newly diagnosed cancer patients. Emphasis is on having a flexible approach to patient recruitment and a customized alternative to one-size-fits-all strategies, where the primary focus is on trial registration panels, Keino explains.

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Recruitment techniques can be modified according to age, gender and target disease. For example, an analog approach may still be suitable and effective for older people unfamiliar with, or little interested in, digital media.

Partnerships For Patient Recruitment

CMIC's strength in having patient recruitment as a group function lies in its broad range of partnerships, which also includes pharmacies, companies that process prescription receipts, organizations providing regular medical check-ups, and nursing-care specialists. All of these are potential channels of communication with patients who may wish to take part in clinical trials.

Medical- and prescription-claims databases provide another means of identifying eligible patient pools through recorded prescriptions and diagnoses, or of assessing site feasibility for clinical studies.

In-market specialists such as CMIC can also help a study run smoothly by taking a meticulous approach to patient awareness and informed consent, or ensuring that any devices used in a trial, such as electronic patient diaries, are user-friendly and fully connected.

As Mitake observes, Japanese people expect their devices to work, and something as simple as using foreign batteries with the wrong voltage for Japan can undermine confidence and trust if it interferes with device functionality.

Continuing Challenges

Despite the many improvements in the Japanese clinical-trial environment, challenges, such as slow progress with access to electronic medical records, patient consent for secondary data use and integration of Japanese clinical-trial data into global databases, remain.

Such challenges can be particularly taxing for small- to medium-sized pharmaceutical companies and bioventures without experienced international staff. In the absence of a Japanese subsidiary able to conduct clinical trials under local GCP requirements, such companies must appoint an in-country clinical caretaker (ICCC) that can jointly assume their legal, regulatory and operational obligations.

Indeed, an ICCC-licensed service provider is the crucial bridge between an overseas company and the PMDA as well as clinical-trial sites. Third parties can open doors in contract negotiations with study sites, as well as reconcile different contract formats for individual sites.

It can also act as a go-between with the PMDA, which welcomes early consultation – whether formally or informally – on clinical-trial designs and data specifications. Japan has very specific requirements for post-marketing surveillance (PMS), with a particular focus on risk management during the first six months after launch, and strict monitoring requirements in specialist areas such as rare diseases.

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All interactions with the PMDA need to be in Japanese, as do most interactions will clinical researchers. Indeed, a strong, traditionally insular national culture pervades all aspects of the business and regulatory environment in Japan, which to outsiders can sometimes appear opaque. Consequently, a local partner can make a huge difference in breaking down any communication barriers.

Disconnecting Development

Companies looking to conduct clinical trials in Japan should be thinking about disconnecting drug development from commercial activities, such as business partnering, so that their development program runs simultaneously in Japan and other key markets such as the US and Europe.

That way, they can take full and early advantage of the new wave of regulatory liberalization in Japan and a growing pharmaceutical and healthcare market geared to innovation. Teaming up with the right partner will go a long way towards ensuring this experience is a positive one.

CMIC is Japan's largest CRO, with more than 25 years' experience, 1,200 clinical research associates, over 140 consultants and medical writers, and services ranging from contract-development-and-manufacturing (CDMO), preclinical, and clinical-trial support through to regulatory consultation, PMS and pricing consultation for negotiations with the Ministry of Health, Labour and Welfare (MHLW).

Pharmaceutical Value Creator

This broad range of services underpins CMIC's unique 'Pharmaceutical Value Creator' business model. With so many varied inputs from different areas of the business, the group has prompt access to large volumes of valuable information on pharmaceutical-market trends. This enables CMIC not only to expand the scope of its business but to provide considerable added value to its industry clients.

Given the growing encouragement for Asia data packages to support global clinical trial programs and product approvals in Japan, CMIC is also well placed as the leading pharmaceutical-services provider across Asia, with headquarters in Japan and operations in China, Korea, Taiwan, Hong Kong, Singapore, Malaysia, Thailand, Vietnam and other countries in the region.

With expertise in key therapeutic areas such as oncology, cardiovascular disease, CNS disorders and regenerative medicine, as well as medical devices and gene or cell therapies, CMIC can be an invaluable partner for companies ready to give a more outward-facing Japan the parity of recognition it now deserves in global drug development.

TO LEARN MORE about Asia as a preferred destination for global clinical trials, the advantages of partnering with a local CRO and how CMIC can support small and mid-sized pharmaceutical companies in their innovation journey download the white paper here: www.cmicgroup.com/e

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