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How To Run Successful Clinical Trials In Japan

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 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).

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.

"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.

To read the full white paper, go to: https://bit.ly/2nVuFof