APPLIED CLINICAL TRIALS

Stumbling Seven Times But Recovering Eight

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By Jae Chung & Masashi Kiyomine

Insights for Pharma Executives Sourcing Global Clinical Trials in the U.S. and Japan

The Japanese pharmaceutical market is the world's second largest behind the U.S., representing 9.7% of the world pharma market in 2013, with sales estimated at $115 billion. According to Deloitte, the industry's annual average growth rate of 2.2% is expected through to 2018, with revenues totaling $128 billion. Though a highly attractive market, historically Japan has been insular—a consequence of a number of factors, such as medical culture and the complexity of the underlying regulatory context. One of the nuances of this environment was the so-called "drug-lag," where new drug approvals could lag up to six years behind U.S. and European Union (EU) approval. Because of these delays, companies often didn't bother to pursue drug development. The end result was that Japanese patients had to wait years, or sometimes decades, to get the same drugs that were available in the U.S., Europe, and elsewhere.

With the advance of modern communication and open access to information, problems associated with drug lag became apparent in Japanese society, and change soon followed. In 2007, the Japanese Ministry of Health, Labor and Welfare (MHLW) reversed some key policies, which, in turn, led to markedly reduced regulatory review periods and a friendlier environment for global trials. In many ways, the Japanese clinical research landscape has shifted. Once viewed as unique and difficult to work with, Japan is increasingly a region where opportunities for global registration studies abound, supported by government policies as well as the medical community and its local population.

Incorporating Japan as an integral part of your global trial execution strategy does not come without its unique challenges. While opportunities are on the rise for those life sciences companies eager to enter the Japanese pharma market, cultural differences and socioeconomic factors have a significant impact on the outcome of those business engagements. Given the importance of the Japanese market and its renewed interest in participating in global studies, it is more important than ever to understand how such factors may impact global study participation and execution, as well as the technologies used to support clinical research.

On the flip side, Japanese companies eager to engage in global clinical studies and work with partners in the U.S. and beyond face their own set of challenges when it comes to understanding key cultural and societal differences which manifest in various forms, such as technology practices, patient recruitment, and even study design.

Culture shock, the personal disorientation a person may feel when experiencing an unfamiliar way of life, is normal when doing business in Japan. “Stumbling seven times but recovering eight” is the literal translation of the Japanese proverb, nanakorobi yaoki, meaning that “perseverance is better than defeat”; faux pas are expected, but with the right preparation and observance of Japan’s culture’s etiquette and understanding of clinical research conduct subtilties, these mistakes can be mitigated. Sophistication and worldliness elements signal executive presence, creating a favorable impression of them and, by extension, their business.

So how do you set your company up for success?

Considerations for U.S. companies engaging with Japanese partners

1 Align clinical research studies with Japanese medical practice.

Aligning studies with Japanese medical practice is important in order to increase study participation and patient engagement, which ultimately helps to get medicines to patients in sooner. Aspects of the healthcare system, norms for technology platforms, as well as patient incentives, carry slight differences that can translate into major barriers if not understood and managed well from the outset. The following are representative aspects of the clinical research environment in Japan, which should be considered when designing global studies for Japanese investigators and patients.

- **30% of healthcare costs are covered by the patient, the government pays the balance.** As a result, patients may have less personal incentive for participating in a trial compared to some countries, which can impact study enrollment. This makes communicating the scientific and clinical importance of the trial to both the patient and the investigator even more important. Patient awareness activities should stress the medical and societal benefit of study participation.

- **The use of electronic medical records (EMRs) is more standard practice than in the West, making searching for trial participants easier for investigators.** In major hospital settings, the incidence of EMR adoption is as high as 65%.1 This highlights how Japan can help U.S. companies drive digital innovation in trial operations.

- **Different medical norms.** There are various medical norms that study teams should explore with their Japanese colleagues during protocol and study design. These risks should be mitigated as part of the study risk assessment. One example is that doctors do not routinely record the reasons for the use of concomitant medications (two or more drugs given at or almost at the same time.) If the study protocol mandates that a reason is required, this may be an extra burden for investigators and can deter participants. In addition, informed consents are not a familiar item in Japanese culture, and signing a form listing detailed risks may be uncomfortable for the average Japanese patient.2 Therefore, it is usually a good idea to have a robust Japanese translation of the informed consent form (ICF), with fluent Japanese staff on hand to facilitate the discussion. Maintaining dual-language ICFs takes time and must be planned for in advance.

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- **Cultural resistance to adverse event (AE) reporting.** Japanese culture generally minimizes spontaneous adverse event reporting, as shame may be associated with experiencing an adverse event. Solicited adverse events should be discussed with the patients to communicate that these are not unexpected and are quite reasonable to experience. A private environment with a supportive, fluent Japanese staff is critical for success.

- **Slight differences between J-GCP and ICH-GCP.** Japanese clinical trials are governed by country-specific standards for good clinical practice (J-GCP). While these are generally consistent with the international standard (ICH-GCP), J-GCP contains aspects that are more comprehensive and include additional requirements. According to a recent white paper from PPD, "Conducting Clinical Trials in Japan: A CRO Perspective3," the two main differences between J-GCP and ICH-GCP are:

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

    2. Site heads 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 make life difficult for both for sites and investigators.

- **Independent pharmacists in Japan are few, and there is a general limitation on pharmacist resources.** This may pose a challenge to find pharmacists who can be unblinded to the study and prepare the drug formulations per the protocol, if necessary.

2 Recognize the importance of Japanese business etiquette.

Ultimately, communication occurs between human beings and not between cultures, and when in doubt, it pays to err on the side of conservatism. With this in mind, it's important to consider the following matters of cultural etiquette if you're doing business with Japanese pharma (or are hoping to win one as a client) – Eight key ways to prepare yourself for the culture differences:

- **Personal relationships are the key to success:** Japan's business culture attaches a high degree of importance to personal relationships, and these take time to establish and nurture. Patience and repeated follow-up are typically required to close a deal, and face-to-face meetings are a critical part of relationship building in the Japanese culture.

- **Japanese business cards are a must-have:** Ideally, have double-sided business cards printed with the Japanese language, designed using the same elements as the English side. If your original business card is not English, then use double-sided English and Japanese business cards when doing business in Japan. Accept a Japanese business card with respect, using both hands, saying "Thank you" or "Hajimemashite" as you do so.

- **Deals are done differently:** The nature and pace of dealmaking in Japan is quite different from the U.S. The hard sell doesn't sell—use persuasive presentations that showcase the benefits of the proposal, rather than focusing overtly on deadlines and decisions.

- **Discuss ideas, don't expect brainstorming:** Understand requirements and propose creative alternatives. Brainstorming sessions will not work, especially if unfamiliar faces or senior management are involved.

- **Silence is Golden:** Silence is linked to credibility. "The duck that quacks is the first to get shot" is one of many Japanese proverbs that speak to the importance of silence. An introverted, formal approach, especially at the beginning of a business relationship, is likely to be better received when doing business in Japan.

- **Third-party validation is critical:** Talk about other customers, especially top-tier companies; an endorsement by a top-tier executive will open doors.

- **Seek local advice and an interpreter:** Hiring a local consultant can eliminate unnecessary stress, especially if that person can double as interpreter. Many Japanese executives and decision-makers do not speak English or prefer to speak Japanese.

- **Responsibility can get lost:** Japan is consensus-based. End meetings with action items and schedule a follow-up meeting/call.

3 Understand the history of technology in the Japanese healthcare system.

As previously noted, EMRs are more prevalent in Japan, which presents increased opportunities for patient recruitment and engagement. But there are complexities due to the fact that various EMR systems were designed and implemented by different vendors. This means that the hospital information systems in Japan typically only operate together through the integration of different platforms, which may be difficult outside of regional networks.1 Though there are challenges, there are also emerging opportunities for clinical research. In 2010, Japan launched the National Clinical Database (NCD), which is a prospective registry linked to various types of board certification systems regarding surgery. When linked to cancer registries, the NCD has great potential for impacting patient care. Collaboration between Japan and the U.S. has recently started and is expected to provide global benchmarking and enable a valuable comparison of cancer treatments.

Considerations for Japanese companies engaging with US partners

The Japanese pharma industry is increasingly opening up to foreign markets, having become a popular destination for multi-regional clinical trials (MRCTs) since 2006, when bridging studies—studies to determine whether foreign trial results are applicable to patients in Japan—were allowed to be included in MRCTs, decreasing the time and expense involved in getting new drugs to Japanese patients.

As clinical trials continue to grow in size and complexity, more and more companies are adopting software-as-a-service (SaaS) applications to manage data and streamline electronic data capture (EDC), study start-up, and monitoring workflows. Particularly in the context of MRCTs, technologies such as interactive voice response (IRT) and electronic patient-reported data sources (ePRO) are becoming more commonplace. These trends underscore the need for Japanese pharma to understand how practices in the U.S. influence clinical research software in global implementations.

Japanese pharma executives will find that business practices at home do not necessary translate into a winning combination in America. Understanding some of the common business practices used in U.S. life sciences companies will help ease frustrations these organizations may feel when dealing with U.S.-based partners.

1 Software development practices may differ.

- **Agile development methodologies are common:** “Agile development” is an umbrella term for several iterative and incremental software development methodologies, which typically involve rapid prototyping and continual software development. Start-ups bringing technological disruptions to the healthcare industry have led the way in making cloud-based, global study workflows possible. Often, technology companies in the U.S. will partner with clients and use agile methodologies and pilot studies to co-create solutions and enhance existing platforms. This may seem foreign to Japanese companies who often see any partnership as a long-term commitment. Pilot study is not a binding commitment, especially in the SaaS business model.

- **Early adopters are respected:** Whereas in the US, early adopters are seen as innovators and thought leaders (“The early bird gets the worm”), Japanese companies tend to be late adopters when it comes to enterprise software. This often creates a negative cycle of the technology being developed by U.S. companies not conforming to their requirements/preferences.

2 Be willing to participate and share your feedback.

From a westerner’s viewpoint, a business meeting is a place to discuss issues, with the clear goal of reaching conclusions about something. Japanese often prefer to use business meetings as a place to report findings only. Suspend that tendency and show willingness to review and discuss challenges. Try and give feedback—even if the product is not exactly what you are looking for. Experiment with alternatives. Remember agile environments welcome changing requirements, even late in development. You may find (ultimately) that your expectations have been exceeded.

3 Rely on a mentor.

Leverage one of the most important relationships in Japanese social context (the revered senpai-kohai relationship) and find a good mentor. Japanese pharma companies are good at developing (or acquiring) drugs, but software isn't necessarily their forte. Why not get your preferred reseller involved? Having a trusted expert who can translate business requirements into everyday language may eliminate an unnecessary steep learning curve.

In closing

Japanese life sciences firms are making an important shift, moving from the role of partner in the clinical research value chain to an integral part of a global study team. As we make that shift, executives will need to do more to "think locally" when designing trials, carefully accounting for regional and cultural differences along the way. Though many study risk assessments already account for regional differences in infrastructure, resources, and patient availability, few go deep enough to consider how culture in a given region may impact issues such as patient enrollment, compliance, and investigator engagement.

The deep cultural differences between the US and Japan in the clinical research context bring home the need to collaborate closely and ensure there is a strong two-way information flow between global, regional, and local teams. They also highlight the importance of staying close to investigators and technology providers, while respecting differences in the various ways of working. With the future of drug development relying more and more on multinational clinical trials and simultaneous submission to the major regulatory authorities, this is a timely and pertinent topic that warrants serious thought and consideration.

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Jae Chung *is the founding visionary of goBalto. A startup evangelist, he works with Rock Health to mentor health-care technology startups. He previously co-founded Celltrion, a leading biopharmaceutical manufacturing company and was a strategy consultant with McKinsey & Company.*

Jae Chung
Founder & CEO | goBalto

Masashi Kiyomine *is interested in technologies that improve human healthcare and optimize delivery. He has served as a board member or observer for MC10, NxThera, Symic Biomedical, ContinuumRx Services, Arravasc, Optiscan Biomedical, ChangeHealthcare (Acquired by Emdeon), Cardiovascular Systems (Nasdaq: CSII), Ekos (Acquired by BTG plc).*

Masashi Kiyomine
Investment Director | Mitsui