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## Conducting Global Clinical Trials in Asia

There is a growing trend for biopharmaceutical and medical device companies to conduct global clinical trials in developing countries in Asia. This article covers four topics:

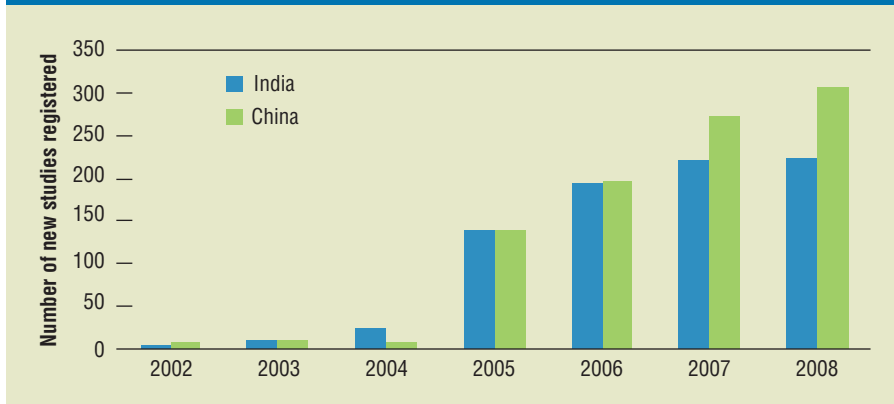
- an overview that compares the conduct of trials in different therapeutic areas, stages, and sizes in Asia and in North America/Europe, outlining the opportunities for conducting clinical trials in Asia;
- a comparison of the diverse regulatory approval processes in various Asian countries with the more unified system accepted in developed countries;
- a discussion of the areas that need improvement in Asian countries; and
- provision of some practical strategies for proper regulatory planning for, and effective management of, clinical sites.

### Multinational Clinical Trials in Asia

The globalization of industry-sponsored clinical trials started in 1996, when the International Conference on Harmonization's good clinical practice (ICH-GCP) guidelines were adopted by drug regulatory authorities in the United States, European Union (EU), and Japan.<sup>1</sup> The implementation of ICH-GCP has enabled the biopharmaceutical and medical device companies (sponsors) to collect clinical data worldwide in a more cohesive and consistent fashion. The past decade has witnessed an increased number of clinical trial sites in emerging countries in Eastern Europe and Asia, contributing 8.9% and 5.9% of the study sites, respectively, according to an analysis of more than 10,000 clinical trials registered between October 2005 and October 2007.<sup>1</sup> From 2002 to 2008, the number of global trials increased 35-fold in China and 20-fold in India, based on trials registered at ClinicalTrials.gov (see Figure 1). A similar analysis of the clinical trials registered between 2002 and 2006 indicated a 21.3% average annual growth rate in the share of active clinical sites in Asia, compared to -2.9% in the traditional regions, such as North America and the EU.<sup>2</sup>

In the early 1980s, Europe was considered by the United States as a mosaic of people, cultures, and medical practices when clinical trials had just started moving there.<sup>3</sup> More trials are now shifting to emerging regions, such as developing countries in Asia, which is perhaps the most diverse continent in terms of cultures, populations, education, healthcare, and drug regulatory policies. Hong Kong and Singapore, as two

**Figure 1** Rapid Growth in the Number of Global Clinical Trials Conducted in China and India. (Source: www.clinicaltrials.gov)



regions holding the best healthcare and most highly educated personnel, as well as streamlined regulatory systems, were attractive sites for clinical trials when multinational clinical trials had just started in Asia. However, these locations host only 0.3% of the population in Asia, which limits their capacity for clinical trial sites. Other countries or regions have started to catch up, including China, India, South Korea, and Malaysia.

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Some interesting commonalities and distinctions may be observed when comparing trends in recent global clinical trials in Asia to those in other regions in the world. The results from an examination of the number of sponsored clinical trial sites in 12 major therapeutic areas in Asia, compared to the global distribution, are shown in Figure 2. Oncology, cardiology, and endocrinology appear to be the three major disease areas, covering 46% of all the sites both

worldwide and in Asia.<sup>1</sup> However, Asia has proportionally more sites for psychiatry, oncology, and infectious disease and fewer sites for endocrinology and neurology, compared to global distributions.

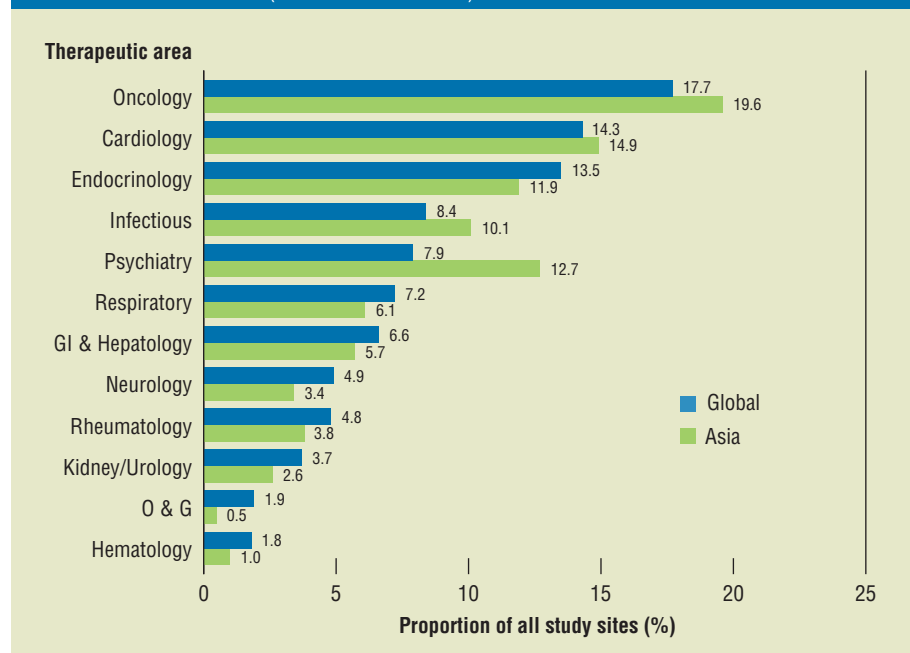
Compared to traditional regions, such as the U.S. and Europe, Asia hosts the smallest percentage of early-stage clinical trials—approximately 12% compared to 24% in North America and Oceania and 21.4% in Eastern Europe.<sup>2</sup> However, confirmatory trials rank highest in Asia and at a rate similar to that

seen in Latin America. This is partially related to the local policies in Asian countries. For example, the regulatory authority in China, the State Food and Drug Administration (SFDA), allows only foreign drugs entering Phase II or Phase III in global trials to be conducted in China.

Compared to the regional distribution of trial sites by size and global trial span, Asia holds the highest percentage of small trials (those using less than 20 sites per trial), whereas all the other regions appear to hold larger trials spanning more than 20 sites per trial.

Companies are under pressure to reduce the time and cost of product development while broadening global markets sooner to recoup their investments. In the United States, clinical trial execution is often delayed due to hiccups in the subject recruitment phase and declines in the number or availability of principal investigators. In contrast, some developing countries in Asia offer lower costs, faster research subject recruitment, drug-naïve populations, and increasing numbers of well-trained physicians and thus are attracting more global trials.

**Figure 2** Proportion of therapeutic areas among all sponsored clinical trial sites: worldwide vs. Asia (Oct. 2005-Oct. 2007).



Note: Figure adapted from Karlberg et al.<sup>1</sup>

Other reasons driving the trials to Asia include improved infrastructures for clinical research and healthcare systems. More importantly, by including Asia in global clinical trials, companies are likely to speed up product launches to the Asian market, which can mean early profits. These benefits are readily demonstrated by the experiences of many companies in Asian countries, especially in China and India, the two potentially largest developing markets for clinical trials.

In terms of cost-effectiveness, according to the FastTrack Systems Global Cost Databases (2006), conducting a clinical trial in China was about 50% more cost-effective compared to the United States.<sup>4</sup> Companies manage 40-60% saving in offshoring clinical trials to India, according to many sources. However, companies will not save money on conducting trials in Japan, mainly because of its much higher health expenditure per capita (\$2,662 in Japan vs. \$61 in China and \$27 in India).<sup>5</sup>

Asian countries offer a large research subject pool, and study subject enrollment takes place relatively quicker than elsewhere. Furthermore, the competition for research subjects in a number of Asian countries (listed in Table 1) is less intense than in the U.S. and Europe, since large numbers of research subjects live in urban areas with convenient transportation, which makes recruitment easier and faster.

Furthermore, the number of well-trained Asian investigators who are able to deliver high-quality clinical data in multinational clinical trials has increased as more global trials have been conducted in their countries. A few years ago, India and South Korea held training sessions on clinical trial management; Merck opened a training center in Singapore in late 2008; the United States launched an online training initiative targeting China in early 2008; and the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have started accepting data generated from the trials conducted in China in recent years.

Country	GCP Adoption	Approval Process	Regulatory Approval Timeline*
Japan	ICH (1998)	Parallel Approval	14–30 days
Singapore	Yes (1998)	IRB Approval→Reg. Approval	30 days
South Korea	Yes (2001)	Parallel Approval	30 days
Hong Kong	ICH	IRB Approval →Reg. Approval	~60 days
Taiwan	Yes (1997)	Parallel Approval	~80 days
China	Yes (1999)	Reg. Approval →IRB Approval	~155/195 days
Malaysia	Yes (1999)	Parallel Approval	~100 days
Thailand	Yes (2000)	Parallel Approval	~110 days
Indonesia	Yes (2001)	NA	~90 days
Philippines	Yes (1993)	Parallel Approval	~100 days
India	Yes (2001)	Parallel Approval	Type A, 14 to 40 days Type B, 60 to 90 days

\* The regulatory approval timeline is based on information from regulatory government agencies.

Finally, according to Pacific Bridge Medical-Asian Medical Publications, the pharmaceutical market size for Asian countries in 2006 was \$350 million for Indonesia, \$6 billion for India, \$6.5 billion for South Korea, \$20 billion for China, and \$60 billion for Japan.<sup>6</sup>

*Asia has diverse regulatory systems affecting the conduct of trials, compared to the more established FDA or EMEA system in Western countries.*

### Regulatory Landscapes for Clinical Research in Asia

Asia has diverse regulatory systems affecting the conduct of trials, compared to the more established FDA or EMA system in Western countries. Asian regulatory systems are still evolving, and regulations change frequently. Japan, a developed country that was an early member of the ICH, is listed in Table 1 for reference. Hong Kong is also a member of the ICH, but the other listed countries are not. In

Singapore and South Korea, the regulatory processes are the most streamlined, quick, and predictable. The timeline of 30 working days for clinical trial approval (CTA) is as fast as in the United States and EU.<sup>7</sup> The CTA timelines in Hong Kong, Taiwan, Indonesia, Malaysia, Philippines, and Thailand range from 60 to 110 days.

For the past two years, the regulatory approval process in India has been more streamlined, with median approval times reduced down to 14 to 40 days for trials already approved by a cognizant regulatory authority in one or more developed countries, such as the U.S., Canada, U.K., and Japan (known as “Type A” trials) and 60 to 90 days for all other studies (i.e., “Type B” trials). In China, it takes approximately 155 days for CTAs of fast-track drugs and 195 days for regular drugs.<sup>8</sup> The recently issued Amended Measures on the Administration of Drug Registration by China’s SFDA, which took effect October 1, 2007, sets a 90-day timeline for new drug CTAs.<sup>9</sup>

Again, aiming to improve their regulatory systems, Asian countries have been actively participating in ICH workshops.<sup>10</sup> These progressive efforts signal that Asian countries are willing to improve their regulatory environment to harmonize with Western standards for developing new drugs in a timely man-

ner, while ensuring research subjects' safety.

Although ICH-GCP is generally accepted as the standard, some countries have their own GCP guidelines. For example, Malaysia adopted the ICH-GCP Guidelines in 2004, with some modifications to suit local requirements, in order to provide public assurance that the rights, safety, and well-being of trial subjects are protected.<sup>11</sup>

Two CTA processes exist in Asia.<sup>12</sup> South Korea, Taiwan, Malaysia, Thailand, the Philippines, and India follow a parallel process, meaning that the institutional review board (IRB) approval and regulatory approval occur at the same time. Singapore, Hong Kong, and China follow a sequential process; Singapore and Hong Kong require IRB approval before regulatory approval, whereas China requires regulatory approval before IRB approval.

Factoring in longer approval processes in Asia, compared to the U.S. and EU, helps companies undertake proper regulatory planning in Asia. The longer CTA timelines may result from more complicated approval procedures and country-specific policies. For instance, obtaining a CTA from the SFDA in China involves multiple steps, including trial application submission, specification verification, and technical evaluation by multiple divisions of the agency,<sup>12</sup> and difficulties that arise during any of these steps contribute to the possibility of delay. In general, a thorough understanding of the local regulatory environment ensures that dossiers are correctly assembled to minimize delays.

## Challenges of Conducting Global Trials in Asia

Asian countries offer many advantages to biopharmaceutical and device companies worldwide. However, more work lies ahead. A 30-day approval process has been accomplished in South Korea and Singapore;<sup>12</sup> other countries can follow their examples or other routes to achieve similar results, which eventually bring in more global trials from sponsors.

Inadequate IP and patent protection have long been another concern for sponsors. For example, China's SFDA sometimes requires sponsors to provide detailed technical data in investigational new drug application dossiers, which sponsors are reluctant to disclose at the beginning of drug development because of potential IP issues. Since 2005, when India became a signatory to the Trade-Related Aspect of Intellectual Property Rights Accord, it stopped allowing generic companies to reverse-engineer drugs. However, the lack of data exclusivity in the 2005 Act allows companies to continue introducing competing products without performing their own safety and efficacy tests.<sup>13</sup>

Some global trials require blood sample testing in one central laboratory outside of a country, such as China. Strict regulations for blood sample importation and exportation can delay ongoing trials. Furthermore, Asian countries need better infrastructures for global clinical trials site and clinical supply chain management.

Moreover, the issues include the inability to obtain informed consent from subjects before the trial and lack of adverse event (AE) reporting during the study. In addition, the success of clinical trials largely depends on accurate translation of documentation. In non-English-speaking countries, the study documents and forms must be translated into native languages. Inconsistent and inaccurate translations in either direction can potentially introduce issues of safety and drug efficacy, and can significantly affect research subject compliance, data accuracy, and AE reporting.

## Recommendations and Conclusions

As discussed above, conducting global trials in Asia provides both opportunities and challenges. To leverage the opportunities in Asia for clinical development in a timely, risk-controlled approach, sponsors should consider the following strategies.

First, regulatory strategy planning is essential to conducting trials in Asia.<sup>14</sup> For instance, in China, a final version of the clinical protocols is not required for an initial CTA. Adjustments to a protocol are allowed after a study is approved by the SFDA. Sponsors can save time by submitting a preliminary protocol for CTA and finalizing the protocol simultaneously.

## Regulatory strategy planning is essential to conducting trials in Asia.

Including Chinese sites in a Phase II or III trial is a strategy of "killing two birds with one stone."<sup>14</sup> Sponsors who plan to launch products in China should adopt this strategy for proper regulatory planning. At the very least, marketing a foreign drug in China requires the presentation of data from Phase III trials that included an SFDA-specified minimum number of Chinese research subjects, even for drugs that have been approved and used in other countries for years. Some companies, such as Bristol-Myers Squibb, in the case of Baraclude® (entecavir), have benefited from utilizing this simple strategy to receive SFDA approval for marketing their drugs in China just months after FDA approval. Otherwise, sponsors must conduct local trials duplicating earlier work, which could take three to four years to meet SFDA requirements for product launch in China.

In addition, sponsors need to gain local know-how by providing sufficient training to clinical professionals to ensure the collection of accurate, complete, and valid test data. Sponsors who lack local knowledge can access the countries through partnership with experienced contract research organizations, suppliers, or investigators. Physicians in many Asian countries have a profound influence on research subjects and regulatory authorities. Therefore, it is crucial to establish rapport between site coordinators or physicians and clinical research associates to facilitate site monitoring and, ultimately, to

ensure the quality and timely completion of a trial.

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### ACRP

**Guilin Huang, MBA**, is a specialist in regulatory and scientific affairs at Huahai US, Inc., where she is responsible for managing drug development projects and regulatory submissions. Previously, she was head of medical and regulatory affairs in Takeda China, focusing on IND, NDA, and ANDA submissions and approvals, and managing

clinical projects and pharmacovigilance activities. She can be reached at [gluang@alum.bu.edu](mailto:gluang@alum.bu.edu).

**Qihong Xu, PhD**, has eight years of experience in drug discovery and development in the pharmaceutical industry, including research conducted at Children's Hospital, Harvard Medical School, after receiving her doctorate from Tokyo University. She can be reached at [xu\\_qihong@yahoo.com](mailto:xu_qihong@yahoo.com).

**Li Zang, PhD**, is an analytical chemist currently working for a large biopharmaceutical company in the U.S. She has more than eight years of experience in analytical chemistry research in drug target identification and validation and drug product development. She can be reached at [zangli77@yahoo.com](mailto:zangli77@yahoo.com).

**Laurie A. Halloran, MS, CCRA**, has 22 years of experience in clinical research. She has worked in various roles of increasing responsibility, including as CEO of Halloran Consulting Group and in senior clinical management positions at PAREXEL, Oxigene, and Antigenics. She has become recognized as an industry expert through her speaking, publishing, consulting, and training activities throughout the world on industry best practices. She can be reached at [halloran@hallorancg.com](mailto:halloran@hallorancg.com).

**Joan Q. Zhong, PhD**, cofounded Bioinsider Consulting, LLC to provide consulting services for biotech and high-tech companies. She has also conducted biomedical research in infectious diseases at the University of Pennsylvania and MIT, pursued drug discovery in infertility and oncology at Serono, and performed market research. Please address all questions about this article to [joan\\_zhong@yahoo.com](mailto:joan_zhong@yahoo.com).