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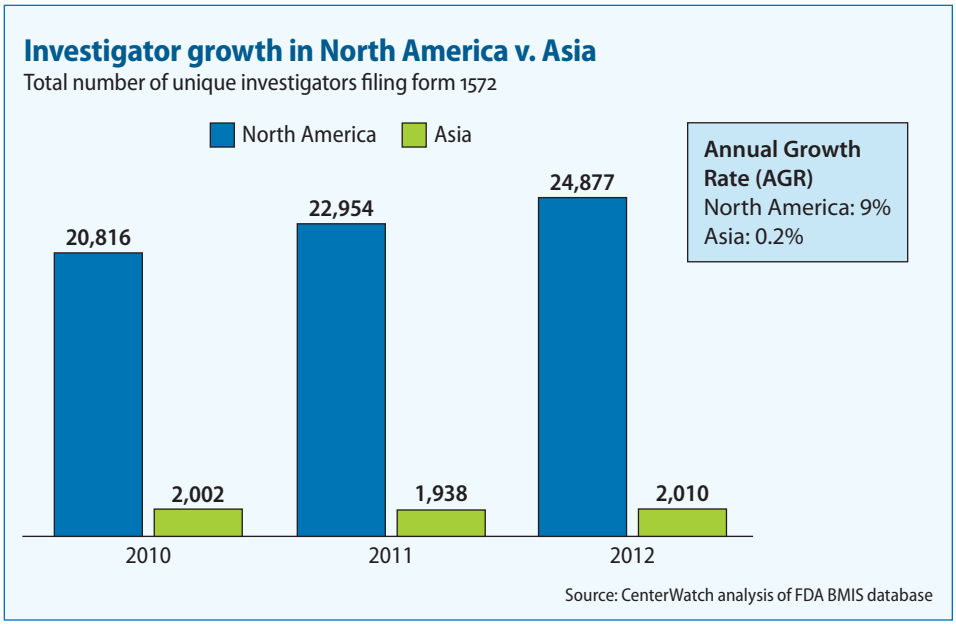
New growth and decline in Asia clinical trials

South Korea, Japan, China see big growth in 1572s, while India posts huge drop

By Karyn Korieth and Annick Anderson



While Asia's clinical research landscape has grown significantly over the past five years, a new CenterWatch analysis paints a radically different picture of the region than anticipated 18 months ago.

Data analysis of individual countries has found new pockets of growth, particularly in South Korea and Japan, but regulatory concerns have caused a dramatic slowdown in India, which the industry had anticipated would become a leading market for clinical research by now.

Much of the research focus has shifted from India to China where, despite substantial challenges including lengthy study start-up times and cost concerns, analysis shows the clinical trial infrastructure has begun to consolidate and mature.

The CenterWatch analysis found overall, the number of registered interventional studies conducted in Asia increased at an average annual growth rate of 8% during the past five years, the highest average growth rate among regions worldwide. In comparison, the number of similar studies conducted in North America fell by 2%, while Western Europe saw a slight increase of 1%.

During the same five-year period, the number of investigators in Asia grew by an average annual rate of 14%, compared to 9% in North America.

As Asia's clinical research landscape begins to reshape itself, with new areas of opportunity emerging, the region remains an integral part of major drug developers' global programs. Pharma companies continue to make significant scientific investments in the region, including construction of R&D facilities; CROs are growing and expanding into new countries. Companies also are showing a greater willingness to invest more in training to ensure investigators meet Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) standards.

Importantly, clinical research will continue to grow in Asia, as the region offers the world's largest populations of both treatment and clinical trial naïve patients.

"It is widely recognized that Asia Pacific offers good opportunities for conducting clinical trials in view of the large patient pool, regulations that comply with ICH guidelines, a Western medical education system and medical practice that meets international standards," said Wei-Ming Goh, vice president of Asia Pacific for CRO Icon, which has more than 1,600 staff based in 13 countries across the region.

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Methodology used

CenterWatch, which has monitored the clinical research landscape in Asia for the past decade, decided this year to take a closer look at variations in growth within

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Editor-in-Chief Cheryl Appel Rosenfeld
Drug Intelligence Tracy Lawton, Stephanie Hill
Production Holly Rose

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Unique Principal Investigators in Southeast Asia

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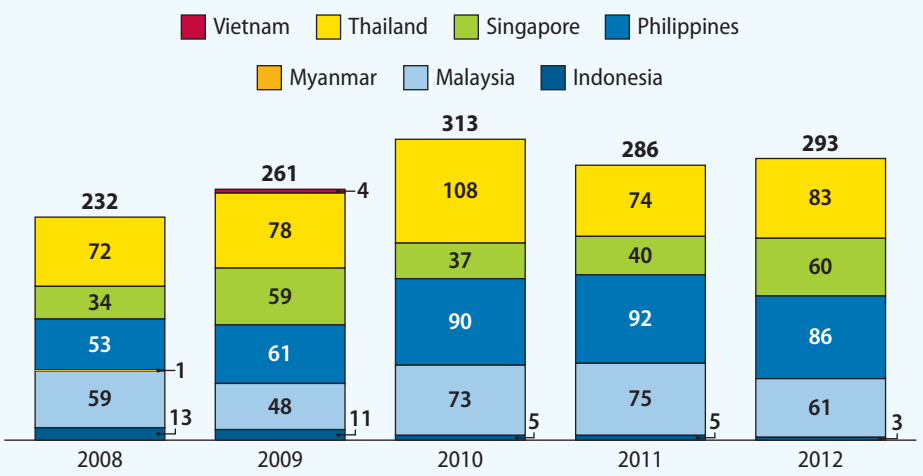


Note: Region also includes Laos, Cambodia and Brunei

Source: CenterWatch analysis of FDA BMIS database

Asian sub-regions and countries. For this analysis, the number of Principal Investigators for each country was determined using the Bioresearch Monitoring Information System (BMIS) database, operated by the FDA's Center for Drug Evaluation and Research (CDER). The BMIS database tracks the number of active investigators through a 1572 form, which sponsors must collect from each clinical investigator in each trial conducted under the FDA's Investigational New Drug (IND) regulations. The number of registered interventional studies for each country was determined through listings submitted to the ClinicalTrials.gov registry, which reflects both federally and privately funded clinical studies conducted under an IND.

Decline in India

An uncertain regulatory environment has made it nearly impossible for global sponsors and CROs to run clinical trials in India. The number of registered interventional studies in India dropped 25% between 2010 and 2012; the number of investigators fell by 9% over the same period.

During the past six months, the slowdown has intensified. Many sponsors and scientific agencies—including the National Institutes of Health—stopped conducting clinical trials in India after the government amended its rules for testing new drugs. Most troubling was a requirement for companies to compensate clinical trial participants who experienced serious adverse events or death, regardless of whether the event was caused by the study drug or the pre-existing disease. Volunteers who received placebo instead of the active study drug also were eligible for reimbursement.

"India has seen a slowdown in growth due to ongoing concerns with regulatory issues. As such, we have seen some global sponsors take a 'wait-and-see' approach to including India in their clinical trials," said Nick Wright, vice president and general manager, clinical development services, Asia Pacific, for CRO Covance, which has operated in the region for 25 years.

The significant drop in activity was unexpected, since just a few years ago the industry projected 15% of global clinical trials would be conducted in India by 2011. Sponsors and CROs were attracted by millions of treatment-naïve patients, low operating costs and a rising incidence

of Western diseases. Clinical activity surged—reaching nearly 350 newly registered interventional studies in 2010—after the government strengthened its regulations to harmonize with those of the U.S. and the ICH. The government also had promised a fast-track approval system. Yet, according to ClinicalTrials.gov, only 1.5% of currently registered studies are being conducted in India.

"There is a complete sense of uncertainty around India as a place for trials," said Kent Thoelke, executive vice president, scientific and medical affairs at CRO PRA, which operates throughout Asia Pacific using both localized operational staff and CRO partners.

Even prior to the recent changes to the regulatory requirements, sponsors and CROs during the last three or four years have experienced significant uncertainty and frustration with the country's regulatory approval process. Concerns have included highly unpredictable approval times and changing requirements that created a difficult environment in which to conduct clinical research.

"That has given people a lack of confidence in the system," said Garth Tierney, executive vice president of CRO INC Research's Asia Pacific division, which has 20 offices across the region. "There's been a dramatic dropoff in clinical trials. Our own organization has consolidated its operation in India in response to the current demand. Our strategic position is to wait and watch India at this stage—further growth initiatives will be dependent upon the changes that will be made and the clarity and stability in the regulatory process."

Companies also are re-thinking their strategies in India after Novartis lost a Supreme Court patent case for its anti-cancer drug Glivec earlier this year. While intellectual property protection has been a longstanding concern in India, since patents granted elsewhere may not be honored in the country, increasing conflicts over this issue have led some companies to consider diverting investments to other markets.

"Regulatory pathways for clinical trial conduct are clear and, with support of partners who understand how to navigate the regulatory environment, the trial activation process can be efficient in meeting the trial's timelines."

—Michael Clay, vice president, clinical development for Asia Pacific, PPD

"Unclear patent policies and regulatory guidelines remain key concerns for sponsors in India," said Icon's Goh.

Consolidation in China

During the past 18 months, sponsors and CROs have shifted their clinical trial activity to other Asian markets, including China, South Korea and Thailand. The industry also is beginning to see the market open in Japan.

Specifically, the number of registered interventional studies in China, which is rapidly becoming a leading region for clinical research, has increased almost 90% from five years ago. The size of the economy and the population has driven considerable interest in China; the potential for growth is significant since China is expected to become the world's second leading pharmaceutical consumer, behind only the U.S., by 2020.

PRA's Thoelke said conducting clinical trials in China used to be a luxury for global sponsors, but today drug development strategies routinely include China. "For the large pharma companies, it becomes a market you just can't really ignore just from a sheer profitability standpoint," he said.

Global drug companies in recent years have made large investments in China. Merck, for example, announced plans to spend $1.5 billion to strengthen R&D in China, including building Asian R&D headquarters in Beijing. Several multi-nationals have completed deals with domestic companies to help integrate their companies into the market. For example, GlaxoSmithKline purchased Nanjing MeiRui Pharma, while Pfizer formed a joint venture with Zhejiang Hisun Pharmaceuticals. Global CROs also are expanding in China and have invested significant resources. Most recently, PRA formed a joint venture with Chinese CRO WuXi PharmaTech to conduct clinical trials in China.

"We are seeing major pharma investing heavily in China, and we're seeing a lot more global decision-makers based in China," said INC Research's Tierney. "I think for everyone—pharmas, CROs, the whole industry—the focus is very much on China as the future growth region for Asia."

Improvements in China's regulatory environment have played an important role in the growth of global clinical trials, yet many challenges remain. Costs can be higher to include China in a global clinical trial since companies often must spend extra money for training, translation and shipping the comparator and active drug for a trial. In addition, clinical trial approvals in China are among the longest in the world; on average it takes at least a year, sometimes 18 months, for an approval. But in recent months, regulators have adopted

a fast-track process that allows approvals in seven to 12 months for studies involving novel agents, unmet medical needs and small molecules.

For large trials, these higher costs can be offset by faster patient accrual, since China has a centralized public healthcare system and large volumes of patients, which can mean shorter trial timelines.

"You see accrual rates that can be two times, five times, 10 times what you would see in other parts of the world," said PRA's Thoelke. "So you are decreasing your overall timelines for a clinical trial, you are decreasing your overall spend, and you are getting your drug to market faster. For some of these drugs, you are talking about hundreds of millions of dollars in difference if you can get a trial done six months earlier and to market sooner."

In addition, the analysis suggests China's clinical trial landscape has begun to consolidate and mature, as the number of investigators has dropped 40% during the past two years. Sponsors and CROs report paying closer attention to the quality of sites they use in China, returning to sites that have performed well and have invested in their infrastructure by hiring study coordinators and other staff.

Many novice investigators have left clinical research; in 2013 the Tufts Center for the Study of Drug Development reported a 50% turnover rate for investigators in Asia Pacific. At the same time, China has seen a wave of Chinese students, who studied medicine in the U.S. or Europe and speak fluent English, return to China and change the dynamic of conducting clinical trials.

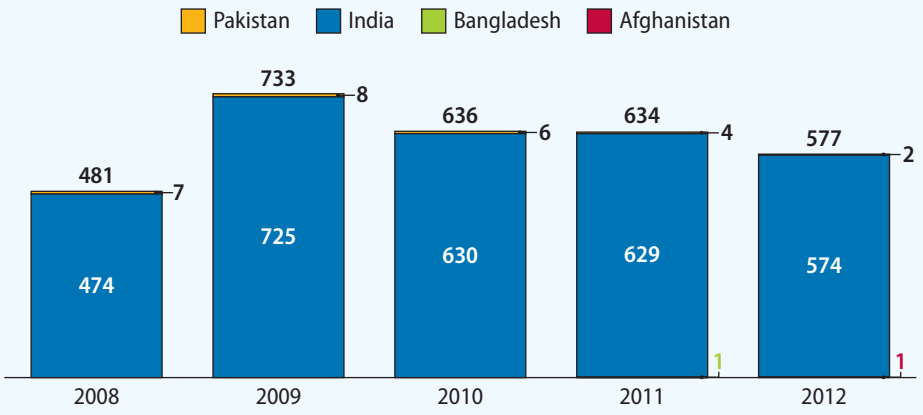
"We are creating more centers of excellence and consolidating the industry," said INC's Tierney. "It's not dissimilar to what we have seen elsewhere. When you have an emerging market, there is a scattered approach with many sites and investigators being utilized. But as the region develops, we see development of centers of excellence and professional clinical research units," he said. "It's becoming less fragmented and developing into a better-organized clinical research structure."

The number of active investigators in China also relies on the China Food and Drug Administration (CFDA), the government agency that must register and approve sites to participate in trials. Approvals must be renewed every couple of years. The CFDA's ability to register and approve sites in a timely manner can affect the number of sites available for trials.

The government's site registration system also will impact the growth of clinical research in the country going forward. Icon's Goh said as of 2010, the CFDA had certified a total of 275 clinical trial institutions, mostly located in Beijing, Shanghai, Guangzhou and other large provincial capital cities, including three hospitals in Hong Kong. He said the number and type of certified institutions can accommodate most trial requirements, and some institutions also specialize in therapeutic areas such as AIDS, vaccines, pediatrics and orphan diseases. Yet growth in the number of clinical trials conducted in China means patient recruitment will become more competitive, and a strategy to identify and train sites in second-tier cities—such as Chengdu, Tiajin and Nanjing—as well as in some third-tier cities will become critical for successful study delivery.

Unique Principal Investigators in South Asia

Submitting at least one Form 1572



Note: Region also includes Sri Lanka, Nepal and Bhutan

Source: CenterWatch analysis of FDA BMIS database

Growth in South Korea and Japan

South Korea has become one of the fastest growing countries for clinical trial conduct in East Asia. The numbers of investigators and registered interventional studies conducted in the country both have more than doubled during the past five years; South Korea had 750 studies registered on ClinicalTrials.gov last year; China had 771.

Interest in the country has been driven by its strong medical infrastructure, which allows for high-quality research and a clinical environment that can support study start-up in only a few short months, since the IRB and Korean Food and Drug submission review processes are conducted in parallel.

"South Korea has demonstrated strong clinical trial processes and standards and has experienced sites with highly committed and skilled investigators," said Covance's Wright. "As such, the operational aspects of the trials are more predictable and compliance with GCP requirements is high. Additionally, in South Korea access to patients is very good and the investigators are interested in clinical research."

It also has emerged as a global hub for multi-national pharma and biotech companies. Global CROs have established offices in the country and are investing in building its clinical research infrastructure. For example, both Icon and Quintiles have formed partnerships with the Korea National Enterprise for Clinical Trials (KoNECT) to support the development of high-quality clinical research professionals and a clinical infrastructure that can support increased demand from local and global sponsors.

"For South Korea, the government has been playing an important role to support its focus on healthcare and clinical development, which leads to a dramatic increase in opportunities for biopharmaceutical companies' drug development," said Icon's Goh.

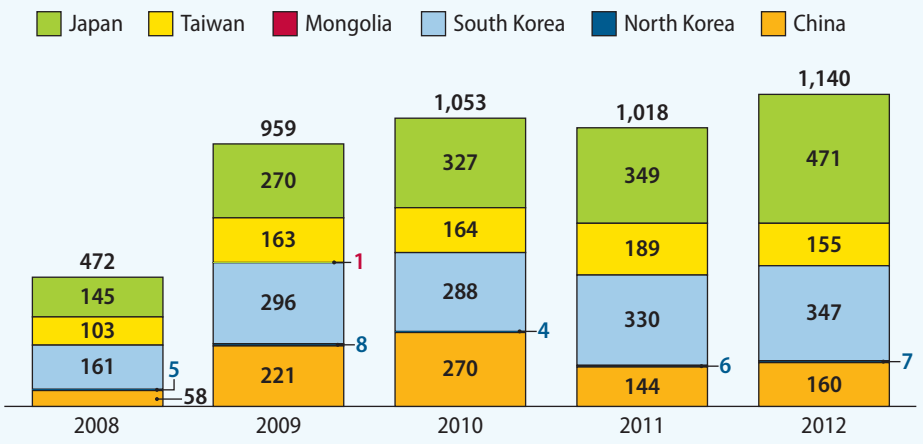
Meanwhile, companies have seen a paradigm shift in Japan, which until recent years had been largely closed to outside research, as the government has recognized the market's potential and taken steps to attract global clinical trials to the region. The number of studies placed in Japan during the past five years increased more than 9%, while the number of FDA-regulated investigators has tripled; Japanese sponsors also are starting to run their own studies regionally and internationally.

Many companies have begun to expand operations in Japan. This summer, INC Research opened new offices in Osaka and Tokyo to build its presence in the region. InVentiv Health established a strategic alliance with Japanese CRO Bell Medical Solutions to push further into the Japanese market.

"There has been more of an initiative from both pharma and government sectors in Japan to have Japan participate in more global research. There is an increasing awareness of the changes that are required to the traditional conduct of trials in Japan to fit in with this globalization and a growing willingness to see the changes made," said INC's Tierney. "That is driving a lot more activity in Japan. We are seeing Japan participate in an increasing number of global studies."

Unique Principal Investigators in East Asia

Submitting at least one Form 1572



Source: CenterWatch analysis of FDA BMIS database

Another benefit of the new policies is that they open the door to greater cooperation for clinical trial data sharing across the region. A number of initiatives among the Japanese, Korean and Chinese governments are addressing ways for the countries to accept data from another jurisdiction. Although these programs are in early stages, they potentially could make it easier for sponsors to conduct large trials in the region. PRA's Thoelke said a number of companies are using the initiatives now, but they have yet to go through a full approval.

New opportunities in Southeast Asia

Despite its small population and limited number of investigative sites, Singapore saw an increase in both the number of studies (15%) and investigators (76%) since 2008. During the same period, the analysis found growth in both studies (14%) and investigators (3%) in Thailand, which has highly trained investigators and low clinical trial costs. Sponsors increasingly seek to conduct studies in both countries because of their strong focus on quality and their quick study start-up without regulatory complications.

Both Singapore and Thailand have been significant areas of growth for CRO PPD. "Trial demands are high for the growing expertise within these countries, due to the increasing capabilities and experience of clinical trial industry professionals and investigators who are becoming experienced working with multinational companies, and the overall healthcare infrastructure required for the conduct of high-quality trials," said Michael Clay, vice president of clinical development for Asia Pacific for PPD, which has operated in the region for more than 16 years.

"Regulatory pathways for clinical trial conduct are clear and, with support of partners who understand how to navigate the regulatory environment, the trial activation process can be efficient in meeting the trial's timelines," he said.

Looking ahead

Industry experts see major growth ahead in Asian countries that have significant patient populations and maturing healthcare systems, including China, Korea and Japan. Studies also are expected to return to India once its regulatory issues are resolved. For China, in particular, infrastructure will strengthen as sponsors and CROs continue

to make large investments in the country and expand operations.

Although sponsors face significant challenges when conducting trials in markets such as China or Japan, including country-specific regulatory, ethical and administrative requirements, they do not expect to bring large numbers of their studies back to more established markets in the U.S. or Western Europe anytime soon, since these regions lack the drug naïve populations and patients with infectious diseases needed to enroll studies.

"The biggest single driver for conducting trials in these countries is the availability of large numbers of treatment naïve patients. While regulatory start-up times can be challenging for some countries, the ability to recruit large numbers of patients once the sites are up and running is a major benefit in terms of meeting the timelines required for overall regulatory approval of the compound," said Icon's Goh.

"In essence, start-up times can be longer than in Europe or the U.S. for some countries, but this additional time is more than made up for by the ability to rapidly recruit patients," said Goh. "This is especially relevant for studies that have extended treatment periods, such as longer-term phase III studies, and enables more rapid drug development and registration."

Karyn Korieth has been covering the clinical trials industry for CenterWatch since 2003. Her 30-year journalism career includes work in local news, the healthcare industry and national magazines. Karyn holds a Master's of Science degree from the Columbia University Graduate School of Journalism. Email karyn.korieth@centerwatch.com.

Annick Anderson has been conducting market research since 1998 in both the health care and consumer packaged goods industries. Annick holds a Master's of Business Administration from the Boston University Graduate School of Management. Email annick.anderson@centerwatch.com.