The Promise and Pitfalls of Clinical Trials Overseas

Big pharma has big incentives, including cost savings and more powerful studies, to launch trials in developing countries. But can companies avoid the ethical potholes?

THE RESULTS OF THE CLINICAL TRIAL WERE puzzling. Some lung cancer patients who received the experimental drug gefitinib several years ago showed almost no benefit; in other patients, tumors shrank so much that one researcher called it a “Lazarus type of response.” After intense study, an answer to the riddle emerged: Tumors that respond to gefitinib have a mutation in a key protein affecting cell growth—a mutation common in Asians but rare in other races.

As a result, gefitinib, which is marketed as Iressa by AstraZeneca, is available only under special circumstances in North America, while in Asia it has become an established therapy for non–small cell lung cancer that fails to respond to other treatments. If AstraZeneca had done the initial trials in a global setting, “they might have made the Asian connection sooner and saved a lot of money and time,” says Benny Zee, a biostatistician and director of the Comprehensive Cancer Trials Unit at the Chinese University of Hong Kong.

Differing ethnic responses to drugs is one of a host of reasons pharmaceutical companies are globalizing clinical trials—and rushing to developing countries. There are cost savings. There are new markets. And trials help a multinational pharmaceutical company establish a presence in a country and learn local needs.

Large pools of recruitable subjects and enormous market potential have drawn drug companies to India and China. A July study by the Associated Chambers of Commerce and Industry of India (ASSOCHAM) foresees India’s clinical trials business growing from less than $150 million currently to $546 million by 2010. Among developing countries, India and China are possibly the best positioned to leverage multinational clinical trials to develop their own pharmaceutical industries, thanks to their rapid economic development and growing scientific capabilities.

But bioethicists worry that in the stampede to Asia, patients’ rights sometimes get trampled. “All those reasons [for doing clinical trials in India] don’t really add up to good ethical oversight,” says Prathap Tharayan, a psychiatry professor at Christian Medical College in Vellore, India. Tharayan says India should view the boom in trials as an opportunity to raise ethical standards.

In the latest flap sparking calls for closer scrutiny of trials, the All India Institute of Medical Sciences in New Delhi acknowledged in response to a query from a nongovernmental organization in August that 49 infants died while enrolled in clinical trials at the institute over the past 2.5 years. “The deaths were among patients who were extremely sick; there is no case of a death because of an intervention,” says institute spokesperson Y. K. Gupta. All trials, he says, were vetted by an ethics committee and conducted in accordance with good clinical practice. In early September, the institute reported the results of an in-house investigation to the health ministry, but the matter may not end there.

Cheaper, faster

Reliable statistics on who is doing which trials, and where, are hard to come by. Few countries require the registration of clinical trials in public databases, and individual trials are becoming more and more global. For drugs for the U.S. market, the lead researcher at each site must file a statement with the U.S. Food and Drug Administration as part of an Investigational New Drug application. According to an analysis of filings by CenterWatch, a Boston-based company that gathers data on clinical trials, the number of investigators in developing countries working on drugs for the U.S. market has risen dramatically: in India, from 46 in 2001 to 493 in 2007, and in China, from 16 to 97 over the same period. (The CenterWatch analysis captures a fraction of ongoing trials.) Also telling, the ASSOCHAM study found that India had been the site of a single clinical trial outsourced by U.S.-based multinationals from 1996 to 2000—but 192 trials between 2001 and 2005.

One factor behind this trend is economics. The Confederation of Indian Industry boasts that trials in India can be 50% to 60% cheaper than in the United States. But cost advantages are narrowing, says Kenneth Kaitin, director of the Center for the Study of Drug Development at Tufts University in Boston. “These
countries realize there is no reason for them to reduce costs to the degree they have in the past,” he says. Still, costs are low by Western standards (see p. 210).

Taking trials overseas can pay off in another way. The cost of running a trial “is a factor to some degree, but not to the degree that people think,” says Jorge Puente, vice-president for medical and regulatory affairs in Japan and Asia for Pfizer Inc. in New York City. He explains that once a drug is patented—typically before trials begin—the clock starts ticking on the period of exclusivity. Trial sites in North America and Europe already have hundreds of ongoing studies, so competition for patients delays recruitment and a trial’s completion. Target patient numbers can be gathered more quickly if trials include sites in developing counties. “If you speed up development by 1 year, you get an extra year of [patent] exclusivity; that’s the most important driver,” Puente says.

It’s in the genes
Liver cancer and gastric cancer kill more people in China every year—600,000—than the number who die from all forms of cancer in the United States, Puente says. Developing drugs against these and other diseases that afflict China disproportionately is the main reason pharmaceutical companies have opened R&D centers in China (Science, 27 July 2007, p. 436). The same goes for India, where the focus is on developing drugs for malaria and other infectious diseases seldom seen in North America and Europe. “We have to be part of those communities to understand the health priorities and be part of the solutions,” says Puente. He says that more than 60% of Pfizer’s revenue now comes from outside the United States, and projections indicate an additional billion people in Asia will be potential consumers of innovative medication.

The buildup of research infrastructure in China and India is leading to “a more strategic approach” to trials, Kaitin says. In the past, overseas trials were primarily part of large phase III studies. “Now companies may do a phase II study to reach proof of concept more quickly so they can determine whether to move forward, and more Western companies are looking to conduct preclinical and research discovery phases of drug development in these countries,” he says.

As the gefitinib experience shows, ethnic groups often respond to drugs in markedly different ways. Genomic data will allow the medical community to better understand and exploit differences, Zee says. “Before talking about personalized treatment, we can talk about the genetic makeup of different ethnic groups,” he adds.

Indian scientists are touting the country’s diversity as an advantage. The Indian Genome Variation Consortium is studying genetic differences among India’s ethnic groups and comparing them to variations in other populations. Preliminary results covering 55 populations and several hundred genetic markers were reported in the April 2008 issue of the Indian Academy of Sciences’ Journal of Genetics. Lead investigator Samir Brahmachari, a genome analyst and director general of the Council of Scientific and Industrial Research in New Delhi, says India offers a one-stop destination for clinical trials, because so many human variations exist in the 1-billion-plus, drug-naïve population.

Courting trials
A final factor that’s fueling the boom in clinical trials in developing countries is their active solicitation—a sharp turnaround from a mere decade ago. “In the early to mid-’90s, there really was no infrastructure for clinical research in Asia,” says Puente, who worked for Pfizer in China and Japan at that time. He says few researchers were interested. These days, China and India are promoting themselves as the places to be for clinical trials. The ASSOCHAM report boasts that India churns out 17,000 new doctors each year, all of whom speak English. Kaitin says conducting trials brings money and staff training to hospitals, medical schools, and local research organizations.

Both countries also have domestic companies eager to move from making copycat generics to developing their own drugs. At the East Asian Pharmaceutical Regulatory Symposium in Tokyo last April, Zhang Wei, director-general of the Department of Drug Registration at China’s State Food and Drug Administration (SFDA), reported that from 2001 to 2005, China’s domestic drug companies had received approval for 45 new drug products and had 41 under review and 109 in various stages of clinical trials. (The U.S. Food and Drug Administration approved more than 50 new drugs in 2007 alone.) China’s government has launched several schemes in recent years to promote drug development, including a National Key New Drug Creation Program approved by the cabinet last December that promises to make up to $1.5 billion available to academics and biotech start-ups over the next 15 years. China and India are working to streamline approvals processes, crack down on corruption, and improve intellectual-property protection. “These countries are really doing whatever they can to become major players.
Clinical Trials and Tribulations

in this expanding global market,” says Kaitin.

Still, China and India are held back by an underdeveloped infrastructure. Zee, who studied and worked for more than 15 years in the United States and Canada and whose research focuses on cancer radiation therapy trials, says having lead scientists trained in North America and Europe is not enough. “You need technicians; you need good laboratory and other supporting services to do a trial properly,” he says. China’s SFDA allows new drug and device trials at only 200 or so approved centers—a “terribly small” number given China’s size, Puente says. “The limiting factor for us,” he says, is the lack of SFDA-certified centers.

The biggest infrastructure gaps in both countries are in trial know-how and ethical oversight. Wu Taixing, an epidemiologist at Sichuan University’s West China Hospital in Chengdu, says only a few hundred of the top hospitals have ethics committees. Wu and colleagues found that just 207 of 2235 “randomized” trials reported in Chinese journals were randomized properly. “Most authors of these reports lack an adequate understanding of rigorous clinical trial design,” Wu’s group concludes. In India, too, “a large majority of potential investigators lack knowledge of regulations, ethics and good clinical practice, and skills for clinical trial management,” says Arun Bhatt, president of ClinInvent Research India, a contract research organization in Mumbai.

Many trial sponsors use ethically dubious recruiting practices, such as offering payments that dwarf participants’ normal earnings and providing medications they could not otherwise afford, alleges C. M. Gulhati, editor of the Monthly Index of Medical Specialties, a reference work on drugs published in New Delhi. Widespread illiteracy makes it easy to sidestep informed-consent procedures, Gulhati adds: “Investigators frequently enroll patients in trials as if their participation were a necessary next step in their care.”

Critics have pounced on such lapses. “There are good reasons to believe that the rights of test subjects in developing countries are less secure than those of their counterparts in the West,” according to a January report, A Bitter Pill, from the Wemos Foundation, an organization in Amsterdam that advocates for developing-world health care.

Among several examples the Wemos report mentions is a case in which a drug-eluting stent developed by Occam International in Eindhoven, Netherlands, was implanted in about 70 Indian patients as part of a 2005 trial. According to a 2006 report by the Netherlands Health Care Inspectorate, the procedure was done without proper informed consent and without ethics committee approval. The Inspectorate slammed Occam for its “amateurish” reliance on a local partner without verifying that the trial would be conducted in accordance with European ethical standards. In a statement responding to questions from Science, Biosensors International in Singapore, Occam’s parent company, said Occam has denied the accuracy of the allegations and noted that investigations in both India and the Netherlands produced “no finding of legal wrongdoing.”

Wemos called for authorities in developed countries to adopt stricter controls to prevent drugs tested unethically from reaching the market. It also urged developing countries to beef up health care systems and ethical review capabilities and asked drug companies to be more transparent in reporting on clinical trials.

Many researchers emphasize that the issue transcends big pharma. “Pharmaceutical [companies] aren’t the only ones that do clinical trials; we’re looking at academic researchers, device companies, and public health researchers as well,” says Davina Gherzi, coordinator of the World Health Organization’s International Clinical Trials Registry Platform (ICTRP), established in August 2005 as a one-stop portal for trial registries around the world.

To subject trials to greater scrutiny, groups in China and India launched registries last year that ask for information such as who is paying for a trial, the health issue being studied, the intervention, and the outcomes. These are the first registries in developing countries; both are cooperating with ICTRP. “Trial registration suggests an opportunity to help facilitate the ethical design, scientific design, and good conduct and reporting of trials,” Tharyan says.

In addition to the minimum data required by ICTRP, Clinical Trials Registry–India asks registrants to provide details such as the method of randomization and blinding. The Indian registry also asks for information on the ethics committee that approved the trial. It hopes to evaluate committee qualifications and performance and eventually to accredit them. The Chinese Evidence-Based Medicine Center, one of the sponsors of the Chinese Clinical Trial Register, plans to help institutions set up and train institutional review boards.

Neither China nor India requires trials to be registered. To encourage registration, journal editors in both countries are following the lead of the International Committee of Medical Journal Editors, which announced 4 years ago that member journals will consider a trial for publication only if it is in a publicly accessible registry before enrollment of the first patient. Last February, editors from 12 of India’s top medical journals announced a similar requirement to take effect in January 2010. In China, a consortium of 56 journals has announced that as of January 2009, reports of registered trials will get priority for publication over unregistered trials. Eventually, they will publish results from only registered trials.

Wu and Tharyan acknowledge that registries and journal policies won’t resolve all ethics issues, but they are a start toward helping ethical oversight keep up with the developing world’s growing participation in clinical trials.

—DENNIS NORMILE

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