

Japan Works To Shorten “Drug Lag,” Boost Trials of New Drugs

By Gunjan Sinha

Since 2005, Japan has cut its notorious drug lag almost in half. The time between approval of a new drug in Europe or the United States and approval in Japan shrank from about 3 years in 2006 to 1.5 or 2 years, according to the latest estimate.

“Things are getting better,” said Kazuo Tamura, M.D., a professor at Fukuoka University School of Medicine and current president of the Japanese Society of Medical Oncology.

But the drug lag is not the only thing keeping Japanese patients from gaining access to the same drugs at the same time as patients in other developed nations. Among other reasons is the difficulty of conducting clinical trials in Japan, according to Tamura

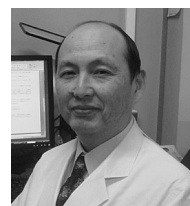
and others. The cost of trials is high and infrastructure is poor compared with other Asian countries, discouraging industry-sponsored trials. And academic researchers face additional barriers when initiating trials for new treatments, meaning that relatively few such trials take place in Japan.

Now, concerted efforts are under way to increase the number of trials. Along with efforts to cut the remaining drug lag, Japanese oncologists are working to change some policies, improve infrastructure, and encourage investigator-initiated research.

Fixing the Drug Lag

The reasons for the time lag in getting drugs approved in Japan are varied, but a

primary cause has been the Japanese Pharmaceuticals and Medical Devices Agency’s (PMDA) requirement that drug companies conduct separate and additional safety studies in Japanese patients. That policy, though modified recently, is based on safety concerns, Tamura said. Several



Kazuo Tamura, M.D.

studies have shown that Asians metabolize drugs differently from white patients, he said.

In 2005 the Japanese Ministry of Health Labor and Welfare began putting measures in place to cut the time lag. These include establishing a special committee

that reviews drugs approved elsewhere and that can recommend fast-tracking a drug in Japan, hiring more review staff at PMDA, and softening drug application requirements to make it easier for pharmaceutical companies to apply to market a new drug in Japan. And in 2008, the PMDA agreed to consider data from global clinical trials in all drug applications as long as safety studies included Japanese patients.

This is an important change for industry, said Ken Kobayashi, M.D., head of oncology, early clinical development, at Novartis in Japan. It means that a company can conduct one trial around the world and potentially use it as the basis for a submission to the U.S. Food and Drug Administration, the European Medicines Agency, and the PMDA. Because Japan would be one of the enrolling countries, companies could apply for drug approval to all three agencies at the same time, substantially cutting the remaining drug lag.

At least that was the theory. In practice, the policy hasn't yet generated huge results: The Japanese National Cancer Center Hospital is now conducting 36 industry-sponsored global phase III trials, said Yasuhiro Fujiwara, M.D., Ph.D., chairman of the hospital's department of clinical trial coordination and developmental therapeutics in Tokyo. Far smaller countries, such as Sweden, have much higher participation rates in global clinical trials, Tamura said.

One reason for the small number of trials involves the administrative costs of trials in Japan, according to Kobayashi. For instance, he said, companies must translate most documents submitted to the PMDA into Japanese. Also, the infrastructure to carry out trials is relatively poor compared with that in Western countries. Most hospitals do not have staff to streamline patient recruitment and manage the necessary paperwork, so the work falls to already-time-strapped doctors.

To tackle the infrastructure problem, the Japanese government has awarded about \$1 million per year since 2006 to 10



Ministry of Health, Labor, and Welfare, Tokyo.

Centers of Excellence, which include more than 50 medical research institutes. But the effort isn't enough, Tamura said, because medical care in Japan is so dispersed. There are many hospitals with small numbers of patients—one reason why recruiting patients into trials takes so long. Without a larger network of hospitals staffed and equipped to conduct trials, the process will continue to be laborious, he said.

Investigator-Initiated Research

Making it easier for industry to conduct trials in Japan will solve only part of the problem, according to Naoto Ueno, M.D., Ph.D., professor of medicine in breast medical oncology at the University of Texas M. D. Anderson Cancer Center in Houston, which has sister relationships with two Japanese medical centers. "If Japanese physicians relied solely on drug development by industry, some anticancer drugs might never be approved in Japan for less-common indications," he said. And yet in Japan "it is quite rare for an investigator to initiate a clinical trial [with a new drug]."

In fact, until 2003, independent investigators could not conduct clinical trials to test new drugs or a new indication for an already approved drug, both of which require an investigational new-drug (IND) application. In 2003, the Pharmaceutical

Affairs Law was revised to allow independent investigators to apply for INDs, but only six investigator-initiated cancer clinical trials with INDs have been registered since then, according to Ueno. In contrast, more than 900 investigator-initiated, non-IND cancer trials (with already approved drugs and indications) have been registered and disclosed to Japan's UMIN (University Hospital Medical Information Network) Clinical Trials Registry since its establishment in 2005.

The reasons that so few apply for IND status are manifold and complex. For one, funding is hard to find. And when it is available, conducting a clinical trial with an IND is more expensive than conducting a trial without one. In IND clinical trials, quality control and quality assurance are closely monitored—more closely than for similar trials in the U.S., said Ueno, who studied medicine in Japan but practices in the United States. For example, the U.S. National Cancer Institute accepts a central online monitoring system for clinical trials, but in Japan, site visits are the rule. Also, drug companies are not allowed to fund investigator-initiated trials, so investigators must apply to the government for funds, and "most people don't want to make that effort," Ueno said.

Another reason for the dearth of investigator-initiated trials is that Japan's health care system does not pay for off-label use of drugs, even in clinical trials. Such drugs must be provided by a company or bought from the company if an IND has been approved.

"We have no system in place yet for compassionate use or off-label use of drugs here," Tamura said.

The problem is not only that government health insurance won't pay for off-label or experimental drugs but also that



Yasuhiro Fujiwara,
M.D., Ph.D.

the policy restricts patients who are already taking an approved drug from participating in clinical trials. Such patients risk losing coverage for that drug.

“This is a real problem,” Tamura said. If a patient is, for example, already taking a medication covered by insurance and doctors want to test whether an additional drug or treatment will improve the patient’s

outcome, health insurance policy does not allow doctors to administer both drugs on the same day. This means that patients must come to the hospital on separate days for each drug or treatment, which is time consuming and arduous for both patients and doctors.

“We really have to solve this problem, or else we won’t be able to do good clinical studies,” Tamura said.

Moving Forward

Gradually, say experts, a combination of efforts is moving the system toward change. Ueno, for example, chairs an international program at M. D. Anderson through which he has established relationships with St. Luke’s International Hospital and Keio University, both in Tokyo. Through these relationships, he said, he hopes to “create next-generation

oncology leaders” who not only provide multidisciplinary care but also push for evidence-based medicine. He is working with both institutions to develop educational programs to get doctors more interested in clinical trial work. Also, medical schools have added coursework to their curricula that teaches how to conduct clinical research and its importance.

In another collaborative effort, the National Institutes of Health Pharmacogenomics Research Network, cosponsored by NCI and the National Human Genome Research Institute, is working with Yusuke Nakamura, M.D., Ph.D., of the Rikin Institute’s Center for Genomic Medicine. “We would like to strengthen Japan–U.S. collaborations in cancer clinical trials,” said NCI’s Ted Trimble, M.D. The institute, with the U.S. Embassy

“We would like to strengthen Japan–U.S. collaborations in cancer clinical trials.”

in Tokyo, the Japanese National Cancer Center, M. D. Anderson, St. Luke’s, and Keio University, organized a workshop in Tokyo last July to explore opportunities for joint trials. “Although there is great enthusiasm on both sides to work together, we still need to overcome the regulatory barriers on both sides of the Pacific,” Trimble said.

For its part, the government has implemented a graduate program for medical students, allowing them to work at the PMDA as reviewers as the basis of a thesis for an academic degree. The aim is to create a pool of qualified people to lead clinical research.

Another program, still in planning, aims to create a mechanism through which companies that apply to the PMDA for a new drug can obtain a “prereview” consul-

tation. Any company would be eligible to apply for a consultation during phase III clinical trials and ask the PMDA to review all available data. The PMDA, in turn, would issue a report within 6 months to address any major issues that might arise and consequently shorten review time.



Edward Trimble, M.D.

“We are trying to do our best,” said Tamura, who emphasized that despite Japan’s issues with drugs and clinical trials, the quality of patient care is on par with or even better than that in other developed countries. “Our quality of care is really not bad,” he said. “But our ability to produce new findings, especially in cancer care, is still a big problem.”

© Oxford University Press 2010. DOI: 10.1093/jnci/djq017