the daily data flow. Last year, Ewald Beck and his colleagues at Justus Liebig University in Giessen, Germany, found that *Plasmodium* has two enzymes belonging to a pathway that plants and bacteria use to produce isoprenoids, a group of compounds that includes cholesterol. Because this biochemical route, called the DOXP pathway, doesn't occur in humans, the researchers realized that the enzymes made interesting drug targets. While looking for a drug that might block one of the enzymes, the group hit upon fosmidomycin, an antibiotic developed by a Japanese company in the 1970s that never made it to the market. A recent report (*Science*, 3 September 1999, p. 1573) found that fosmidomycin was effective in mice; clinical trials in Africa are next, says Beck. Meanwhile, the group is trying to find even more enzymes along the DOXP pathway.

Discoveries such as Beck's, which would have been impossible without sequence data, are exactly what Malaria Genome Project researchers were hoping for. "That paper in *Science* warmed my heart," says Richard Hyman, who leads the sequencing effort at Stanford. Adds Goldberg: "All of a sudden we have a wealth of targets that we can choose from. It will be an enormous boon to drug development."

**Reducing the risk**

But new drugs won't help much if they aren't economically viable. One way to hold down costs, researchers say, is to hitch a ride on work under way to combat other, more profitable, diseases. Atovaquone, for example, was developed as a cure for *Pneumocystis* lung infections in AIDS patients. Indeed, "if an old drug is found to have some activity in malaria, I can personally guarantee the companies would fight each other to license it," says PhRMA's Spilker. Similarly, the development of drugs based on the DOXP pathway may be helped by the fact that the same pathway occurs in microbes that plague residents of industrialized countries, such as *Escherichia coli* and *Helicobacter pylori*. In fact, that prospect helped lure investors to a company Beck and co-workers started to further develop fosmidomycin and other drugs. "Our strategy," Beck says, "was to tell them we will find a lot of new antibiotics against very critical bacteria."

Another strategy is to prepare the ground for industry. That means identifying interesting leads and turning them into candidate drugs by doing animal, human safety, and small-scale efficacy tests. The goal is to minimize risk for any company interested in capitalizing on the results. "You have to have [the drug] ready to go without any problems," says Walter Reed's Milhous, "before a company will jump in." For many years Walter Reed handed out such compounds for free, as the government had no procedures to share royalties; Hoffmann–La Roche, for instance, didn't pay for the rights to mefloquine in the 1980s. Today, says Milhous, the institute asks for a percentage of the proceeds of newly developed drugs.

Enticing industry to step in by curbing its financial risks is also the philosophy behind the Medicines for Malaria Venture (MMV), a foundation sponsored by the World Health Organization and several governments and nongovernmental organizations. MMV funds academic researchers with promising drug-discovery projects and tries to hook them up to companies. The companies, in turn, help out with support in kind, such as advice and access to chemical libraries. Founded last year, MMV has an annual budget of about $4 million and is currently supporting three research collaborations in which academics work with Glaxo Wellcome, SmithKline Beecham, and Hoffmann–La Roche. Its goal is a budget of $30 million, says MMV director Robert Ridley, enough to generate one new malaria drug every 5 years.

Although industry may be reluctant to undertake malaria research on its own, initiatives like this help to get it on board, says former Pfizer executive Campbell, who volunteers as chair of MMV's scientific advisory panel. "The industry will do everything possible to help in kind, to offer advice, et cetera," he says. "They're delighted to hear about this initiative. Whenever I talk about it, people's ears prick up."

Some, such as Harvard's Wirth, think it's time for the government to step in, perhaps with tax breaks and longer patents for certain drugs on the condition that the revenue be used for new antimalarials. "The industry recognizes this [disease] as a problem, but it's not going to move without some sort of incentive," says Wirth. "And with so many great drug targets on the horizon, it's critical that we somehow come to grips with this."

–MARTIN ENSERINK

NEWS

# U.S., Europe, Japan Look to Speed Up Drug Reviews

**Drug companies are hoping to save time and money by submitting the same safety and efficacy data to regulators in the three leading global markets**

**TOKYO**—Why did the Japanese government take more than 30 years to approve "the pill" and only 6 months to OK Viagra, a drug for male impotence? Some blame cultural attitudes toward women for the snail's pace acceptance of the oral contraceptive and decry a double standard. Others say that the answer is not sexism but rather the first fruits of a little-known international effort to streamline the drug review process. This fall, if all goes well, officials from the United States, Europe, and Japan will agree on a common application form in hope of speeding the delivery of other new treatments and, perhaps, lowering the cost to consumers.

**Team effort.** Japan's Osamu Doi looks forward to global regulations for drug approval.

CREDIT: D. NORMILE

The expected agreement is part of a 10-year-old reform project in the three regions that is known as the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). "Harmonization" makes it possible for regulators in one country to review more quickly safety and efficacy data already submitted to another country. Although the ICH has drawn little attention, it could have a big impact on consumers. "Drugs should be able to reach larger populations faster because a company can do studies and meet the requirements of all three regions," says Sharon Smith Holston, deputy commissioner of the U.S. Food and Drug Administration (FDA). The streamlined format, she says, should also result in "lower costs, because [companies] are not doing multiple [repetitive] studies."

Since 1990, a select group of bureaucrats, drug executives, and academics from the United States, Europe, and Japan have gathered at ICH conferences every other year to identify differences in regulatory approaches and hammer out common standards. They have produced and adopted, at last count, 37 guidelines covering almost every conceivable detail of pharmaceutical development, from the design of clinical trials to the interpretation of statistics. The guidelines have been intro-

duced one by one and are already having the desired effect of standardizing and simplifying procedures, says Rolf Bass, an official with the European Agency for the Evaluation of Medicinal Products. But to fully realize the promised benefits of common standards, says Bass, who has been involved with ICH since it began, the parties must agree on a "common technical document" that, in theory, will enable manufacturers to compile a single dossier on a proposed drug and submit it for review in all three ICH regions.

The common application form, which participants hope to approve at a November meeting in San Diego, would be a "mega breakthrough," says Bert Spilker, a member of the ICH steering committee and senior vice president of scientific and regulatory affairs for the Pharmaceutical Research and Manufacturers of America in Washington, D.C. Bass says that the parties have already settled on the scientific principles but that altering practices developed over decades is a major undertaking. "It's not easy to say, 'OK, let's start over and do it better,' " he says. Still, he and others are optimistic about reaching an agreement this fall.

However, sometimes the differences among national standards go far deeper than procedures for clinical trials and paperwork. Traditionally, drugmakers that wanted to sell globally had to repeat time-consuming and costly clinical trials in each major market. This has been a particularly slow process in Japan. Although ICH is starting to improve the situation, drugs often reach the Japanese market 3 to 5 years after being introduced in the United States or Europe. The reason for the delay, say Japanese health officials, is data showing that Asians respond differently to certain drugs and, therefore, may require different dosages.

To address this issue within ICH, Japanese officials offered what came to be known as the Ethnic Factors Guideline. It spells out criteria to determine whether a drug is likely to have variable effects in different populations. Drugs determined to be "ethnically insensitive," based on historical experience with similar types of drugs and other factors, may be approved with no additional testing. Others may require a small clinical trial, called a "bridging study," to verify that the dose-response, safety, and efficacy data from the original clinical trials can be extrapolated to the target population.

Conferees see these guidelines as one of their key accomplishments, paving the way to a system in which clinical trials need not be repeated. "This was a major step forward," says Spilker. The system of adjusting for ethnic factors is "now being discussed with other countries in Asia," he adds, "and the industry is very pleased with the progress."

The ICH adopted the guideline in February 1998, and Viagra was the first major drug to take advantage of it. The drug went on sale in the United States in March 1998, and by the summer its manufacturer, Pfizer Inc., had submitted it to Japan's Ministry of Health and Welfare. Relying on ICH guidelines and a bridging study, Japanese officials approved it in January 1999. Viagra also benefited from new fast-track procedures under which the ministry gives preferential treatment to drugs backed by high-quality data. Not all drugs will go through so rapidly, although Osamu Doi, councilor for pharmaceutical and medical safety at Japan's Ministry of Health and Welfare, says the goal is to review every drug within 1 year of submission.

> "Drugs should be able to reach larger populations faster because a company can do studies and meet the requirements of all three regions."
>
> —Sharon Smith Holston


**Fast action.** Japanese regulators gave speedy approval to the male impotence drug, Viagra, thanks to new international guidelines to standardize drug applications. This Pfizer ad, which appeared in several newspapers and magazines, is headlined "ED ... It's ok. It can be treated."

So far the ICH process has attracted little criticism. However, a Ralph Nader–led U.S. group has expressed concern that the drive to reach a global common denominator could lower U.S. drug safety or efficacy standards. In particular, Peter Lurie, a physician for Public Citizen in Washington, D.C., complains that ICH documents push for the use of placebos in clinical trials whenever possible. Lurie believes that placebos are often unnecessary, and that it's unethical to use them when a viable therapy is already available. But many ICH participants, including the FDA's Smith Holston, say that the emphasis on placebos favors the best research, as placebo-controlled trials often produce a more dramatic difference between the test group and the control group, yielding stronger statistical results. She argues that, rather than opting for the lowest common denominator, "we're agreeing on the highest standards."

But reaching a consensus on how data are to be submitted doesn't mean that ICH participants will necessarily agree on how to evaluate them. Each regulatory authority will continue to exercise its judgment under local laws. And in Japan, at least, clearing the scientific and medical hurdles may not always be straightforward, as the experience with birth control shows.

The rapid approval of Viagra incensed advocates of the birth control pill, who had been trying for decades to win over the government. Doi says that officials were initially concerned about side effects. In 1990, after a new, low-dose version of the drug was submitted for review, opponents changed their tune and began arguing that it would discourage the use of condoms, leading to a rise in AIDS. Last spring, after newspaper editorials and women's groups attacked the ministry's stance, the government finally approved sale of the contraceptive. "The ministry felt that the situation regarding public knowledge of AIDS had changed," says Doi, and that the risk of spreading AIDS had declined.

Doi and others see the next frontier for ICH as developing standards for evaluating emerging technologies, such as gene therapy. "The challenge in the 20th century was harmonizing the regulations that had been put in place in each country," he says. The next century, he predicts, must find ways "to jointly develop regulations from the start."

–DENNIS NORMILE AND ELIOT MARSHALL