individuals in some countries is shockingly high. Nearly 4 in 10 adults in Botswana and Swaziland are infected with the virus.

China, India, Indonesia, and Russia are threatened by a new wave of HIV spread, mostly through injecting drug use and unprotected sex. In Eastern Europe and Central Asia, where an estimated 1.5 million individuals are living with HIV, the most severely affected areas are the Russian Federation, Ukraine, and the Baltic States.

"Extraordinarily large numbers of young people regularly or intermittently engage in injection drug use, and this is reflected in increasing HIV prevalence among injecting drug users throughout the former Soviet Union," the report noted.

In China, a low national HIV prevalence "obscures the fact that serious, concentrated epidemics have been under way for many years in certain regions . . . ," the report said. The epidemic has spread to 31 of the country's provinces.

In some parts of China, very high rates of HIV prevalence have been found among injecting drug users, 35% to 80% in Xinjiang and 20% in Guangdong; evidence also suggests that injecting drug use is on the rise and that condom use remains low among commercial sex workers and men who have sex with men. Unsafe blood collection practices by unlicensed operators in 1990s also has left affected communities with a severe HIV problem.

"My biggest concern in Asia is India," Piot said. The overall rate of HIV infection there is low—less than 1%—but in a country with a population of more than 1 billion, a low prevalence rate can still translate into millions of infections. Between 3 and 6 million individuals in India are already infected with HIV.

Despite these alarming figures, there were also encouraging signs that a global response to fight the epidemic is growing.

"The good news is that this has been a fairly good year in terms of global response," Piot said.

In 2003, about $4.7 billion has been spent on AIDS treatment and prevention in the most affected countries, about a 50% increase over 2002, he noted. But the amount is less than half the $10 billion per year sum that experts have estimated is needed for an adequate response to the pandemic.

The WHO and partners are developing the "3 by 5" initiative, a global strategy to bring antiretroviral treatment to 3 million people by 2005.

"So the glass is either half full or half empty," said Piot.

The UNAIDS/WHO report, *AIDS Epidemic 2003*, is available online at http://www.unaids.org. □

# FDA Seeks Genome-Based Drug Data

Tracy Hampton, PhD

NOW THAT THE HUMAN GENOME has been sequenced, the challenge ahead is to translate the information into clinical utility. Enter the field of pharmacogenomics—where information from individuals' DNA sequence variations is used to tailor drug treatments for patients—and the Food and Drug Administration (FDA).

The FDA has now issued a draft of a guidance document for drug companies that encourages them to conduct pharmacogenomic tests during drug development and to submit resulting data to the agency (http://www.fda.gov/cder/guidance/5900dft.pdf). The goal is to promote research that fine-tunes therapies so that each patient gets as much benefit as possible with the fewest adverse effects.

To support open communication and scientific exchange about drug-gene interactions, the FDA is asking companies to voluntarily submit information on their pharmacogenomic research.

"A company may think a drug works on a particular genetic pathway, and they will test that. We want them to send us that information," said Janet Woodcock, MD, of the FDA's Center for Drug Evaluation. But the agency will not use the information to make any regulatory decisions, she added.

That is a key point. Pharmaceutical companies have expressed concern that the information they submit could be used to keep a drug off the market or limit its approval to a small subpopulation of patients. Woodcock has assured them that FDA's actions will be based on the existing standard for safety and effectiveness.

But Woodcock does point out that once a company compiles enough pharmacogenomic information relating to a drug that would have clear implications in the clinic, the company would then need to submit the data to the agency. This applies to both new drug approval and modifications of currently approved drugs.

## WORKING OUT THE KINKS

Pharmacogenomics is virtually unknown territory for both government agencies and the pharmaceutical industry; several workshops have brought both sides together to address issues and concerns (*J Clin Pharmacol*. 2003;43:342-358).

"This is turning into a truly collaborative effort. There's been a lot of interaction between the FDA and industry groups to come up with a way for industry to use these technologies and for the agency to use the information in drug regulation, but at the same time to avoid the concern that we may be getting ahead of ourselves," said Brian Spear, PhD, of Abbott Laboratories, in North Chicago, Ill, a member of the

steering committee of a workshop held in November.

While it is difficult to make forecasts about clinical applications of scientific research and how such advances should be regulated, workshop participants said that enough is known about the potential for pharmacogenomics to warrant discussion of scenarios in which companies might submit information to the FDA.

"This is new ground," said Gualberto Ruano, MD, PhD, of Genomas LLC, in New Haven, Conn. "No one is claiming to have the answers. But the field is mature enough to have established cases."

## SPINNING SCENARIOS

One scenario involves developing pharmacogenomic information about a drug that has already been approved and is on the market, but causes one or more serious adverse events. In such a case, the company that developed the drug could try to identify the patients most negatively affected to fine-tune the drug and make it safer. For example, researchers have found that administration of the commonly prescribed chemotherapy agent 6-mercaptopurine can be fatal for people with a genetic variant in the thiopurine methyltransferase gene (*Cancer Invest.* 2003;21:630-640).

Another scenario addresses drugs found to be metabolized differently by different individuals. When given the same dose of such a drug, a difference in metabolism may mean that some patients receive a higher exposure to the medication's effects than other individuals.

"That's a huge problem, because what's considered a normal dose of a drug can be toxic for some people," said Woodcock. "If you can dose according to a patient's genetic profile, that would be good."

A third scenario envisions the development of a drug tailored for patients with a specific genetic profile. In essence, a company would try to determine up front which individuals will respond to a treatment.

Examples of such drug tailoring already exist in the clinic. In some women with breast cancer, the *HER-2/neu* oncogene is overexpressed, resulting in an overabundance of the corresponding cell surface receptor. The monoclonal antibody trastuzumab, designed to target the receptor, was shown to be therapeutic for this subset of patients (*N Engl J Med.* 2001;344:783-792).

## POTENTIAL GAINS

Most pharmacogenomic data are of an exploratory nature, but FDA officials said that the agency wants to be kept abreast of findings so it can be prepared to appropriately evaluate future submissions. Ruano conceded that in the past, industry has not been forthcoming with providing such information to the FDA.


**The FDA and the drug industry both foresee a time when physicians will tailor drug treatments for individual patients based on variations in their DNA sequence.**

"From the agency's perspective, I do appreciate part of the difficulty," said Ruano. "They have to see more data so they can get educated [about pharmacogenomics]. The agency is essentially asking for help," he said.

Woodcock said industry's benefit would come from having "an informed group of scientists at the FDA who can give the big picture—getting from basic science in the lab to how that applies to patients."

From the pharmaceutical industry's point of view, a collaboration with the FDA is important. "We'd like to get a sense of when the results are meaningful and will be useful in the clinic," said Spear.

While there is a clear consensus to move forward, industry leaders want more clarity on the issue, said Spear. "The guidance contains more on what industry should submit than what happens once it gets to the FDA," he said. "More information is needed to give the industry a better sense of what's going to happen," he said.

## ETHICAL CLARITY

More clarity is also needed in terms of ethical considerations. Issues of informed consent, privacy, and discrimination will be at the forefront as sophisticated genetic diagnostics make their way into the clinic (*N Engl J Med.* 2003;349:562-569).

The FDA is calling for more input, and comments will be accepted through February 2004. After reviewing all public comments, a final guidance will be issued.

Although few physicians at this point order genetic tests before writing prescriptions for their patients, scientists, drug companies, and regulators predict pharmacogenomics will have an increasing impact in the clinic.

"It's happening now, and it will pick up momentum over the next few years," said Woodcock.

But such momentum should not be without appropriate oversight. Just this fall, the FDA blocked the sale of a diagnostic microarray chip marketed by Roche Molecular Diagnostics that was designed to detect genetic variations related to drug metabolism. The agency said the test "cannot be commercially distributed without an appropriate premarket determination from FDA." □