

# The Body Hunters: Overwhelming the Watchdogs

By Mary Pat Flaherty, Deborah Nelson and Joe Stephens  
Washington Post Staff Writers  
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## *Second of six articles*

A global boom in overseas drug experiments is changing the way new drugs are tested on humans and approved for U.S. consumers as pharmaceutical companies shift to countries where regulations are looser, costs lower and trusting patients plentiful.

Companies searching for lucrative drugs are turning abroad to hold faster human experiments, offering poorly paid foreign doctors handsome fees for every subject they recruit into tests that help speed drugs to market. In some cases, the companies test drugs deemed too risky to try out in the United States, a Washington Post investigation has found.

The globalization of drug testing has resulted in a system increasingly dominated by profit incentives, where no single regulator can see the whole picture or inspect experiments effectively, according to interviews on five continents with doctors, health officials and patients. For Americans, it means some of the newest drugs on U.S. shelves are tested at sites far removed from U.S. regulators – sometimes in countries with few inspectors and little history of examining drugs for safety and effectiveness.

"I'm scared. I'm real scared," said Stan Woollen, deputy director of the Food and Drug Administration division that monitors human drug testing, at a conference last June in San Diego. "With these huge trials that are being conducted on a faster and faster basis, maybe the system is becoming overwhelmed."

The FDA inspects only a sliver of foreign test sites and rarely does so while the tests are underway. It gets involved when a pharmaceutical company submits foreign test results to back up a request to sell its drug to American consumers – which is often years after the overseas tests are concluded.

The FDA's paper review of foreign trials is "very late in the pipeline to worry about the consumer or the patients in those trials," said Marcia Angell, former editor of the *New England Journal of Medicine*. And when the FDA reviews a drug this way, "it's essentially saying 'caveat emptor' ['buyer beware'] when the drug is approved for sale."

When the FDA refused to let California-based Maxim Pharmaceuticals Inc. test a new drug on Americans with liver disease – the FDA wanted more safety tests on animals first – the company went to Russia. In three weeks last year, Russian doctors screened 149 patients, but the doctors were not told about the FDA's concerns.

By going to the former Soviet Bloc, Maxim avoided a delay that could have cost millions. The firm was about to raise \$20 million in a private stock sale touting its leading drug's potential. It needed to try the drug on humans quickly to speed its development.

The company said it did not evade any FDA rules and followed Russia's.

"We abided by all of their local rules," said Maxim's chairman, Larry G. Stambaugh. "Why would they care what FDA wanted?"

## The Offshore Boom

Overseas drug experiments have grown at a staggering rate during the last decade.

The FDA has accepted new drug applications supported by foreign research since 1980. By last year, nearly 27 percent of them contained a foreign test result – about three times as many as in 1995.

In South America, the number of researchers registered with the FDA to conduct experiments on drugs aimed at the U.S. market grew from five in 1991 to 453 by last September. Registered East European researchers now number 429; there was only one in 1991. In southern Africa, the number has rocketed from two to 266.

Eli Lilly and Co. says that in 1994 it tested 590 patients in Africa, the Middle East, and Central and Eastern Europe. This year, it expected to test 7,309 persons in those regions, a spokeswoman said. In Latin America, about 1,000 tests are underway with predictions of "10 times that many in the next five years," said the director of clinical operation at Covance, a firm that locates test sites for drug companies.

Those numbers suggest rapid growth, but no comprehensive statistics are available. Indeed, there is virtually no public information in the United States about the number of overseas drug tests, who is participating or overseeing them, what rules they follow and what risks they pose.

The FDA aggressively protects drug companies' trade secrets. Many facets of the agency's approval process – including the details of overseas experiments – are secret. The Post obtained FDA reports of overseas inspections under the Freedom of Information Act, but the agency blacked out the names of companies and drugs not yet approved for sale. So while some reports showed problems with foreign drug research, it was not always clear what drug or company was at issue.

Securities and Exchange Commission filings, medical journal articles and medical researcher Web sites provided clues about current tests. So did interviews conducted at industry conferences, meetings and training sessions attended by Post reporters, who registered openly as journalists.

The overseas testing explosion has several causes. Americans and Europeans often don't want to join risky experiments, creating a need for alternative pools of human subjects. Meanwhile, drug companies face rising competitive pressure to develop drugs and market them faster.

An average of 4,000 people are needed to test a drug before it can be sold in the United States, according to several studies, and hundreds of drugs are developed each year, touching off intense competition for test subjects. Each day's delay getting a major drug to market costs \$1.3 million in unrealized sales, by industry estimates.

Industry gatherings often give off the air of a brazen bazaar. At the annual session of the Drug Information Association, globes spun on countertops and electronic maps pulsed with lights showing countries hot for recruiting. "We've Got Patients," trumpeted one sign. "Millions of potential study participants," boasted another.

The hard-sell atmosphere unsettled some. "If John Q. Public walked off the street, they would have been

appalled," said Janet F. Zimmerman, who runs Impact, a Philadelphia-area company that trains drug research teams. "It really looked like we were bargaining with the devil and trading in people."

Many drug company executives don't see it that way. They emphasize that faster testing hastens new drugs to market to save lives. The reason for putting a drug experiment in a developing nation might be as simple as "that's where the patients are," said Bert Spilker, senior vice president for the Pharmaceutical Research and Manufacturers of America. "You need patients to create new products that help us here and help people around the world. You cannot do it without test subjects."

Wall Street also has been nipping at the companies' heels. Major pharmaceutical corporations revenues grew as much as 10 percent a year throughout the 1990s and stock prices soared. It can be hard to sustain such growth in an industry in which lucrative patents last only two decades and investors pound companies that miss quarterly earnings forecasts.

To stay ahead, the big drug firms have embarked on a fast-paced, competitive search for the next bonanza drug like Viagra or Celebrex. At the same time, smaller entrepreneurs have been raking in billions from venture capitalists looking for a promising product.

With biotechnology so hot, time pressure on researchers is intense. "The quicker the better. The quicker we can complete clinical trials, the more money for our companies," Juan Pablo Guzman, who has worked on clinical trials in Latin America for Searle and Pharmacia, told colleagues at the same San Diego conference.

Sick patients have lobbied for faster drug approvals, too. "The clock is ticking rapidly and that sets up the urgency," said Nancy Nelson, a vice president of the ALS Association, an advocacy group for patients with amyotrophic lateral sclerosis, or Lou Gehrig's disease.

All of these forces help push drug tests into newly capitalist Eastern Europe, the former Soviet Union and the Third World.

Not only are patients plentiful, but experiments cost less. One Bristol-Myers Squibb executive described a complex test that cost about \$10,000 per patient in Western Europe but only \$3,000 per patient in Russia.

Poorer countries may also have higher prevalances of certain diseases, making tests easier to organize. Advanced cancers, for instance, may be more common in countries where early treatment isn't generally available.

And foreign patients with little exposure to medicines offer a blank slate for experimentation. Medical deprivation makes patients "better for our purposes," said Anna Romany, a Johnson & Johnson marketing director in Eastern Europe. "It's a very pessimistic outlook but a very true one."

## Bound for Mexico

With such a vast global testing system, policing problems with drugs becomes enormously complex and difficult.

Glaxo Wellcome, for example, still had 7,500 people taking its drug Lotronex in worldwide tests when the company agreed last month to pull the drug from the U.S. market because of FDA safety concerns. It will take until the end of December for the company to phase out the experiments, a spokeswoman said.

Lotronex had been approved for sale by the FDA in February to treat irritable bowel syndrome. Glaxo agreed to voluntarily withdraw it in the United States based on reports to the FDA of dozens of complications and three deaths possibly linked to Lotronex. Glaxo officials say the drug did not contribute to the deaths.

In the case of five-year-old Triangle Pharmaceuticals of Durham, N.C., an adverse FDA ruling in 1997 led the company to look abroad for a more favorable regulatory climate.

Triangle hoped to hit it big with new AIDS drugs. In August 1997, after a \$45 million stock offering, the start-up company bought rights to mozenavir dimosylate, a drug then in early testing.

Two months later, the FDA stepped in. Experiments on dogs had linked mozenavir to a heart arrhythmia that can cause blackouts or sudden death. The FDA imposed a "partial clinical hold," effectively halting all mozenavir trials in the United States.

Triangle eventually won permission to conduct a limited U.S. study on how the body absorbs mozenavir. For its large-scale experiments, though, the company moved overseas. It first tested the drug on a small group of Western Europeans to see if heart problems turned up. When none did, Triangle's research broadened into Mexico as well.

"With [the FDA] there was a difference of scientific opinion," said Triangle Chairman and CEO David W. Barry. "We felt that a presentation of the same data to other scientists and regulators could produce a different opinion."

Mexican health officials knew of the FDA's decision but still blessed the experiment, persuaded by the company's assurances that patients would be monitored for heart problems and informed of risks.

To date, no heart problems have been reported, although a much larger study is needed before the company can determine mozenavir's safety. Meanwhile, the drug has lived up to its promise as a potent AIDS weapon, and at least one European researcher said Triangle's decision to conduct trials abroad was justified on humanitarian grounds.

[Continue to Page 2 of 2](#)

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*Page 2 of 2*

"The company obviously has an interest in making a profit, but we also have an interest in treating our patients," said Schlomo Staszewski, director of an AIDS research clinic at the Johann Wolfgang Goethe University in Frankfurt, Germany.

Barry, a top FDA official in the 1970s, said he hopes the FDA will lift the mozenavir ban early next year.

FDA officials would not discuss the Triangle case, but some said they are distressed to see drug companies going abroad to circumvent rules intended to protect the public.

"The fact that we put a drug on a clinical hold means we believe there is a concern," said Murray M. Lumpkin, an FDA deputy director for new drug review, "and usually those concerns have to do with safety."

## Cash for Doctors

To recruit human subjects, pharmaceutical companies pay doctors for every patient they bring in – fees that in poor countries amount to many times more than a doctor's annual salary.

"Drug companies make us offers they know turn our heads," said Laszlo Lajtavari, a Budapest psychiatrist who said he has worked on drug tests for Eli Lilly, Johnson & Johnson and West European firms. Lajtavari said he earns \$178 a month in salary, but the drug companies pay between \$1,000 and \$2,000 for his work with each test subject he recruits. "How can I afford not to?" he asked.

That's a calculation hundreds of doctors now make across the developing world and in Eastern Europe. Pharmacia & Upjohn pays Latin American doctors about \$1,300 per patient for a "typical study," a hefty income supplement.

New studies are announced with "blast faxes" that whirl across the machines of hospitals and clinics worldwide, advising doctors of a firm's needs and recruiting fees.

Phone calls "come all of the time," said Tamas Pinter, a Hungarian cancer specialist at a small county hospital. He far outpaces his \$5,000 annual salary by signing on for test after test. This year, Pinter said he ran brain tumor work for Schering-Plough, anti-nausea drug tests involving chemotherapy patients for Merck, four studies for Aventis and one for Eli Lilly.

Pinter's test patients have helped demonstrate the value of medications, including advanced breast cancer drugs that went on to worldwide distribution but are so expensive that Hungary's healthcare system has set strict guidelines for their use, he said. The equity issue leaves "a bad feeling, but is a fact of life," Pinter said.

As companies inject elements of a sweepstakes into work that demands deliberate and meticulous effort,

concerns have surfaced about scientific quality.

When drugmakers and regulators talk openly at industry seminars, they share accounts of flawed research, particularly among foreign doctors new to large drug experiments.

In a Latin American epilepsy study, Parke-Davis had trouble getting doctors to report pneumonia in infants, which the company considered a serious adverse reaction. The foreign doctors regarded pneumonia as a normal complication, said Blake M. Paterson, then the company's senior director for clinical and medical research in Latin America. Paterson is now with Eli Lilly.

Sometimes overseas researchers are simply too eager to please. Central and East European researchers hold back on reporting complications "because they think they are doing you a favor," said Harold Neal, a quality assurance consultant.

Better training helps, but takes time and money, said Elsa Fernandez, of the Avanti consulting group. Drug companies, she said, "want to start the trial today and treat the patients tomorrow and prove efficacy next week."

## Weak Foreign Regulators

Inspectors and ethics boards in the Third World and Eastern Europe often are poorly staffed and trained. "Many of the countries where trials are going on do not have the resources to do the in-depth reviews of the protocols that we would expect," said R. Alta Charo, a University of Wisconsin law and medical ethics professor and member of the National Bioethics Advisory Commission.

In some cases, those same regulators are working with drug companies to encourage new tests, hoping to fund ailing health care systems.

One evening last spring, strobe lights flashed, disco music pounded and a fog machine spewed haze onto a nightclub dance floor in Borovets, Bulgaria, after a conference in which executives from U.S. and European drug companies were recruiting local doctors for drug tests.

"Can you see the FDA doing this?" Nicholas Carroll, an executive with the British firm AstraZeneca asked, nodding toward the dance floor. There, Bulgaria's entire drug testing police force was boogeying in a cloud of dry ice.

That force consists of one person, Ilian Ivanov, a bearded 31-year-old who keeps chilled whiskey at the ready for office visitors. Ivanov earns about \$100 a month. He simultaneously protects Bulgarians from ill-advised drug tests and promotes Bulgaria as a test site.

Ivanov persuaded Eli Lilly and 15 other companies to sponsor the Borovets conference. And he said he one day hopes to work in the industry he now oversees, just as his predecessor did.

But Ivanov insisted companies and doctors know where he draws the line. He said he cracked down last year on a pair of Bulgaria's most respected drug researchers for conducting an experiment without government approval.

Their fine: \$10.

The picture is no more reassuring elsewhere. Hungary relied on a single full-time inspector who each year visits about 30 of his country's 200 testing sites, said Tamas Paal, director general of the country's National Institute of Pharmacy. He said his agency had no provision to fine or bar researchers.

If a grave problem were uncovered, "we would likely not stop a trial," said agency medical director Janos Borvendeg. "We tell them how to improve. I don't like stopping a trial because it costs a company so much to put one on."

Thailand's central ethics board lacks the staff to collect safety and data reports on all drug research, said Vichai Chokevivat, a former ethics board vice chairman. It is left to doctors to monitor side effects and deaths, he said.

## The Short Arm of the FDA

More than 90 percent of testing staged overseas is not reported in advance to the FDA, according to an estimate by David A. Lepay, the FDA's director of investigations.

FDA inspectors travel overseas only for compelling reasons. Of the many test sites listed in a company's drug approval application, the FDA usually inspects three or four, preferring American sites, said FDA staff members who have worked on the reviews.

When they do go abroad, FDA inspectors use interpreters supplied by the drug companies.

To cover foreign sites, the FDA relies on 11 inspectors from its Rockville headquarters – a number that has held steady even as foreign test sites have skyrocketed. Additional inspectors are drawn from regional offices – generalists who may be reviewing spoiled fish one week and EKG charts the next.

When FDA inspectors do venture abroad, it is often long after a test is concluded. They focus on paperwork: Were the right forms filed? The right diagnostic tools used? Medical records kept accurately?

The FDA "sends people ill-equipped [and] at the wrong time to inspect studies long since done. How is that the best method?" asked Paul Leber, a former FDA division head for neuropharmacologic products. "They should be inspecting in real-time and telling companies they intend to."

Even with limited effort, the FDA rejects data from between 12 and 15 percent of the sites it inspects in developing countries, compared with less than 4 percent from the United States, Lepay said. Problems with patient protections and research quality in poor countries mirror those found in the United States 30 years ago, he said.

Reports of overseas FDA inspections show embarrassing delays. In 1998, an FDA team went to a Romanian endocrinology institute that had tested a Novartis drug. The principal researcher, the team found, had been dead since 1995.

A South African center escaped being cited for "serious lapses" after an FDA inspector concluded in 1996 that issuing a violation was pointless since "two and a half years have elapsed" since testing finished.

The FDA's inspectors are operating under tighter deadlines imposed in 1993 when the agency promised to speed its drug reviews. From 34 months in 1993, the mean approval time had dropped to 13 months last year. "It's squeezing everybody," said retired FDA inspector Gurston D. Turner.

Top FDA enforcement officials take a "user friendly" stance toward companies they consider "stakeholders." As the FDA's Woollen explained: "We've taken a collegial approach. I don't know how that is being seen at a distance."

Responded Steve Reich, a senior vice president for clinical research for Ligand Pharmaceuticals, Inc.: "As someone who works for a sponsor [of tests], I wish you would be more aggressive" about sites whose data may be in question, he said. He sat down to applause from the audience.

But the FDA has few tools with which to discipline foreign doctors, who are not generally subject to U.S. law.

In the United States, the agency can issue warnings, bar researchers from further work or seek criminal charges. With foreign doctors, the FDA can only throw out their results.

By refusing to share inspection information with its counterparts in other countries, the FDA also makes it hard for foreign regulators to act on their own.

Liliam Arguella, Costa Rica's chief regulator for drug testing, was surprised to recently learn of a 1996 FDA inspection report citing problems with a local doctor's work. "We've never seen that report," she said. "It is important for us to know; yes, of course it is."

"It's a fair question why we don't" share such inspection results, said the FDA's Robert J. Temple, associate director of the office of medical policy. Privacy and legal obstacles get in the way, he said, "but there is also part of me that thinks it's good to have differences of opinions" about whether research was done well and had value.

The FDA does not solicit information about foreign researchers from other regulators. "We don't need that help," Temple said. "That may be arrogant but I believe we can do the job."

But others worry about the system's integrity. "We need to be asking whether we have placed too much faith in a system that has some obvious flaws," said Moira A. Keane, who directs the University of Minnesota's Research Subjects' Protection Programs.

Maxim's testing of hepatitis patients suggests the limits of the agency's reach.

After the FDA insisted on more animal tests, "we were left in the dilemma of 'we need to go offshore, we need to get this trial started soon and we need to get some interest,'" said Sandy Hyle, manager for clinical development. Maxim wanted to proceed with testing its lead drug candidate, Maxamine, in hepatitis C patients.

Maxim said it began the animal tests the FDA required while searching overseas for human subjects. When recruiting in Western Europe proved difficult, Hyle said, the company turned to a contract research organization – a middleman company that pinpoints overseas drug test sites. The firm suggested Russia.

Russian regulators approved the research plan in 30 days. They were persuaded by arguments the FDA had rejected, Stambaugh said. Maxim contended that tests on hundreds of cancer patients who already had taken Maxamine demonstrated the drug's safety. The Russians agreed, Stambaugh said.

The Maxim testing also included patients from Israel, Belgium and Britain, but Russia contributed the majority. Patient recruitment in Russia went so quickly in part because "patients weren't as educated" as Western European patients were, said Hyle.

Stambaugh put it more diplomatically: "We were not looking for uneducated patients. We were looking for patients with hepatitis C and good researchers."

The FDA's action was not mentioned in patient consent forms in Russia, Stambaugh said. Lead researcher Yoav Lurie of Tel Aviv said he was unaware the FDA wanted more animal tests. "I don't know anything about what FDA did or did not say about this drug," he said.

Did he wonder why the United States was not a test site? He paused. "I would have guessed speed. Speed is the name of the game these days, and you can get things done faster in our countries."

Three Russian researchers declined to be interviewed, citing confidentiality agreements with Maxim. FDA officials also declined interview requests, saying they could not discuss drugs under development.

For Maxim, going outside the United States has already paid off. In August, the company announced a \$100 million collaboration with Swiss pharmaceutical giant Hoffmann-LaRoche to develop treatments for hepatitis C and some cancers using Maxamine and an experimental LaRoche interferon agent. The Russian results, which the company says have been promising, helped drive that deal, Stambaugh said.

Last Wednesday, an FDA advisory committee rejected Maxim's request to market Maxamine for advanced skin cancer. The company said it was disappointed but would move forward with other tests.

Maxim said it intends to test its hepatitis C drug next year in large international trials that will include Americans. Maxim has since completed its animal tests, Stambaugh said, and would include those and the Russian results in its request to the FDA to do the bigger tests.

"It's atrocious a company would go overseas in those circumstances. It should violate FDA rules and it certainly violates ethics considerations," said Adil E. Shamoo, a University of Maryland ethicist and professor of biochemistry. "And to my mind, if the FDA does not act against this when the company returns for [marketing] approvals, they are complicit in putting foreign citizens at risk."

Staff writer Joby Warrick contributed to this report.

[Back to Page 1](#)

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