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Report Assails F.D.A. Oversight of Clinical Trials

By GARDINER HARRIS

Correction Appended

WASHINGTON, Sept. 27 — The Food and Drug Administration does very little to ensure the safety of the millions of people who participate in clinical trials, a federal investigator has found.

In a report due to be released Friday, the inspector general of the Department of Health and Human Services, Daniel R. Levinson, said federal health officials did not know how many clinical trials were being conducted, audited fewer than 1 percent of the testing sites and, on the rare occasions when inspectors did appear, generally showed up long after the tests had been completed.

The F.D.A. has 200 inspectors, some of whom audit clinical trials part time, to police an estimated 350,000 testing sites. Even when those inspectors found serious problems in human trials, top drug officials in Washington downgraded their findings 68 percent of the time, the report found. Among the remaining cases, the agency almost never followed up with inspections to determine whether the corrective actions that the agency demanded had occurred, the report found.

“In many ways, rats and mice get greater protection as research subjects in the United States than do humans,” said Arthur L. Caplan, chairman of the department of medical ethics at the University of Pennsylvania.

Animal research centers have to register with the federal government, keep track of subject numbers, have unannounced spot inspections and address problems speedily or risk closing, none of which is true in human research, Mr. Caplan said.

Because no one collects the data systematically, there is no way to tell how safe the nation’s clinical research is or ever has been.

The drug agency oversees just the safety of trials by companies seeking approval to sell drugs or devices. Using an entirely different set of rules, the Office for Human Research Protections oversees trials financed by the federal government.

Privately financed noncommercial trials have no federal oversight.

“It’s crazy that we have all these different sets of rules,” said Dr. Ezekiel J. Emanuel, chairman of the bioethics department at the National Institutes of Health. “It would facilitate things a lot if we had one agency overseeing things.”

Dr. Janet Woodcock, chief medical officer at the drug agency, acknowledged that it needs to put more “teeth” in its enforcement. “We are working to address these problems very aggressively,” Dr. Woodcock said.

The case of Audine Graybill demonstrates the flaws in the system. According to the F.D.A., in the spring of 2005, she decided to try an experimental drug to treat mania associated with bipolar disorder. The consent form that she signed on May 29 stated that she could change her mind at any point in the study.

She checked into High Pointe Healthcare in Oklahoma City, a psychiatric center owned by a psychiatrist, Dr. David Linden. On June 3, Ms. Graybill changed her mind and asked to leave.

Dr. Linden refused to let her go.

On June 6, she was given the experimental medicine. Ms. Graybill’s lawyer, Anthony Sykes, obtained a writ of habeas corpus for her to appear in court and took the writ to the hospital, where the staff refused to honor it and said it would not give it to Dr. Linden, Mr. Sykes said.

Mr. Sykes tracked Dr. Linden to another office and had him served with the writ, Mr. Sykes said. Within hours, Dr. Linden’s lawyer called Mr. Sykes and said Ms. Graybill was free to go. Mr. Sykes took her home on June 7.

Ms. Graybill could not be reached.

More than nine months later, an F.D.A. inspector appeared at Dr. Linden’s research center and uncovered myriad other problems.

The agency sent its warning letter more than two years after Ms. Graybill’s experience.

Last November, the Oklahoma Board of Medical Licensure and Supervision suspended Dr. Linden’s license for 45 days because he had sex with two patients and gave them genital herpes infections, according to board records. Dr. Linden, who also owns a psychiatric center in Las Vegas, did not return repeated telephone messages.

Dr. Linden has conducted clinical trials for most major pharmaceutical companies and continues to do

research, according to his Web site.

The F.D.A. disqualified investigators from conducting further clinical trials 26 times from 2000 to 2005 and disqualified their data just twice even though the agency found serious problems at trial sites 348 times in that period, the inspector general found.

While some of the report's findings surprised ethicists, its conclusion that the agency's oversight of clinical trials is disorganized and underfinanced has long been known and is, in many ways, identical to criticisms leveled at other agency functions, including its oversight of imported food, foreign drug manufacturers, animal food and the safety of older medicines.

In each case, the size and complexity of the tasks facing the agency have grown enormously as the number of inspectors for those tasks has generally declined.

An inspector general's report in 2000 criticized the oversight of clinical trials and noted that the inspections mostly focused on whether study information was accurate and not on whether human subjects were protected. That is still true.

In the present report, the inspector general recommended that the agency create a registry of all continuing clinical trials, an idea signed into law by President Bush on Thursday.

The report also recommended that the agency create a complete registry of research ethics boards, create a single comprehensive database to track its research inspections and obtain greater authority to regulate research assistants.

Senator Charles E. Grassley, Republican of Iowa, said the agency "needs to implement these recommendations to meet its duty."

Representative Rosa DeLauro, Democrat of Connecticut, said it needed more money and guts.

"They're passive, they're reactive, and they often side with industry over public health," Ms. DeLauro said.

The agency's reserve is apparent in some of its warning letters.

On May 24, 2005, an inspector, Barbara Breithaupt, went to the office of Dr. Frank A. Wingrove of Ames, Iowa, and for weeks asked to see records of his study of an experimental topical treatment for periodontal disease. Dr. Wingrove refused. Dr. Wingrove did not return telephone messages seeking comment.

More than two years later, the agency sent Dr. Wingrove a warning letter. The inspector general's report

suggests that if Dr. Wingrove promised to reform, the agency was unlikely to show up again to see whether he had followed through.

Correction: October 10, 2007

An article on Sept. 28 about the Food and Drug Administration's oversight of clinical trials misstated the amount of time that the Oklahoma Board of Medical Licensure and Supervision suspended the license of Dr. David Linden, a psychiatrist, who was given a warning letter by the F.D.A. for his handling of clinical trials. It was for 45 days, not three months.

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