FDA Warning Letter Hints at Crackdown on Unregulated Research, IND Enforcement

By M. Alexander Otto
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A recent letter from the Food and Drug Administration to Johns Hopkins University in Baltimore contains what may prove to be the start of agency efforts to bring unregulated human experimentation under federal oversight, according to BNA interviews with key FDA personnel.

In the March 31 warning letter, FDA cited Johns Hopkins University researcher Dr. Alkis Togias for ignoring basic safety rules in a hexamethonium experiment that killed volunteer Ellen Roche in June 2001.

Among other problems, Togias never told Hopkins that the chemical appeared to be damaging patients' lungs, and Hopkins' consent form did not tell Roche how dangerous the experiment was, FDA said. There was little new in the letter; the problems were widely reported after Roche, a healthy 24-year-old, died (1 MRLR 142, 5/15/02).

However, the letter cited an additional problem that could have wide-reaching implications for the research community: Togias failed to get the agency's approval to use hexamethonium through an Investigational New Drug (IND) application.

The situation is not unique. Thousands of chemicals are used in humans without the agency's knowledge in research laboratories throughout the United States, but until now FDA has done little to curb the practice, said University of Maryland School of Medicine professor Adil E. Shamoo.

That soon could change, according to Dr. Robert Temple, associate director of medical policy at FDA's Center for Drug Evaluation and Research, and Dr. Joanne L. Rhoads, CDER director of scientific investigations.

"We are conscious of the problem and believe it has to be dealt with," Temple said.

Getting Aggressive?

Usually, the chemicals are used for physiological studies and other low-level human experiments. In the Hopkins case, Roche was told to inhale hexamethonium--a known lung poison--to see how her lungs reacted in an attempt to elucidate asthma's underlying mechanisms. The chemical severely damaged her lungs, causing her death.

Safety concerns led FDA to cancel Togias' plan for an earlier respiratory study using a different chemical in 1997, the agency noted in its letter. In that case, Togias had applied for an IND, which gave the agency the opportunity to review the plan. By citing the case, FDA implied it could have prevented the hexamethonium trial if given the chance.

"We recognize with the hexamethonium case that we need to come to grips with what chemicals [can be used] off-the-shelf," Temple explained. "We don't want another one of these [cases]. We are aware that this is not the only instance of this going on and know that reporting of this to us is variable."

Temple would not say exactly what the agency plans to do, but revealed that a working group is determining the scope of the problem and attempting to develop solutions. Additional guidelines or regulations could be in the works.

It's an area "we have not been aggressive about," Temple noted.

The Department of Health and Human Services Office for Human Research Protections, which oversees safety in federally funded trials, also is concerned about unregulated research, especially in the nation's in vitro fertilization laboratories where doctors can experiment with different fertilization techniques with no oversight, according to OHRP Public Health Analyst Yvonne Higgins.

OHRP gets complaints regularly about problems in studies it has no jurisdiction over, Higgins told a medical research audience last fall, but so far has not taken action to address the issue.

Protection Versus Regulatory Burden.

The Hopkins letter was meant to be a message to researchers about tightening adherence to IND requirements,Temple said. It was delayed while FDA staff and others within the Department of Health and Human Services wrestled with its implications.

Rhoads and Temple admitted that there is ambiguity in the IND rules. Researchers and sponsors must tell the agency when they develop a chemical for commercial use. However, a drug already on the market can be studied without an IND if it is used in a way similar to that for which is has been approved. That involves a judgment call, Rhoads said.

However, unapproved chemicals--like hexamethonium--used to alter body structure or function must have an IND regardless of whether the chemical is being developed commercially, she said.

Shamoo, founder of Citizens for Responsible Care and Research, and other patient advocates have lobbied for years to broaden application and enforcement of IND rules, believing that patients like Roche would be protected. Some researchers have balked at what could, in some cases, prove to be an unnecessary regulatory burden.

Temple said he is sensitive to the dilemma, noting the agency has no desire to burden investigators where there is no real risk of harm.

Several bills introduced during recent sessions of Congress would have required chemicals tested on humans to be reported to the agency regardless of commercial development plans, but none has been passed into law.

The Togias letter is available at http://www.fda.gov/cder/warn/2003/02-hfd-45-0303.pdf on the Web.

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