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University Researchers Are Seen as Enablers in Latest Major Drug Fraud

By Paul Basken

Federal prosecutors on Thursday concluded another multibillion-dollar settlement with a major pharmaceutical company accused of illegally marketing its drugs.

In this case, the company was Johnson & Johnson, the total payment was $2.2-billion, and the key drug was Risperdal, which was approved by federal regulators to treat schizophrenia in adults but was being marketed for other patients, including children with behavioral problems.

As with similar instances involving other major drug companies in recent years, the case file includes a list of academic researchers who wrote articles for medical journals that the company allegedly used to overstate the benefits and understate the risks of a blockbuster drug.

"These are not victimless crimes," the U.S. attorney general, Eric H. Holder Jr., said on Monday in

announcing the settlement, which was filed on Thursday in federal court in Philadelphia. "Americans trust that the medications prescribed for their parents and grandparents, for their children, and for themselves are selected because they are in the patient's best interest."

A primary investigation underlying the case identified 44 articles written by university scientists and colleagues, many of them joint collaborations that included Johnson & Johnson researchers, described as being overseen in some manner by the company.

The authors listed in the investigation included more than 50 researchers at some two dozen universities, mostly in the United States, including Harvard, Johns Hopkins, and Stanford Universities; the Universities of California at Los Angeles, Illinois at Chicago, and Texas at Austin; Georgia Regents University; the University of Toronto; and Dalhousie University.

Among the researchers were Robert L. Findling, now a professor of psychiatry and behavioral sciences at Johns Hopkins, and Denis Daneman, a professor and chair of pediatrics at the University of Toronto, who have written a series of articles about the effects of Risperdal on children.

The federal investigation said Johnson & Johnson intentionally promoted Risperdal to child psychiatrists before 2006, when it was not approved for any use with children. The drug was known to have negative side effects on children, including

instances of boys' growing breasts, the government said in a court filing.

Boys With Breasts

Dr. Findling and Dr. Daneman, in their evaluations of Risperdal, helped counter such fears. In the conclusion of a 2003 article in the *Journal of Clinical Psychiatry* that they wrote with colleagues from Johnson & Johnson, Dr. Findling and Dr. Daneman said that levels of prolactin, a hormone that can stimulate breast development and milk production, "tended to rise and peak within the first 1 to 2 months and then steadily decline to values within or very close to the normal range by 3 to 5 months."

Intentionally or not, that gave a misleading impression of the actual risk of breast development in boys, said Stephen A. Sheller, a lawyer whose firm has been representing families suing Johnson & Johnson over Risperdal.

Some university authors—including Joseph Biederman, a professor of psychiatry at Harvard who gained renown for collecting at least $1.6-million in consulting fees from drug makers, and Dr. Daneman—appeared to be more personally aware than others of their misrepresentations, said Mr. Sheller, whose lawyers also handled one of the whistle-blower cases that formed the federal government's case against Johnson & Johnson.

Dr. Biederman, through a lawyer, declined to comment on his work with Risperdal. Dr. Findling did not respond to requests for comment. Dr.

Daneman denied any attempt to deceive. He said the data he was given by his colleagues clearly showed a rise and then a decline in prolactin levels among children taking Risperdal, and he added that researchers today still don't have a firm idea of how much prolactin exposure leads to breast development in males.

Dr. Daneman acknowledged relying on others for data, and he said his 2003 article acknowledged as a shortcoming the study's lack of an untreated control group. He denied he had any relationship with Johnson & Johnson but conceded the possibility of having been misled by the company. It's "a chilling thought," he said. He planned to investigate it, but added, "How to go about that is uncertain."

In a 2012 deposition conducted by Mr. Sheller's firm, Dr. Daneman conceded several problems with the 2003 article, including a mathematical error that cut by half the actual rate at which young boys taking Risperdal developed breasts.

A spokesman for Johnson & Johnson, Ernie Knewitz, said the company clearly was trying to get Risperdal approved for children and other patients beyond its initial use for schizophrenia. And the U.S. Food and Drug Administration, the federal agency responsible for approving medicines it determines to be safe and effective for public use, did finally agree, in 2006, to extend its approval to some use in children.

The company settled this week with the government, Mr. Knewitz said, because it

calculated that accepting the $2.2-billion penalty was better than continuing to pay for lawyers and other costs.

Other major drug companies that have reached federal settlements recently for marketing drugs beyond their approved uses include GlaxoSmithKline, last year for $3-billion; Abbott Laboratories, last year for $1.5-billion; and Pfizer, in 2009 for $2.3-billion.

A Cost of Doing Business?

The cases suggest some legitimate confusion about what exactly is legally permissible in sales of drugs outside their FDA-approved use, Mr. Knewitz said. It's not "coincidence that all the companies that marketed antipsychotic drugs at the same time period have similar charges brought against them," he said.

Others say the companies were aware of the rules and simply accepted multibillion-dollar fines as a relatively small cost of doing business, especially given the lack of criminal repercussions. In the case of Risperdal, Johnson & Johnson reported 2007 sales totaling $3.4-billion for the pill form and $1.1-billion for the injectable version. Altogether the company had $25-billion in pharmaceutical sales that year.

Critics of such marketing strategies said the settlements suggest companies will continue to find willing allies in university research labs. "Is shame enough to make it stop?" said Erick H. Turner, a

professor of psychiatry at Oregon Health and Science University and a former drug reviewer for the FDA. "Apparently not."

The investigation that identified the 44 scientific articles was carried out for Mr. Sheller by David A. Kessler, a former head of the FDA. He cited an internal company memorandum of December 2003 that describes the articles as "being managed" by Johnson & Johnson.

Dr. Kessler also described a 2003 presentation by the medical-communications company Excerpta Medica, which by then had spent 11 years carrying out the "strategic publication plan" for Risperdal and listed a series of articles in major medical journals for which it was responsible. Excerpta Medica, in the presentation to a Johnson & Johnson subsidiary called Janssen Pharmaceuticals, cited the benefits of its ownership by Reed Elsevier, publisher of medical journals that include *The Lancet*, Dr. Kessler said.

Johnson & Johnson's efforts to promote Risperdal also included numerous instances of sponsoring continuing-medical-education courses for doctors, both Dr. Kessler and Mr. Holder reported. Many states require such periodic courses as a condition for medical professionals to keep their licenses.

'Never Any Pressure'

Several university researchers identified in the December 2003 company memo flatly denied Johnson & Johnson exerted any control over their

work. One, Lawrence Scahill, a professor of pediatrics formerly at Yale University and now at Emory University, said he had carried out two studies of Risperdal and had written about three dozen papers from them, all with federal financing. The company's only financial support involved supplying the medication, he said.

The recommendations flowing from those and other studies are complicated, certainly not an open endorsement of the drug, Mr. Scahill said. "We have not been at all bashful about saying what its liabilities are," he said. "On the other hand, if you have a kid with autism who is nonverbal and is self-injurious and aggressive," the positive impact of the medicine can be "pretty dramatic," he said.

Joseph Gonzalez-Heydrich, an associate professor of psychiatry at Harvard who appeared with Dr. Biederman on two of the 44 papers cited in the investigation, said he wanted to help parents of children with epilepsy and associated behavioral issues who were not sure whether Risperdal would exacerbate their seizures. His study found it did not.

A company scientist was a co-author on one of the papers, but that fact was disclosed, Dr. Gonzalez-Heydrich said. "There was never any pressure to make things look rosier or anything else," he said.

Dr. Gonzalez-Heydrich said he finds significant benefits in working with industry, and fears a "witch hunt" mentality that may scare away colleagues. In an ideal world, he said, government

financing of science would be quadrupled, so that no university scientists would need to rely on corporate support. "But that's not the system we have now," he said.

http://chronicle.com/article/University-Researchers-Are/142865/?key=SWN2dFZvP3VHZX1qZTdKbGxRP3c4OElzZn8dPnV0bl9RFg==