Data falsification

Food and drug data fudged

Washington

A PROMINENT cardiologist, Dr Wilbert S. Aronow, has agreed to disqualify himself from future new drug trials in the face of evidence that he submitted false data to the Food and Drug Administration (FDA) on the efficacy of several drugs being tested for FDA approval. FDA has ordered drug companies to produce supporting evidence for the safety and efficacy of all drugs previously tested by Aronow.

FDA's findings have also provoked an investigation by the Environmental Protection Agency (EPA) of several studies by Aronow of the effect of low levels of carbon monoxide (CO) on heart patients, which figure prominently in EPA's ambient air standard for CO, which is in the process of being revised.

Aronow, formerly chief of the cardiovascular section at the Veterans Administration (VA) Hospital in Long Beach, California, has conducted a "vast number" of new drug investigations, according to FDA. For several years he was a member of FDA's advisory committee on cardiology. According to FDA documents, Aronow apparently signed the agreement not to participate in future drug studies in order to avoid formal "disqualification" proceedings. Aronow resigned from the VA Hospital last summer and is now at Creighton University Medical School in Omaha, Nebraska.

His troubles began in the summer of 1979, when FDA officials were going over, as a matter of routine, a study he had performed on the drug Minipres (prazosin). His study had been sponsored by Pfizer, the drug's manufacturer, which was seeking FDA approval to market it as a treatment for congestive heart failure. The drug was already on the market as an antihypertensive. Aronow's results seemed too perfect in showing the drug's success in treating congestive heart failure, and FDA investigators made an appointment with Aronow to go over his data.

The day before the investigators were to arrive, Aronow, apparently in a state of panic, called Dr Marion Finkel, associate director for new drug evaluation, and, admitted that he had "fudged" X-ray reports from his studies of prazosin and one other drug. A note by Finkel of the conversation says "The reports he submitted to the sponsors were different from the radiologists' interpretation of those X-rays. He was very upset about the matter, explained that he had been under an emotional strain, that that accounted for the alteration of the X-ray findings and he would never do anything like it again."

The audit was conducted as planned, and turned up further discrepancies. The FDA investigator reported that only one out of 10 X-rays examined matched Aronow's case reports. And in an affidavit that Aronow then signed, he admitted that he had not even examined most of the X-rays himself, but had simply filled in the case reports to match his beliefs about the drugs' effectiveness.

Serious problems were also found in Aronow's study of the drug timolol which was supposed to test the drug's effectiveness in reducing angina attacks. The subjects were supposed to be patients who were experiencing frequent angina attacks, but five of them had in fact experienced none or at most one per week before the test began. Aronow reported that the subjects' pre-test rate was as high as 14 per week — a discrepancy that would exaggerate the apparent effectiveness of the drug.

Other records could not be found. Aronow admitted discarding them, even though he was aware of the legal requirement to retain all records for two years.

In all, FDA found irregularities in five studies involving four different drugs between 1974 and 1978. The FDA investigator reported that "all discrepancies noted were on the side of favoring drug efficacy".

Aronow later retracted his admissions. At a meeting with FDA officials in 1980, he excused the X-ray discrepancies by saying that "the radiology residents' reports are considered to be very unreliable", and that he had therefore gone over all the X-rays himself and arrived at a different interpretation. And he said that when he confessed to Finkel and when he signed the affidavit, he was in state of severe emotional distress. Aronow made repeated reference to the fact that he has been under a psychoanalyst's care for the past several years. But while denying FDA's charges, Aronow again promised not to participate in further drug studies without FDA's approval.

FDA documents show that the agency's officials were clearly dissatisfied but that they decided to accept the promise and drop formal disqualification proceedings. The final consent agreement, reached in October 1982 (but revealed only two weeks ago in the *Washington Post*), confirms Aronow's pledge, and provides that the only outside parties to be informed of his voluntary disqualification were sponsors of drug studies he had conducted. He was thus spared having his name published on a list of "Investigators ineligible to receive investigational new drugs", which is one consequence of official disqualification.

According to Dr Alan Lisook, chief of FDA's clinical investigations branch, the agency has reached similar agreements in seven other cases. Lisook said the consent agreement provides a "short cut" to the cumbersome official disqualification procedure, which can take more than three years. Fifty researchers have been officially disqualified nonetheless.

Aronow's involvement in key studies for EPA has raised some questions about the appropriateness of an unpublicized consent agreement. EPA officials learned of FDA's investigation only through the *Washington Post* article. EPA has quickly assembled a committee of four "well-recognized experts" to meet Aronow and review the studies he did for the agency.

The studies played a pivotal role in the development of the agency's proposed ambient air standard for CO. By law, these standards must be stringent enough to protect the most sensitive population — and according to Aronow's studies, the most sensitive population consists of angina patients, who, he found, experience earlier onset of symptoms at levels as low as 2 per cent carboxyhaemaglobin (COHb).

Kent Berry of EPA's office of air quality planning and standards said the agency had received some comments on its proposed standard that "flag the problem that the data [at 2 per cent COHb] looked too consistent."

But EPA officials insist that there is no reason as yet to doubt Aronow's results and that it is "inappropriate for people to be jumping to conclusions about these studies". The committee reviewing the data is to report by the end of the month, and no final action on the proposed CO standard will be taken before then.

Another question raised by the unpublicized agreement is whether FDA should have informed journals that published the questionable research. FDA's Lisook said that although Aronow's prazosin study was published in *Circulation*, it was decided not to demand a retraction because other independent data supported the overall conclusion. Lisook said that FDA has demanded retractions in other cases.

But the editor-in-chief of *Circulation*, Dr Elliot Rapaport, took a different view. Like EPA, he learned of the questions about Aronow's work from newspaper reports. "I would have to say it was inappropriate for them [FDA] not to notify us if that data was faulted", he said.

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