Former FDA Reviewer Speaks Out About Intimidation, Retaliation and Marginalizing of Safety

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(Photo: ThomasThomas)The Food and Drug Administration (FDA) is often accused of serving industry at the expense of consumers. But even FDA defenders are shocked by reports this week of an institutionalized FDA spying program on its own scientists, lawmakers, reporters and academics that included an enemies list of "actors" and collaborators.

The paranoid and retaliatory email monitoring program, which sought to suppress the safety opinions of those hired to *give their safety opinions*, has provoked swift action from Capitol Hill. "I am writing to express my disappointment and disbelief with the way the Food and Drug Administration (FDA) has retaliated against whistleblowers who expressed concern to Members of Congress and the Office of Special Counsel (OSC) regarding safety concerns about medical products," wrote Sen. Charles E. Grassley (R-Iowa), ranking member on the Judiciary Committee, to FDA Commissioner Margaret A. Hamburg, the day after the breadth of the surveillance was reported in The New York Times.

Government agencies cannot discourage whistleblowing and reporting of wrongdoing by monitoring employees, echoed a White House memo sent to all government agencies about the FDA spy program.

"Devicegate" dates back at least to January 2009 when scientists in the FDA's Center for Devices and Radiological Health wrote President Obama that top FDA managers "committed the most outrageous misconduct by ordering, coercing and intimidating FDA physicians and scientists to recommend approval, and then retaliating when the physicians and scientists refused to go along." Review procedures at the agency (which approves stents, breast implants, MRIs, and other devices and machinery) were so faulty that unsafe devices - including those that emit excessive radiation - were approved, charged the scientists, provoking an OSC investigation.

For reporting the safety risks, the scientists became targets of the now-disclosed spy program and some lost their jobs. "It has been brought to our attention that FDA management may have just recently ordered the FDA Office of Criminal Investigations (OCI) to investigate us, rather than the managers who have engaged in wrongdoing!" wrote the FDA scientists in a follow-up letter a few weeks later to President Obama. "It is an outrage that our own Agency would step up the retaliation to such a level because we have reported their wrongdoing to the United States Congress."

During the same time period, Ronald Kavanagh B.S.Pharm., Pharm.D, Ph.D., an FDA drug reviewer in the Center for Drug Evaluation and Research, encountered similar intimidation and suppression of safety research. Truthout met with Dr. Kavanagh on several occasions to learn about his FDA whistleblowing experiences.

Martha Rosenberg for Truthout: You were an FDA drug reviewer from 1998 to 2008, working on well-known drugs like Cymbalta, Zyprexa, Concerta, Invega, Provigil and Saphris, and encountered the same kind of

coercive working environment as the device reviewers.

Ronald Kavanagh: That's correct. In the Center for Drugs [Center for Drug Evaluation and Research or CDER], as in the Center for Devices, the honest employee fears the dishonest employee. There is also irrefutable evidence that managers at CDER have placed the nation at risk by corrupting the evaluation of drugs and by interfering with our ability to ensure the safety and efficacy of drugs. While I was at FDA, drug reviewers were clearly told not to question drug companies and that our job was to approve drugs. We were prevented, except in rare instances, from presenting findings at advisory committees. In 2007, formal policies were instituted so that speaking in any way that could reflect poorly on the agency could result in termination. If we asked questions that could delay or prevent a drug's approval - which of course was our job as drug reviewers - management would reprimand us, reassign us, hold secret meetings about us, and worse. Obviously in such an environment, people will self-censor.

MR: What are some of the ways in which safety risks were minimized in drug evaluation and review?

RK: Well, first of all I think most people would be shocked at how malleable safety data is. Human studies are usually too short and the number of subjects in them too small to adequately characterize the most dangerous risks. That's why even a single case has to be taken seriously. A safety signal from any study - and not just safety data from short term efficacy and safety studies (used for labeling) - needs to be evaluated. This means data from long term safety studies needs to be evaluated as well as the data from even longer, ongoing safety studies and from clinical pharmacology studies. Some of this information also needs to be examined during development of a drug. Yet I have seen new drug reviews where none of this was done by the medical safety reviewer.

MR: Would you give an example?

RK: For example, human clinical pharmacology trials are typically done in Europe, yet clinical pharmacology reviewers at FDA have been barred from analyzing this information prior to studies being conducted in the US. Without being able to do this, we are unable to detect evidence of risks early and cannot provide guidance that would help with the development of the drug in terms not only of safety and proving efficacy, but also with the efficiency and cost effectiveness of the drug's development. New labeling policies can also mask risks as they exclude the labeling of adverse events if they are under a certain percentage and/or not double the rate found with a placebo. By this rule, certain serious and potentially lethal adverse events that eventually resulted in a drug being withdrawn from the market would not have had any mention of the adverse events made in the labeling at all. On top of that, I frequently found companies submitting certain data to one place and other data to another place and safety information elsewhere so it could not all be pulled together and then coming in for a meeting to obtain an agreement and proposing that the safety issue is negligible and does not need further evaluation.

MR: Like they are trying to pull the wool over the FDA's eyes?

RK: During development, if reviewers say things that companies don't like, they will complain about the reviewer or they will call upper management and have the reviewer removed or overruled. On one occasion, the company even told me they were going to call upper management to get a clear requirement for approval that they did not want to fulfill eliminated, which I then saw happen. On another occasion a company clearly stated in a meeting that they had "paid for an approval."

MR: That is shocking. Wouldn't the FDA managers want safety risks investigated?

RK: Just the opposite. Sometimes we were literally instructed to only read a 100-150 page summary and to accept drug company claims without examining the actual data, which on multiple occasions I found directly contradicted the summary document. Other times I was ordered not to review certain sections of the submission, but invariably that's where the safety issues would be. This could only occur if FDA management was told about issues in the submission before it had even been reviewed. In addition, management would overload us with huge amounts of material that could not possibly be read by a given deadline and would withhold assistance. When you are able to

dig in, if you found issues that would make you turn down a drug, you could be pressured to reverse your decision or the review would then be handed off to someone who would simply copy and paste whatever claims the company made in the summary document.

MR: You have recounted that this is what happened to you with the nerve gas drug pyridostigmine.

RK: Yes, pyridostigmine is intended to be given preventatively in case of a nerve gas attack with the nerve agent Soman and it was used experimentally on Gulf War troops. After the first Gulf War, there were concerns it was linked to Gulf War Illness. Then, prior to Operation Iraqi Freedom, the Defense Department (DoD) tried to have President Bush waive informed consent for pyridostigmine, even though it was still an investigational drug.

MR: Why?

RK: Possibly because there is less hassle medicating troops if no informed consent is required. When President Bush refused to waive informed consent, the FDA approved pyridostigmine using the "Animal Rule" which allows the approval of drugs for human use based on animal data. It was employed because it was unethical to dose humans with the nerve agent Soman to see if pyridostigmine would actually prevent death. However, the way the drugs were used in the animal studies didn't reflect how they would be used in humans and resulted in misleading conclusions.

MR: Another FDA reviewer turned down pyridostigmine before you?

RK: Yes. I was assigned to re-review his conclusions regarding pyridostigmine and even before I began my review I was pressured to approve it and this pressure continued through nearly two dozen meetings with FDA management. After it became clear that I would not be pressured into an approval and it became apparent that it would be approved according to the animal rule in spite of the science, I raised an even stronger objection: not only did it not work against nerve agents other than Soman, but *pyridostigmine actually increased lethality in the presence of other nerve agents and we knew that Saddam Hussein was not using Soman and was instead using these other nerve agents.*

MR: So, you were just stating what should have been obvious?

RK: This information was not secret - both FDA and DoD public documents acknowledge increased lethality with other nerve agents such as Sarin, and DoD and other government documents that are public also document that Saddam Hussein was not using Soman and was instead using these other nerve agents exclusively. Yet because I raised this as an objection, I was immediately replaced as the primary reviewer so that I could not document my concerns and so that pyridostigmine could be approved. It's since been proposed that if we ever face the prospect of nerve agents in the future, that this approval will be used as a justification to convince the President at that time to waive informed consent without presenting a full picture. Even though using pyridostigmine would likely only invite the use of nerve agents.

MR: Why would the FDA and DoD allow troops to be put in this kind of harm's way?

RK: I don't know and don't want to speculate. However senior managers made statements indicating knowledge that the approval was illegal. In any case, it was clear and known that use of pyridostigmine would interfere with the operation of our troops.

MR: Your training as a pediatric clinical pharmacologist has made you especially sensitive to drug risks for children. What are some of the unique drug risks children face?

RK: Pediatric approvals are based on the assumption that children will respond similarly to similar exposures. Yet dosages that are used for studies in children are often based on approved adult dosages rather than a scientific determination of whether children achieve the same or higher exposures than adults. This is because companies don't want to develop lower dosages for children if they don't have to. Thus exposure studies in children are done

after the efficacy studies have been begun instead of before when it's needed. The exposure studies then may also use overweight children as well as too few children. Since no allowance is made for race, age, puberty, or actual weight and since there are differences in children's clearance of drugs, there are often higher exposures to active and toxic metabolites in children compared to adults. Thus there are often unnecessary risks with the doses that are approved.

MR: Are there other risks with one-size-fits-all doses?

RK: There are racial differences in drug metabolism that are not taken into consideration. For example, one anticancer drug breaks down faster in African Americans, so patients don't get sufficient exposure to the drug to kill tumors. Yet African Americans were not included in the safety and efficacy studies. When drugs break down faster by one particular pathway, the patients will also sustain greater toxicity and even death from the toxic metabolite that is formed. This is especially true when the company subsequently recommends higher doses to overcome the lower exposure due to faster metabolism. In one case, this occurred with a drug used in pregnant women, where hormonal changes during pregnancy cause a greater breakdown to a metabolite that is suspected to cause mental retardation in children exposed during the pregnancy. Not only does the labeling suggest possible use during pregnancy, the labeling recommends a higher dose during pregnancy. All the while, it appears that the company was aware of the formation of a metabolite that likely affects brain development from well before the drug was ever submitted to the FDA.

MR: Are the risks just ignored?

RK: FDA's response to most expected risks is to deny them and wait until there is irrefutable evidence postmarketing, and then simply add a watered down warning in the labeling. In fact, when patients exhibit drug toxicity, it is usually attributed to an underlying condition which we know is likely to make the drug toxicity worse. This also allows the toxicity to be dismissed as being unrelated to the drug in any way. Consequently, toxicities are only attributed to the drug when the evidence is irrefutable. Thus the majority of cases where there is a contributing factor are simply dismissed. When you do raise potential safety issues, the refrain that I heard repeatedly from upper management was,"where are the dead bodies in the street?" Which I took to mean that we only do something if the press is making an issue of it.

MR: You have also spoken about the dangers of certain ADHD drugs and presented some damning data about Cephalon's stimulant Provigil.

RK: In 2006, a medical reviewer found several cases of what he thought might be Stevens Johnson Syndrome (SJS) in children who took Provigil or modafinil. SJS and the related conditions erythema multiforme and toxic epidermal necrolysis (TEN) are life-threatening skin conditions where huge swathes of skin covering large sections of the body die and slough off and the mucus membranes are also affected. The diseases are incredibly painful and kill 10 and 40 percent respectively of the people who develop them. The reviewer believed he was going to be overruled and asked me for help. We were able to get an advisory committee meeting in which I was allowed to present slides of the data that supported a diagnosis of SJS in a child in the study. I also showed that a metabolite of modafinil was 16 times higher in children than in adults and similar to the worst drug that exists for causing SJS, Blephamide. The drug company doctors were unprepared for my presentation and claimed they had no information on the child, including no photos and that they had lost contact.

MR: One of the pharma doctors actually tried to downplay SJS with modafinil, saying a child was hospitalized, but was not in the "burn unit," according to the transcript.

RK: Yes. Largely because of my presentation, the advisory committee voted 12-1 against approval, but Cephalon claimed in the press that the rash was viral and was not from the drug. The next year, armodafinil, a related drug, was approved with a contraindication for children with a contraindication following three months later for modafinil. Contemporaneously, Cephalon agreed to pay $425 million for off-label marketing of modafinil. That means that for

18 months, the FDA kept quiet about the issue of SJS in children, while Cephalon continued off-label marketing at full steam. Later, I found that the FDA had internal documents that had the same conclusion as my analysis but they had been withheld from the advisory committee.

All drugs have dangers including death, and psychiatric drugs tend to be particularly dangerous, but as long as we make reasonable attempts to minimize risks, and provide adequate information for prescribers and patients, I am not opposed to them. On multiple occasions I have stood up for smaller drug companies against FDA management.

MR: The recent revelations of reprisals against FDA device reviewers must not have surprised you at all.

RK: No they didn't. After FDA management learned I had gone to Congress about certain issues, I found my office had been entered and my computer physically tampered with. I saw strange cursor movements on my computer when I was just sitting at my desk reading that I suspected was evidence of spying. After I gave Representative Waxman's (D-CA) office a USB drive with evidence, FDA staff was admonished that it was prohibited to download information to USB drives. Then, after I openly reported irregularities in an antipsychotic drug review and FDA financial collusion with outsiders to Senator Grassley's office and the House Committee on Oversight and Government Reform, I was threatened with prison if I should release trade secret information to Congress.

MR: That is similar to the FDA's claim with the device reviewers. Why do efforts to silence free speech always seem to be couched as "trade secrets"?

RK: Because much of the information we receive are trade secrets and companies explicitly label everything they provide the FDA as such and explicitly prohibit their dissemination. In spite of this, the Food Drug and Cosmetics Act explicitly allows communication of trade secrets by FDA employees to Congress, but since most people are unaware of this, FDA management can use the threat of jail for violation of the Trade Secrets Act, not only to discourage reviewers, but in my case they got Senator Grassley's staff to destroy the evidence I provided them. The threats, however, can be much worse than prison. One manager threatened my children - who had just turned 4 and 7 years old - and in one large staff meeting, I was referred to as a "saboteur." Based on other things that happened and were said, I was afraid that I could be killed for talking to Congress and criminal investigators.

MR: Still, the FDA transparency meeting transcripts indicate you not only went to members of Congress, you appealed to the Health and Human Services inspector general.

RK: Congress did put me in contact with the Justice Department, however, I don't believe my complaints were taken seriously by the FBI or investigated. I believe that actual felonies may well have occurred. For example, I found evidence of insider trading of drug company stocks reflecting knowledge that likely only FDA management would have known. I believe I also have documentation of falsification of documents, fraud, perjury, and widespread racketeering, including witnesses tampering and witness retaliation.

MR: And in addition to this alleged wrongdoing, the public is at risk from unsafe drugs that were approved?

RK: Yes. In fact, thanks in part to the Prescription Drug User Fee Act, [in which drug companies pay for expedited reviews] thalidomide could not be stopped today.