**Ron** [redacted]

**From:** Kavanagh, Ronald E
**Sent:** Friday, May 30, 2008 1:57 PM
**To:** [redacted]
**Cc:** Woodcock, Janet; [redacted]
**Subject:** RE: FU to Meeting re: Criminal Activities

**Sensitivity:** Confidential

Thank you. However at this point I prefer to deal with Congress.

It is clear to me now that many of the side effects I'm seeing are due to effects at one or more serotonin or other receptors. There is information in the literature indicating some of these effects have been known since the early 1990's. The FD&CA requires nonapproval when any information has not been submitted to evaluate safety. I was previously concerned about mitochondrial effects of drugs but knew that in addition to direct effects that there had to be upstream receptors that effected mitochondrial function now I know that at least some of these effects may be mediated by serotonin receptors.

It is standard practice in the industry that when information of this sort is known that drugs are screened and even old drugs and competitor's drugs are examined. This does not mean that the information has been shared in a submission or that an appropriate interpretation has been provided. In fact I have several contacts within the pharmaceutical industry who have indicated to me that the sponsor has the data as it's standard practice within a company involved to generate it.

On Tuesday in a meeting on my current review when I indicated that information I had requested had not been provided I felt that I was being bullied and intimidated. In fact last Fall the same individual started swearing at me on the phone when I could not provide him with information that he requested from me on his timeframe because I hadn't even written the review yet and I also still needed to have concurrence of my chain of command and it simply was not possible to honor his request. I was so scared that I immediately e-mailed my team leader. I don't blame the person as his supervisor had previously come to my office to tell me that I was not to discuss drugs I was reviewing with another reviewer who I had thought was part of the review team and I had truly felt afraid and intimidated.

In addition I made a request of Dr. Temple at Tuesday's meeting that the sponsor be asked to provide the receptor information I need and I felt bullied by Dr. Temple's manner in in denying my request.

I do not make requests of sponsor's lightly, I've got enough data to review in a limited time frame. I only make requests when I believe that the information would be truly informative regarding evaluating a drug and would make a difference in what I would do based on that information. I use this as a criteria for need to know in contrast to nice to know. I have in retrospect realized that in one case that I had made a mistake in making a request but it didn't cost the sponsor any time towards approval and likely only had direct costs of a few hundred dollars for an experiment.

With the wide variety of clinical effects I've seen with the present drug review it's too easy to dismiss them as differing mechanisms instead of understanding their interrelatedness and the implications for long term consequences. This is why I believe that this is necessary for a full evaluation. Physicians are taught always first perform a complete history and physical and I believe my request was analogous. However even lacking this I now believe the evidence is overwhelming. I have found too many review articles in places like the New England Journal of Medicine and information from other drugs.

I know I'm not supposed to provide information on something under review to congress in order to avoid inappropriate influence on the process, and although I have decided to honor that standard I no longer trust that we have an honest process including the appeal process for scientific disputes.

Why the fact that I've just stopped taking a chronic medication that I'm supposed to be the expert reviewer on because I'm now afraid information that was likely available to FDA management was hidden from me and the medication might result in my own premature death does not engender my confidence in FDA's argument in preemption. If can't protect my own life or my children's lives from the medicines that I review, when I am consistently rated as exceeds in my review skills my confidence is not engendered in the drugs that I can't review. There's a saying, 'What to you call the person who graduates at the bottom of their medical school class? 'Doctor'. I don't want drugs on the market that I might take that have been approved without a truly competent evaluation and based upon a reasonable amount of information.

I will complete my review however due to the time constraints and lack of resources and assistance it will not be up to my usual level of work. Consequently, I fear that this will make it too easy to inappropriately dismiss my concerns.

I don't like what has happened over the past few years. Based on my experience I believe the review process has gone (at least at the reviewer level) from collegial, collaborative, efficient and trying to make to balanced decisions. To being bogged down in bureaucracy, reviewers just cutting and pasting what the sponsor's say without critical evaluation, being grossly inefficient, cutting corners just to make deadlines and to avoid being retaliated against, and everyone being defensive.

The sponsor's have abused the process and overwhelm us with useless repetitive claims and obtuse submissions including excessive tables and figures while avoid what is the obvious needed information. Plus they don't even include the raw data. Consequently, there is no time to digest and integrate incredibly complex information and distill it into useful labeling in timeframes of hours just prior to the PDUFA deadline.

The REMS is nearly useless. Sponsor's say whatever they want to and it's sent to a totally different division for review to reviewers who don't know the actual data from the drug and who the primary reviewers can't discuss it with. Heck by putting us into separate buildings we the new people don't know the other people on the team and for physicians in particular what they even do or contribute.

By dividing postmarketing chemistry and manufacturing changes into a separate group, even if they have the proper scientific background there is no possible way that they can become sufficiently familiar with the intricacies of a drug to understand what the clinical consequences of a manufacturing change are.

I have repeatedly spoken honestly and tried to give honest feedback. I am not a malcontent as a malcontent simply complains because of bitterness, I am a gadfly, someone who speaks out and complains in order to effect positive change.

I believe in sunshine. I believe that only when we are required to provide virtually all information about a drug publicly so that our decisions can be scrutinized will we have a chance of an honest process. I realize that I don't know everything and that I can't do everything and I will make mistakes. In fact we may realize our mistakes only years later. However, I'm willing to open my reviews and analyses to the public. I expect to hear both criticisms that are valid and what I may consider invalid. When I consider something invalid I expect to have to and be able to defend it with intellectual honesty.

It is disappointing to me that as one of the most highly trained, productive, and effective reviewers in the FDA that I feel that I have to have the ear of powerful members of Congress and hard evidence of criminal activity before FDA management might be willing to pay attention to any feedback I might provide.

With regards to you comment regarding revising the MAPPs it might be a start but I'd like to share a quote I read from The Honorable Henry Waxman, "You can't legislate ethics". (Since this is from memory I hope I haven't misquoted him.)

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**From:** [redacted]
**Sent:** Friday, May 30, 2008 12:05 PM
**To:** Kavanagh, Ronald E
**Cc:** Woodcock, Janet; [redacted]
**Subject:** RE: FU to Meeting re: Criminal Activities
**Sensitivity:** Confidential

Ron,

Thank you for articulating your thoughts in writing -- it is certainly a start.

CDER has processes in place to help resolve this type of scientific issue. First and foremost, please continue your hard work reviewing the current NDA and bring your conclusions (in writing) to your team leader and possibly to the review team, as appropriate. As you can see in MaPP 4151.1, if your management does not agree with you they must document the reasons why they disagree. And even if this happens, ultimately, if it's a significant risk to the public health, you can take your differing professional opinion to the Center Director and an ad hoc panel using MaPP 4151.2 (attached).

I'll take this opportunity to remind you that employees are protected under the 2002 NO FEAR Act and the Whistleblower Protection Act of 1989. I have no knowledge of past retaliation against you, so I can't really speak to that. You are welcome to come discuss these concerns with me in person and perhaps I can give you some advice from an ombudsman's perspective.

As I mentioned to you, I am in the middle of evaluating and revising both of the attached CDER MaPPs that pertain to the resolution of scientific dissent and certainly welcome your input on how to make the process more meaningful and less cumbersome to CDER employees.

I am the Ombudsman for our Center and my door is always open to you for independent advice.

[redacted]

*FDA/Center for Drug Evaluation and Research*

*Email:* [redacted]

[redacted]

<< File: MaPP 4151-1 diff scientific opinion.pdf >> << File: 4151.2 diff sci opinion with panel.pdf >>

**From:** Kavanagh, Ronald E
**Sent:** Friday, May 23, 2008 10:23 AM
**To:** [redacted]
**Cc:** Woodcock, Janet
**Subject:** FU to Meeting re: Criminal Activities
**Sensitivity:** Confidential

Dear Ms. [redacted]

Thank you for stopping by yesterday and listening to my concerns regarding potential criminal activity and internal cover-ups. Since I didn't notice you taking notes and since both of you indicated that you were not scientists and were thus unlikely to understand the issues with regard to science I would like to summarize the major points I made.

This is regards to an application for a new molecular entity Asenapine (NDA 22-117).

I have found several deaths as well as a group of symptoms that suggests a particular underlying mechanism that indicates that when the drug is given for a prolonged time it will have a cumulative toxicity that will result in will result in a large number of deaths years after the patient has started taking the drug. Also these potentially lethal effects may not even become evident until years after the drug is stopped. The symptoms are extremely vague and varied that it's unlikely to be detected until many years after the drug is placed on the market and after many people have been permanently maimed and killed.

The drug is proposed for two indications. For the first indication neither efficacy study that the clinical division is claiming proves it works meets our usual criteria. For the second indication standard analyses typically used for psychiatric drugs clearly indicate that the drug does not work in patients with moderately severe disease. Yet the clinical division has recommended approval for this population. In addition, I have data from 4 other drugs that indicate that they don't work either for the moderately severe illness for which they're approved.

I have notified the clinical division in writing of apparent criminal activity by the sponsor (i.e. not reporting SAEs and deaths as required) and have recommended a criminal investigation. Yet the clinical division has apparently tried to cover this up. This is what prompted my original complaint to Dr. Buckman.

In spite of pointing out my recent findings to the clinical division and citing the FD&CA that prohibits approving a drug under these circumstances, the clinical division and my management have gone ahead and are preparing labeling to provide to the sponsor in spite of the fact that the sponsor has not provided sufficient information that would even allow my division to write labeling for our section. In addition, there have even been labeling meetings that I was not notified of. This has occurred while I am supposed to be working on collating the safety information. The only reason I can see to proceed with such labeling is if the intent is to send an approval or approvable letter prior to my being able to finish the amendment to my review.

I have since found that Dr. Laughren was aware of these safety signals from when the US IND was initially opened and both he and the sponsor were quite concerned about them. As I mentioned there are even notes in Dr. Laughren's own hand indicating his concerns. The clinical division even requested immediate telephone

notification within 10 days of even potentially related side effects which is even more stringent than the law requires.

Based on the medical review it's clear that not even the individual case reports of the deaths that were reported in the NDA were examined by the medical reviewer and that he simply cut and pasted what the sponsor wrote.

Based on the sponsor's development program and what they report in the NDA it appears that they know the mechanism and that it's due to a metabolite and they designed their development program and reported adverse effects and wrote their NDA in such a way so as to minimize any possibility of detection.

You referred me to OIA, however I indicated that I was uncomfortable with OIA as several of my colleagues with whom I have worked with personally have been investigated by OIA. (Post meeting note: These were based on concerns that they may have or actually did spoke to Congress.)

In response to your question I stated that I have discussed this with my chain of command, however as I have had my children threatened in the past, which was investigated by the very person who was helping my management to retaliate against me. Plus as my management is apparently working with the clinical division to approve the drug in spite of the safety concerns and the lack of efficacy, I no longer trust my chain of command.

In response to your question about why this is an imminent public health concern, I stated that these toxicities appear to be a class effect and other drugs with similar structures and effects are presently on the market (e.g. olanzapine) and being prescribed and pushed both off and on label to children who have the less severe forms of the disease that the data indicates the drugs do not work for. In addition the mechanism is causing neonates to die shortly after birth and this was also seen in the animal studies. Plus these drugs are typically used in pregnant women. In addition recent drug approvals and proposals for combined use of an atypical antipsychotic and antidepressants are likely to compound the toxicities.

I hope this helps.

Dr. Woodcock,

Thank you for following up on this so quickly and sending Ms. Axelrod and Ms. Behr to discuss this.

Ron Kavanagh