Ron [redacted]

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 [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 [redacted]

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 [redacted] to discuss this.

Ron Kavanagh

Tracking:

Recipient	Delivery	Read
Woodcock, Janet	Delivered: 5/23/2008 10:23 AM	Read: 5/23/2008 10:30 AM
[redacted]	Delivered: 5/23/2008 10:23 AM	Read: 5/23/2008 10:46 AM
[redacted]	Delivered: 5/23/2008 10:23 AM	Read: 5/23/2008 11:06 AM