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October 14, 2005

Dr. Russell Katz
Director, Neuropharmacological Drug Products
Food and Drug Administration, FDA 120
1451 Rockville Pike, Room 4037
Rockville, MD 20852

Re: FDA Neurontin Safety Analyses

Dear Dr. Katz:

Due to the continued public danger facing a substantial class of prescription drug users, I am compelled to write to you regarding the FDA's ineffective oversight related to appropriate warnings for Neurontin. Since our initial telephone conference on March 31, 2004, wherein you were informed of numerous suicides by individuals taking Neurontin, the FDA has not taken the necessary action to thoroughly examine the association between Neurontin and self-injurious behavior. The FDA's ineffective action is centered around the narrow request by the FDA for Pfizer to analyze limited clinical trials rather than all clinical trials. Not only will the narrow request result in Pfizer significantly underreporting the full extent of suicidal activity by patients taking Neurontin during clinical trials, it is contrary to the FDA's prior protocol when seeking such safety information.

On March 31, 2004, you were advised of thousands of serious psychiatric adverse events that occurred while Americans were taking Neurontin. At that time the FDA recognized a potential imminent health crisis existed, yet nothing was done to require enhanced warning labels. Due to the FDA's inaction, my firm filed a citizen's petition on May 17, 2004 with the hope that the FDA would investigate the potential for Neurontin contributing to self-injurious behavior. The FDA took six (6) months to respond and stated no decision had been reached and more time was needed to investigate. All investigations, if any, have been couched in secrecy and not open to public scrutiny while the same serious health crisis continues.

Recently my office obtained your March 16, 2005 letter to Pfizer requesting information regarding Neurontin and suicide. While an inexperienced, uninformed reader may interpret your letter as evidence that the FDA is finally taking appropriate investigatory action, my review indicates the FDA carefully framed the request to assist Pfizer in hiding the true association between Neurontin and suicide. This was accomplished by the FDA being unnecessarily overly narrow in the request.

Specifically, the FDA requested Pfizer to limit its submission only to serious psychiatric adverse events that occurred in short-term, placebo controlled trials. Therefore, Pfizer will **not** report any of the following serious adverse events which occurred in clinical trial 945-183 simply because the trial protocol did not have a placebo arm:

EVENT 1: Adverse Event: **Suicide**

Patient No. 70163, a 46-year-old Caucasian female, committed suicide while receiving 1800 mg/day of Neurontin. This event occurred on study day 15.

EVENT 2: Adverse Event: **Suicide Attempt by Drug Overdose**

Patient No. 17012, a 29-year-old Caucasian male attempted suicide by overdosing on divalproex sodium (Depakote) and Neurontin while receiving 900 mg/day of Neurontin. The event began on study day 14. The Pfizer investigator considered the event to be definitely related to Neurontin. The event was considered serious because the patient was hospitalized. Neurontin was interrupted due to this event.

EVENT 3: Adverse Event: **Psychosis Leading to Self Inflicted Chest Wound**

Patient No. 29324, a 29-year-old Hispanic female, experienced a period of psychosis and a self-inflicted stab wound to the chest while receiving 2700 mg/day of Neurontin. The psychotic episode began on study day 73 and the self-inflicted stab wound to the chest occurred on study day 76. Both events were considered to be severe in intensity with the psychosis lasting for 9 days and treatment for the stab wound for 21 days.

EVENT 4: Adverse Event: **Psychosis with Suicidal Ideation**

Patient No. 23812, a 52-year-old Hispanic female, experienced an episode of psychosis while receiving 1500 mg/day of Neurontin. The event began on study day 68. The patient presented for psychiatric admission to the Emergency Room. She was hearing voices telling her to kill herself and she feared for her life.

Clearly, the FDA's narrow request of Pfizer will result in underreporting of important suicidal adverse events that occurred during clinical trials. Why is the FDA not interested in examining the above serious adverse events?

My firm is aware of hundreds of other Neurontin clinical trials that did not have a placebo arm, many of which contain similar serious psychiatric adverse events. Pfizer, however, is not obligated to disclose them to the FDA. Is the FDA not concerned about other suicidal adverse events during clinical trials that the Pfizer investigators considered definitely related to Neurontin?

It cannot be overlooked that the narrow protocol was established by the FDA working directly with Pfizer. During your teleconferences with Pfizer on April 26 and May 6, 2004 as well as in the e-mail correspondences dated June 10, 22, 28 and July 2 and 16, the FDA acquiesced to the narrow protocol proposed by Pfizer. A clear appearance of impropriety exists when the FDA's investigative protocol was developed in conjunction with the very company the FDA is investigating, overseeing and purportedly regulating. Pfizer is aware that the number of reportable events will significantly increase if they are required to include psychiatric adverse events from all clinical trials. Pfizer successfully manipulated the FDA in a fashion that permits full compliance with the current FDA protocol while not fully disclosing the full extent of known psychiatric adverse events of patients while taking Neurontin. The FDA should be seeking *all* suicidal adverse events that occurred in *all* clinical trials of Neurontin, not just from clinical trials with a placebo controlled arm.

Seeking all adverse events from all clinical trials is the established protocol for the FDA when analyzing safety information. When the FDA was concerned that Baycol was causing too many serious adverse events, the FDA's August 2001 request from the manufacturer for safety information was far broader and performed with greater urgency than what the FDA has done with Neurontin. Specifically, the Baycol letter demanded safety data from *all* clinical trials the manufacturer conducted, without limitations to time or study design. Clearly, the FDA was interested in *all* safety events related to Baycol. Why is the FDA not interested in all suicidal events with users of Neurontin? Study design is critical in analyzing efficacy analyses. Study design is not critical when seeking to obtain the universe of all adverse events.

Additionally, why would the FDA limit Pfizer's reporting of suicidal events to no more than one day after discontinuing Neurontin? Neurontin is a drug that affects the central neurotransmitter levels. It is well known that upon initiation of Neurontin, perturbation in central neurotransmitter levels does not occur instantaneously. Similarly, upon discontinuation of Neurontin, normalization in the central neurotransmitter level does not occur instantaneously. Even with a seven (7) hour half life, there are still circulating levels of Neurontin on the first day of drug discontinuation. In patients with renal compromise, the half life is extended to as much as fifty (50) hours. More importantly, the alteration of the brain chemistry continues beyond the first day of discontinuation. Interestingly, the Baycol letter did not limit the inquiry to adverse events that occurred within one day of discontinuation.

Moreover, it appears the FDA intentionally did not request from Pfizer important materials that were sought in the Baycol request. No request for relevant safety data from the animal trials regarding Neurontin was made. No request for any current worldwide post marketing surveillance data was made. Pfizer is duty bound to obtain, compile and maintain safety data regarding Neurontin on a worldwide basis. Is the FDA not interested in knowing whether Neurontin has caused suicides or suicidal activity in other parts of the world?

Another striking difference between the FDA's request for Neurontin safety information and the FDA's request for Baycol safety information is that Pfizer is not required to provide a full translation of all approved worldwide labeling for Neurontin, as was required with Baycol. Significant differences in the warnings exist between the US label for Neurontin and other countries. For example, the British warning for Neurontin contains the following enhanced warning:

4.4 Special warnings and precautions for use

Patients taking Neurontin can be the subject of mood and behavioral disturbances. Such reports have been noted in patients on Neurontin although a causal link has not been established.

Caution is recommended in patients with a history of psychotic illness. On commencing Neurontin therapy, psychotic episodes have been reported in some patients with, and rarely without, a history of psychotic illness. Most of these events resolved when Neurontin was discontinued or the dosage was reduced.

No such enhanced warning exists on the U.S. label, therefore few US physicians know to take a history for psychotic illness before prescribing Neurontin. Is there a reason the FDA does not want to learn whether foreign regulatory agencies require stronger warnings than its own? Is there a reason the FDA does not want to warn U.S. physicians to take a history for psychotic illness before prescribing Neurontin, especially when the FDA knows 92% of the prescriptions are for off-label, unapproved uses?

The answers to these troubling questions all come to the same conclusion: the FDA wants to protect the largest pharmaceutical manufacturer in the world. Why else would you begin your March 16, 2005 letter suggesting the suicide rate for epileptics is important when analyzing the risks of Neurontin leading to suicide. Such a pretext was dismissed by the FDA when evaluating the causal association between Accutane and suicide.

Indeed, in addressing the suicide issue with Accutane, the FDA properly stated that comparisons to national averages for suicide cannot be made when analyzing the association between Accutane causing suicide. Due to the significant degree of underreporting of ingested prescription drugs taken at the time suicides are committed, no scientifically valid conclusion can be made by comparing national averages of suicides and Accutane users. The mere fact that the number of known suicides of individuals while on Accutane was lower than the expected national average did not prevent the FDA from requiring an enhanced warning of suicide related to Accutane. Therefore, your pretext that users of Neurontin are somehow predisposed to commit suicide based upon national averages is not only completely flawed, it clearly demonstrates you are inclined to conclude no association exists between Neurontin and suicidality before reviewing the requested limited, skewed data.

Regrettably, this is an example of why the American people have lost faith in the FDA's ability to protect them from unsafe drugs. While your real motivations are not known at this time, it is clear your interest is not in discovering the truth or protecting the health and safety of the American people.

Very truly yours,

FINKELSTEIN & PARTNERS, LLP



BY:

ANDREW G. FINKELSTEIN

Cc: Dr. Andrew C. von Eschenbach, Acting Commissioner FDA
Dr. Robert Temple, Office of New Product Evaluation, FDA