CITIZENS PETITION TO FOOD AND DRUG ADMINISTRATION

Division of Dockets Management
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

ALLIANCE FOR NATURAL HEALTH USA 1350 Connecticut Avenue, NW, Fifth floor Washington, D.C. 20036 202-467-1985 Petitioners, v. FOOD AND DRUG ADMINISTRATION Division of Dockets Management Room 1061 5360 Fishers Lane Rockville, MD 20852	Docket Number ____

August 11, 2011

PETITION SEEKING BLACK BOX WARNING CONTAINING RISK OF VIOLENCE FOR SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI) MEDICATIONS

Action Requested

Pursuant to the right to petition the government clause contained in the First Amendment of the United States Constitution,[1] the Administrative Procedure Act,[2] and the Food Drug and Administration regulations,[3] Petitioners submit this petition for rulemaking under the authority of the Food and Drug Cosmetic Act 21 USC §355(e)(3) to request the U.S Commissioner of the Food and Drug Administration to undertake the following action: Issue a regulation that:

1. All makers of Selective Serotonin Reuptake Inhibitors (SSRI) antidepressant medication for humans expand the existing black box warning on their product's labeling to include warning about increased risk of violence towards others.
2. All makers of Selective Serotonin Reuptake Inhibitors (SSRI) antidepressant medication for animals create a black box warning on their product's labeling to include warning about increased risk of violence towards others.

Statement of Grounds

Both animals and humans are included in the definition of 'drugs' in the Food Drug and Cosmetic Act and therefore the laws pertaining to the labeling of drugs applies to both animal and human drugs.[4]

Accordingly, the Alliance for Natural Health petitions the FDA on the grounds of the Federal Food, Drug and Cosmetic Act 21 U.S.C Section 355(e)(3):

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[1] "Congress shall make no law ... abridging ... the right of the people ... to petition Government for a redress of grievances." U.S.Const. amend. I.
[2] 5 U.S.C. § 553 (e) (2009).
[3] 21 C.F.R. § 10.30
[4] 21 U.S.C § 321

Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds…

(3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof;[5]

SSRI antidepressant medications used for humans include fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), and escitalopram (Lexapro). And in 2007, the FDA approved the SSRI fluoxetine hydrochloride (a form of Prozac) for dogs.[6]

SSRI antidepressants are generally treated as a single category or class of pharmacological agents during observations made of the impact of these drugs in clinical practice and scientific literature. Therefore, it is typically recognized that an adverse mental or behavioral reaction that is observed in relation to one SSRI is likely to be found in other SSRI antidepressant drugs.[7]

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[5] 21 U.S.C § 3

[6] "Lilly Receives FDA Approval For Antidepressant For Dogs," *Inside Indiana Business,* April 25, 2007. Accessed August 5, 2011. http://www.insideindianabusiness.com/newsitem.asp?ID=22982

[7] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) (*Washington DC: American Psychiatric Association, 1994)

Overwhelming research suggests that SSRI antidepressant medication increases the risk of violence towards others. In a study of the FDA's Adverse Event Reporting system 31 drugs were found responsible for most of the FDA case reports of violence towards others. Antidepressant medication featured prominently on the list.[8] The study extracted all serious adverse event reports for drugs with 200 or more cases received from 2004 through September 2009. Any case reports indicating homicide, homicidal ideation, physical assault, physical abuse or violence related symptoms were identified for the study. At the end of the study, 31 drugs were responsible for a disproportionate 1527 violent cases reported as a side effect of taking the drug. Of the 31 drugs, 11 were antidepressant drugs. Five of the top ten drugs linked with reports of violent behavior were selective serotonin reuptake inhibitors (SSRI) antidepressants: fluoxetine (Prozac), paroxetine (Paxil), fluvoxamine (Luvox), venlafaxine (Effexor), and desvenlafaxine (Pristiq).

The cited analysis establishes that the reporting individual suspected a relationship existed between violent behavior and antidepressants. These reports help to contribute to a broader picture of causality between taking SSRI antidepressant drugs and acts of violence. The study was also designed to mitigate many limitations faced by a study of self-reporting systems. By excluding general terms to describe violent events such as "aggression" or "anger" and instead specifying event terms that were directly described as a violent act or thought, the study disregarded thousands of vague and less specific cases that might have falsely amplified the results.

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[8] Thomas J. Moore et al, "Prescription Drugs Associated with Reports of Violence Towards Others". *PLoS ONE* 5 no 12 (Dec 2010): e15337. doi:10.1371/journal.pone.0015337

The manufacturers of these SSRI drugs have even documented data of adverse events resulting from their own SSRI medication. In 2006, the peer-reviewed journal *PloS Medicine* published an article outlining the association between antidepressants and violence. In the article, David Healy and David Menkes from Cardiff University, and Andrew Herxheimer from the UK Cochrane Centre, cite data on the SSRI antidepressant drug paroxetine (Paxil) submitted by the manufacturer GlaxoSmithKline to the UK Committee on Safety of Medicines Expert Working Group. In these trials aggression and violence were coded as hostility. Summing the hostile events occurring in both adult and pediatric trails, 60 of the 9,219 patients overall had hostile events. GlaxoSmithKline also studied the effects of paroxetine on healthy individuals. In this study hostile events occurred for 3 out of 271 volunteers taking paroxetine, whereas 0 hostile events occurred in the 138 individuals taking the placebo. As the article points out, these findings are noteworthy considering that it is unusual for hostile events to occur among a healthy population.

The article outlines three of the mechanisms through which SSRI antidepressant drugs are linked to violence. [9]

1. SSRI antidepressant drugs can trigger akathisia. Akathisia is a painful inner agitation that typically manifests as the inability to sit still or to stop moving. This inner agitation can be extremely uncomfortable and can lead to extreme irritability, suicide or violence. Lipinksi et al reviewed the literature and found rates of 9.7 to 25% akathisia induced by fluoxetine. And The Public Citizen Health Research Group estimated a rate of 15-25%. While there is variation in the

[9] David Healey et al., "Antidepressants and Violence: Problems at the Interface of Medicine and Law," *PLoS Med* 3 no 9 (Sep 2006): e372. doi:10.1371/journal.pmed.0030372

frequency with which the disorder is observed in the two publications, they confirm that it is common. [10]

2. Treatment-induced emotional blunting is another possible effect. Emotional blunting includes a sense of detachment or an amotivational syndrome. The article cites several reports published since 1990 that have linked SSRI intake with the production of emotional blunting, detachment, or an amotivational syndrome.
3. SSRI antidepressant drugs are reported to induce manic or psychotic states. As stated in the article, in a study of all admissions to a general hospital psychiatric unit during a 14-month period, 8.1% (43) of the 533 patients were found to have been admitted due to SSRI antidepressant associated mania or psychosis. These finding were found to be significant.[11]

These effects have also been subject to FDA warnings. On March 22, 2004 the FDA issued a Public Health Advisory in regard to children and adults in which it stated:

> *The agency is also advising that these patients be observed for certain behaviors that are* ***known*** *to be associated with these drugs, such as, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania* [emphases added][12]

One extension of such behavior is that patients might commit violence against others.[13]

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[10] Peter R Breggin, "Suicidality, Violence and Mania Caused by Selective Serotonin Reuptake Inhibitors (SSRIs): A Review and Analysis." *International Journal of Risk and Safety in Medicine* (2003/2004): 31-49. *www.breggin.com/31-49.pdf*

[11] Adrian Preda et al., "Antidepressant-associated Mania and Psychosis Resulting in Psychiatric Admissions," *Journal of Clinical Psychiatry,* 62 no 1 (Jan 2001): 30-3, http://www.ncbi.nlm.nih.gov/pubmed/11235925

[12] Food and Drug Administration. "FDA issues Public Health Advisory on cautions for use of antidepressants in adults and children." Accessed May 10, 2011. http://www.antidepressantsfacts.com/2004-03-22-FDA-Talk-Paper-use-SSRIs.htm.

[13] Peter R. Breggin, "Recent Regulatory Changes in Antidepressant Labels: Implications of Activation (Stimulation) for Clinical Practice," *Primary Psychiatry* 13 no 1 (2006):57-60. http://www.primarypsychiatry.com/aspx/articledetail.aspx?articleid=440

Creating a clear black box warning to warn against the potential risk of committing violence against others while under the influence of the medication is a necessary preventive step to ensure that this outcome does not in fact occur. As SSRI anti-depressant medication is being modified for animal consumption, it is important to include the black box warning on those medications as well.

The Canadian government has already recognized the link between violence and antidepressant medication for humans. Warnings about the risk of antidepressant drug-induced violence towards others have been in place in Canada since 2004 in the information package received by patients and in the prescribing information available to health professionals. According to the Canadian government, "Selective Serotonin Re-uptake Inhibitors (SSRIs)…now carry stronger warnings. These new warnings indicate that patients of all ages taking these drugs may experience behavioral and/or emotional changes that may put them at increased risk of self-harm or harm to others."[14]

In light of the evidence establishing the relationship between SSRI antidepressants and violent behavior it is essential that the FDA update the existing black box warning on human drugs, and create a black box warning on animal drugs, to include this effect. According to 21 CFR 201.57(c)(6)(i)

> *In accordance with 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.*

[14] Health Canada. "Health Canada Advises Canadians of Stronger Warnings for SSRIs and Other Newer Anti-depressants - Health Canada Advisory 2004-06-03." Accessed May 12, 2011, http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2004/2004_31-eng.php.

And under 21 CFR.57(c)(1), a black box warning may be required for certain serious warnings, particularly those that may lead to death or serious injury:

> *(c) (1)Boxed warning . Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information.*

Requested Change:

The following revision to the existing black box warning for SSRI antidepressant drugs for humans is requested: [**Additions in bold**]

> The following changes should be made to the current language under the "WARNINGS-Clinical Worsening and Suicide Risk**"** section.
>
> DRUG NAME

Suicidality, **Violence Towards Others** and Antidepressant Drugs Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. **Antidepressants also increase the risk of violent thinking and behavior towards others.** Anyone considering the use of [Insert established name] or any

other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, **the tendency to inflect violence towards others,** or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Insert Drug Name] is not approved for use in pediatric patients. [The previous sentence would be replaced with the sentence, below, for the following drugs: Prozac: Prozac is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). Zoloft: Zoloft is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). Fluvoxamine: Fluvoxamine is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD).] (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

The following black box warning for SSRI antidepressant drugs for animals is requested:

Violence Towards Others and Antidepressant Drugs

Antidepressants also increase the risk of violent thinking and behavior towards others. Anyone considering the use of [Insert established name] or any other antidepressant in an animal must balance this risk with the clinical need. Animals who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, and any tendencies to inflect violence towards others, or unusual changes in behavior. Pet owners and animal caregivers should be advised of the need for close observation and communication with the prescriber.

The FDA must issue this rulemaking to expand the black box warning for antidepressant drugs for humans, and create a black box warning for animals, to include the risk of violence towards others to ensure that SSRI antidepressants "will have the effect it purports or is represented to have under the conditions of use

prescribed, recommended, or suggested in the labeling thereof" in compliance of 21 USC §355(e)(3) and therefore as mandated by law.

Environmental Impact

Nothing requested in this petition will have an impact on the environment.

Certification Statement

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition.