IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF PENNSYLVANIA

UNITED STATES OF AMERICA	:	**CRIMINAL NO. _____**
v.	:	**DATE FILED: _____**
ELI LILLY AND COMPANY	:	**VIOLATION:**
	:	**21 U.S.C. §§ 331(a), 333(a)(1) and 352(f)(1) (distribution of misbranded drugs: inadequate directions for use - 1 count)**
	:	**Notice of forfeiture**

INFORMATION

COUNT ONE

THE UNITED STATES ATTORNEY CHARGES THAT:

At all times material to this information:

BACKGROUND

1. Defendant ELI LILLY AND COMPANY ("ELI LILLY") was a corporation operating and existing under the laws of the State of Indiana, with headquarters and manufacturing facilities located in Indianapolis, Indiana. ELI LILLY was engaged in the development, manufacture, promotion, and sale of pharmaceutical drugs intended for human use. ELI LILLY distributed its pharmaceutical drugs throughout the United States.

2. The Federal Food, Drug, and Cosmetic Act ("FDCA"), among other things, governed the interstate distribution of drugs for human use, as codified in 21 U.S.C. § 301, et seq. The FDCA and its implementing regulations prohibited the distribution of any new drug in interstate commerce until the sponsor or manufacturer of that new drug had received

approval from the United States Food and Drug Administration ("FDA"), based on an intensive application and review process. 21 U.S.C. § 355.

3. The FDCA required that the sponsor of a new drug submit a New Drug Application ("NDA") to the FDA, which identified all of the proposed uses of the drug intended by that sponsor, together with the proposed labeling for those uses, and data, generated in randomized and well-controlled clinical trials, that demonstrated to the FDA's satisfaction that the drug would be safe and effective for those intended uses. 21 U.S.C. §§ 331(d) and 355(b).

4. Until the FDA approved the NDA, including the proposed labeling, and found sufficient evidence of the drug's safety and efficacy for the uses proposed by the sponsor, the FDCA prohibited the sponsor from introducing the new drug into interstate commerce. 21 U.S.C. § 355(a). Only after the FDA approved the application was the sponsor permitted by law to promote and market the drug, and then only for the medical conditions of use specified in the approved labeling. Uses not approved by the FDA, and not included in the drug's approved label, were known as "unapproved uses" or "off-label uses."

5. Under the FDCA, if the sponsor of a drug wanted to market that drug for an unapproved or off-label use, the sponsor first was required to submit to the FDA each additional proposed use, together with evidence, in the form of randomized and well-controlled clinical studies, sufficient to demonstrate that the drug was safe and effective for each additional proposed therapeutic use. The sponsor could not label or promote the drug for any new intended use without the prior approval of the FDA.

6. The FDCA provided that a drug was misbranded if, among other things, the labeling did not bear adequate directions for its use. 21 U.S.C. § 352(f)(1). Adequate

directions for use could not be written for medical indications or uses for which the drug had not been found by the FDA to have been proven to be safe and effective through well-controlled clinical studies. Drugs that were promoted for uses that had not been approved by the FDA were thus deemed misbranded as a matter of law under Section 352(f)(1).

7. The FDCA prohibited the distribution in interstate commerce of a misbranded drug. 21 U.S.C. § 331(a) and (k).

FDA APPROVAL AND REGULATORY ACTION

8. On September 22, 1995, defendant ELI LILLY submitted an NDA seeking approval of a drug called Zyprexa (also known by the chemical name olanzapine) to treat schizophrenia and related disorders.

9. On September 30, 1996, the FDA approved Zyprexa for the short-term management of the manifestations of psychotic disorders.

10. On November 14, 1996, shortly after defendant ELI LILLY started to promote Zyprexa, the FDA sent ELI LILLY a letter informing the company that it found the company's promotional materials and activities "to be false or misleading, and in violation of the Federal Food, Drug, and Cosmetic Act." In particular, the FDA cautioned ELI LILLY about its marketing for elderly patients, advising the defendant that it was misleading to suggest that dosing of Zyprexa in the elderly was easy. In addition, the FDA cited false and misleading statements by an ELI LILLY officer, which characterized weight gain resulting from Zyprexa use as a therapeutic benefit, when in fact it was an adverse event noted in the approved labeling.

11. In October 1998, defendant ELI LILLY submitted a supplemental new drug application for the use of Zyprexa to treat psychosis associated with Alzheimer's disease.

In August 1999, defendant ELI LILLY withdrew its supplemental new drug application for the use of Zyprexa to treat psychosis associated with Alzheimer's disease.

12. Although defendant ELI LILLY submitted an application for use of an injectable form of Zyprexa to treat agitation associated with dementia, the FDA did not approve that use.

13. Defendant ELI LILLY never submitted a supplemental new drug application for the use of Zyprexa to treat dementia or Alzheimer's dementia.

14. The FDA never approved Zyprexa for the treatment of dementia, Alzheimer's dementia, psychosis associated with Alzheimer's disease, or the cognitive deficits associated with dementia.

15. In March 2000, the FDA approved the addition of the subheading "schizophrenia" in the Indications and Usage section of the Zyprexa label to modify "the short-term management of the manifestations of psychotic disorders." Also in March 2000, the FDA approved Zyprexa for the short-term treatment of acute manic episodes associated with Bipolar I Disorder. In November 2000, the FDA approved new labeling for Zyprexa for the short-term treatment of schizophrenia in place of the management of the manifestations of psychotic disorders, and for maintaining treatment response in schizophrenic patients who had been stable for approximately eight weeks and were then followed for a period of up to eight months.

16. On January 14, 2004, the FDA approved a label change for Zyprexa that added the following warning to the label, addressing the association of drugs such as Zyprexa (an atypical antipsychotic drug) with abnormalities in patients' glucose levels:

> Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

17. On February 16, 2006, the FDA approved a label change for Zyprexa that added a Black Box warning for increased mortality in elderly patients with dementia-related psychosis treated with atypical antipsychotics, including Zyprexa. The Black Box for Zyprexa stated:

> Increased Mortality in Elderly Patients with Dementia-Related Psychosis — elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis (see WARNINGS).

A Black Box warning was the highest level of warning that the FDA could require on a drug's label.

18. On October 5, 2007, defendant ELI LILLY announced that it had updated the warnings section of the labeling for Zyprexa. The new changes included warnings for weight gain and hyperlipidemia (elevation of triglycerides and cholesterol), and updated information in the warning for hyperglycemia, including additional language on a greater association of increases in glucose levels with Zyprexa than with some other atypical antipsychotic medications. Specifically, the warning section of the label reads in part: "While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics."

ELI LILLY'S OFF-LABEL PROMOTION AND SALES PRACTICES

19. From approximately September 1999 through at least November 2003, defendant ELI LILLY unlawfully promoted Zyprexa for the treatment of agitation, aggression, hostility, dementia, Alzheimer's dementia, depression, and generalized sleep disorder. These intended uses were not approved by the FDA. In promoting Zyprexa for these off-label uses, ELI LILLY caused the drug to be misbranded under 21 U.S.C. § 352(f)(1).

20. Defendant ELI LILLY's management created marketing materials promoting Zyprexa for off-label uses, trained its sales force to disregard the law, and directed its sales personnel to promote Zyprexa for off-label uses.

21. Beginning in 1999, defendant ELI LILLY expended significant resources to promote Zyprexa in nursing homes and assisted living facilities, primarily through ELI LILLY's long-term care sales force. ELI LILLY focused its efforts on long-term care facilities

and the elderly, even though schizophrenia rarely occurs in elderly patients. ELI LILLY sought to convince doctors to prescribe Zyprexa to treat patients with disorders such as dementia, Alzheimer's dementia, depression, anxiety, and sleep problems, and behavioral symptoms such as agitation, aggression, and hostility, all of which are prevalent in the elderly population.

22. Defendant ELI LILLY's long-term care sales representatives executed this company plan, and promoted Zyprexa for the treatment of dementia, Alzheimer's dementia, depression, anxiety, and sleep problems, and behavioral symptoms such as agitation, aggression, and hostility.

23. Defendant ELI LILLY promoted Zyprexa for the treatment of psychotic and behavioral symptoms in patients with Alzheimer's dementia and for the treatment of behavioral and psychological symptoms of dementia using medical reprints that purportedly demonstrated Zyprexa's effectiveness in treating these diseases, even though ELI LILLY knew that its studies of Zyprexa for the treatment of Alzheimer's psychosis had yielded mixed clinical results, thus calling into question the effectiveness of Zyprexa for the treatment of this disease.

24. In late 2001, defendant ELI LILLY's most senior management decided to abandon ELI LILLY's efforts to obtain FDA approval for the use of Zyprexa for Alzheimer's psychosis. ELI LILLY's management made that decision in part because the drug's use in that disease produced mixed clinical results, a full clinical trial would be required, there were concerns about Zyprexa's safety risks, and the FDA threshold for approval was high. ELI LILLY never pursued FDA approval for Zyprexa for the treatment of dementia or Alzheimer's dementia.

25. Building on its unlawful promotion and success in the long-term care market, defendant ELI LILLY's executives decided to market Zyprexa to primary care

physicians. In October 2000, ELI LILLY began this off-label marketing campaign targeting primary care physicians, even though ELI LILLY knew that there was virtually no on-label use for Zyprexa in the primary care market.

26. Defendant ELI LILLY trained its primary care physician sales representatives to promote Zyprexa by focusing on symptoms, rather than Zyprexa's FDA approved indications. ELI LILLY created patient profiles for the sales force to use to promote Zyprexa in this market, including a fictitious patient called "Martha," who had behavior difficulty and dementia with agitation. ELI LILLY trained its primary care physician sales representatives to lead with the "Martha" patient profile.

27. Defendant ELI LILLY's primary care physician sales representatives promoted Zyprexa using the "Martha" patient profile, including Zyprexa's ability to treat the symptoms of dementia, such as agitation. "Martha" was a very successful tool for promoting and selling Zyprexa.

28. Anticipating the possibility of resistance from primary care physicians in prescribing Zyprexa, defendant ELI LILLY specifically trained its sales representatives on how to respond to doctors' concerns about off-label uses of Zyprexa, and how to continue to promote Zyprexa for off-label indications.

29. Defendant ELI LILLY retained medical professionals to speak to doctors during peer-to-peer sessions about off-label uses of Zyprexa, including depression, dementia and Alzheimer's dementia.

HARM CAUSED BY ELI LILLY'S OFF-LABEL PROMOTION

30. Defendant ELI LILLY's off-label promotion of Zyprexa raised safety issues, affected the treatment of patients, and undermined the FDA drug approval process. ELI LILLY undertook this illegal off-label promotion for its own financial gain, despite the potential risk to patients' health and lives.

31. Defendant ELI LILLY knew that significant weight gain and obesity were adverse side effects of Zyprexa. ELI LILLY knew that significant weight gain and obesity were factors in causing hyperglycemia and diabetes.

32. Despite the November 14, 1996 letter from the FDA, defendant ELI LILLY continued to promote adverse events as therapeutic benefits, particularly in elderly populations. For example, when promoting Zyprexa to health care providers for use in elderly populations, ELI LILLY's sales representatives stated that weight gain was a therapeutic benefit, not an adverse event of Zyprexa.

33. In addition, when promoting Zyprexa to health care providers for use in elderly populations, defendant ELI LILLY's sales representatives informed health care providers that somnolence was a therapeutic benefit, not an adverse event of Zyprexa. ELI LILLY's sales representatives informed health care providers that 5 milligrams of Zyprexa at 5 P.M., referred to by the sales slogan "5 at 5," would help patients at night with sleep problems, behavioral issues, and dementia.

34. More generally, the promotion of an off-label use for a prescription drug can interfere with the proper treatment of a patient. Off-label promotion can lull a physician into believing that the drug being promoted is safe and effective for the intended off-label use, and that the FDA has approved the drug for that use. Thus, off-label promotion can cause a doctor

and patient to forgo treatment with an FDA-approved drug that has been proven to be safe and effective, and instead to substitute a treatment urged by the sales representative that is not known to be safe and effective, and that may in fact be harmful.

PROFIT TO ELI LILLY

35. Defendant ELI LILLY profited by hundreds of millions of dollars by misbranding Zyprexa through off-label promotion, and distributing Zyprexa in interstate commerce.

36. From in or about September 1999 through on or about March 31, 2001, in the Eastern District of Pennsylvania and elsewhere, defendant

ELI LILLY AND COMPANY

introduced and caused the introduction into interstate commerce of quantities of Zyprexa, a drug within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 321(g), which was intended for use in treating dementia, including Alzheimer's dementia, and which drug was misbranded within the meaning of Title 21 United States Code, Section 352(f)(1), in that Zyprexa's labeling lacked adequate directions for such uses.

In violation of Title 21, United States Code, Sections 331(a), 333(a)(1), and 352(f)(1).

NOTICE OF FORFEITURE

THE UNITED STATES ATTORNEY FURTHER CHARGES THAT:

1. As a result of the violation of Title 21, United States Code, Sections 331(a), 333(a)(1), and 352(f)(1) set forth in this information, defendant

ELI LILLY AND COMPANY

shall forfeit to the United States of America any quantities of Zyprexa, which between September 1999 and March 31, 2001 were misbranded when introduced into or while in interstate commerce, or while held for sale (whether or not the first sale) after shipment in interstate commerce, or which may not, under the provisions of Title 21, United States Code, Section 331, be introduced into interstate commerce.

2. If any of the property subject to forfeiture, as a result of any act or omission of the defendant:

(a) cannot be located upon the exercise of due diligence;

(b) has been transferred or sold to, or deposited with, a third party;

(c) has been placed beyond the jurisdiction of the Court;

(d) has been substantially diminished in value; or

(e) has been commingled with other property which cannot be divided without difficulty;

it is the intent of the United States, pursuant to Title 21, United States Code, Section 853(p), to seek forfeiture of any other property of the defendant up to the value of the property subject to forfeiture, that is $100,000,000.

All pursuant to Title 21, United States Code, Sections 334 and 853, and Title 28, United States Code, Section 2461(c).

LAURIE MAGID
ACTING UNITED STATES ATTORNEY

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DIRECTOR
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