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ZOLOFT PROSECUTORS' MANUAL

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I.

INTRODUCTION

A. Purpose

This manual is prepared in anticipation of litigation to assist Pfizer's lawyers, and lawyers in prosecutors' offices with common interests, in responding to a civil claim or criminal defense in which someone alleges that his wrongful, violent conduct should be excused because, when he committed the violent act, he was taking the antidepressant medicine that is marketed under the brand name Zoloft (generic name: sertraline or sertraline HCl). This manual describes how Zoloft works, its indications (that is, when it should be prescribed), and its side effects, and offers guidance on how attorneys can rebut scientifically unsubstantiated claims that Zoloft can induce violent behavior. The manual also describes the themes that Pfizer's lawyers or similarly-situated attorneys are likely to encounter and how those themes can be rebutted.

The manual is not intended to provide a complete scientific understanding of depression and its treatment, nor does it seek to explain all of the scientific underpinnings of antidepressant therapy. Therefore, it is important for attorneys to consult with an expert knowledgeable about those matters (generally, a psychiatrist or pharmacologist) who can further assist in rebutting allegations the defendant makes regarding Zoloft. Reputable physicians are in the best position to inform the jury of accepted scientific principles that rebut allegations that Zoloft caused or contributed to violent behavior.

B. What is the "Zoloft defense"?

As used in this booklet, the term "Zoloft defense" refers to any effort by a criminal defendant or civil litigant to persuade the jury that his criminal conduct is the result of a side effect of Zoloft, not the result of a voluntary or intentional act. Depending on the law of the particular jurisdiction and the facts of the case, the defendant may argue (1) that Zoloft diminished his capacity either to form a specific intent or to understand the nature of his actions; (2) that he was involuntarily intoxicated as a result of Zoloft; (3) that Zoloft rendered him "unconscious" (under California law); or (4) that at the time of the crime he suffered from a significant mental defect induced by Zoloft.

Irrespective of the specific legal theory advanced, in most circumstances, defendants asserting a "Zoloft defense" must prove at least two elements:

1. It is a reasonable medical probability that Zoloft can cause persons to act in a criminal manner (general causation);

2. Zoloft caused this particular defendant to commit a criminal act (specific causation).

Both general causation and specific causation are difficult, if not impossible, for a defendant asserting a "Zoloft defense" to prove. This is so for three basic reasons:

* **There is no study that provides credible scientific support to the allegation that Zoloft can cause a person to become violent toward others.**

* **The effect of Zoloft, as established by studies in animals and man, is to decrease aggression.**

* **Defendants for whom Zoloft has been prescribed are most often individuals who were and are suffering from significant disorders that are associated with violence or hostility.**

No defendant has ever invoked a "Zoloft defense" successfully to escape or reduce a criminal charge.

C. What is Zoloft?

Zoloft is a member of a class of antidepressants known as selective serotonin reuptake inhibitors ("SSRIs"). Prozac (generic name: fluoxetine), manufactured by Eli Lilly & Company, is another antidepressant in the SSRI class, as is Paxil, manufactured by SmithKline Beecham PLC (generic name: paroxetine Hcl).

Zoloft was approved by the United States Food and Drug Administration ("FDA") for the treatment of depression on December 30, 1991. It is manufactured by Pfizer Inc and distributed by Roerig and Pratt Pharmaceuticals, divisions of Pfizer Inc. Zoloft was first released for sale in the United States in February 1992. It has been marketed in the United Kingdom under the trade name Lustral since December 1990. As of May 1993, over 4.9 million prescriptions of Zoloft had been written in the United States, making Zoloft one of the antidepressants most widely prescribed by the medical profession.

Zoloft is available only by prescription. It is supplied in the form of tablets containing either 50 mg or 100 mg of sertraline hydrochloride. All Zoloft tablets have the name "Zoloft" engraved on them.

D. How does Zoloft Work?

The brain is a network of interconnected cells called neurons. These cells do not actually touch each other; instead, there is a small gap, called the synapse, between any two cells. The synapse is the site at which two neurons exchange information, or "talk to each

other." The neurons communicate using chemical messengers called neurotransmitters. The neuron sending the message releases a neurotransmitter into the synapse. The receiving neuron receives the neurotransmitter by means of a receptor specifically designed to accept that particular type of neurotransmitter. This process may be visualized as though the sending neuron releases a key (the neurotransmitter) that travels across the synapse to meet a lock (the receptor of the receiving neuron) on the other side of the synapse. If the key fits the lock, it will "turn" and produce a biological effect on the receiving neuron. Each neuron can transmit or receive a message and pass it along, as appropriate.

Once it has produced its biological effect in the receiving neuron, the neurotransmitter must be deactivated, or "disposed of." The brain uses each of two processes to accomplish this: biochemical degradation and reuptake. Biochemical degradation is a chemical process that occurs when the brain releases enzymes that chemically attack and destroy a neurotransmitter. Reuptake is a physical process in which a neurotransmitter is taken back up by the neuron that released it. Antidepressant medications affect one or both of these processes in order to increase or diminish the number or concentration of neurotransmitters available in the synapses.

The brain contains many different types of neurotransmitters. One of the most heavily studied is serotonin. Serotonin appears to influence several brain functions, including mood, appetite, sexual behavior, aggression, and sleep. [1,2]

Zoloft acts by inhibiting the reuptake of serotonin by the releasing neurons. Zoloft thereby increases the concentration of serotonin in the synapses. Because low concentrations

of serotonin have been associated with depression, it is believed that Zoloft and other SSRIs help alleviate depression by increasing the synaptic levels of serotonin. [3]

Zoloft and the other SSRIs are referred to as second-generation antidepressants. The first-generation, or "classical," antidepressants fall into two categories: (1) Tricyclics, which inhibit the reuptake of serotonin and other neurotransmitters, including norepinephrine, and (2) monoamine oxidase inhibitors (MAOIs), which inhibit the production of an enzyme that degrades serotonin and norepinephrine in the synapses.

The classical antidepressants have been marketed since the 1950's and are still widely prescribed today because no antidepressant is effective for all patients. All else being equal, however, Zoloft and other SSRIs are preferable to the classical antidepressants because SSRIs selectively inhibit the uptake of serotonin and have little effect on the concentrations of other neurotransmitters, and therefore have fewer of the kinds of side effects that may be problematic with tricyclics and MAOIs. SSRIs also are considerably safer in overdose than are tricyclics and MAOIs because they are not as toxic.

E. Indications For Zoloft

Zoloft is approved by the FDA for the treatment of depression. Depression is more than simply feelings of sadness or "the blues." The American Psychiatric Association has published a manual entitled The Diagnostic and Statistical Manual of Mental Disorders, now in a revised third edition (the "DSM III-R"). The DSM III-R divides depression into depressive "episodes" and depressive "disorders." A patient suffering a Major Depressive Episode (as defined in the DSM III-R) will experience at least five of the following symptoms nearly every

day during a two-week period, with one or both of symptoms 1 and 2 being among the exhibited symptoms:

1. depressed mood most of the day as indicated either by subjective account or observation by others;

2. markedly diminished interest or pleasure in all, or almost all, activities most of the day;

3. significant weight loss or weight gain when not dieting, or decrease or increase in appetite;

4. insomnia or hypersomnia;

5. psychomotor agitation or retardation;

6. fatigue or loss of energy;

7. feelings of worthlessness or excessive or inappropriate guilt;

8. diminished ability to think or concentrate, or indecisiveness; and

9. recurrent thoughts of death, recurrent suicidal ideation [suicidal thoughts] without a specific plan, a suicide attempt, or a specific plan for committing suicide.

Thus, depressed mood is only one characteristic of a Major Depressive Episode.

A depressive "disorder" can be one of two different types: a single-episode depressive disorder or a recurrent depressive disorder. A single-episode depressive disorder is a Major Depressive Episode, as defined above. A recurrent depressive disorder is two or more major depressive episodes, each separated from another by at least two months during which there is a return to more or less usual functioning. A "Major Depressive Episode" is also referred to as "unipolar disorder." [4]

There is another affective disorder known as "Bipolar Disorder," often called "manic-depressive illness." A person suffering from Bipolar Disorder will have exhibited at least one Manic Episode. [5] A patient experiencing a Manic Episode (as defined in the DSM III-R) will experience A, B, and C below:

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood.

B. During the period of mood disturbance, at least three of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

(1) inflated self-esteem or grandiosity

(2) decreased need for sleep, e.g., feels rested after only three hours of sleep

(3) more talkative than usual or pressure to keep talking

(4) flight of ideas or subjective experience that thoughts are racing

(5) distractibility, i.e., attention too easily drawn to unimportant or irrelevant external stimuli

(6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation;

(7) excessive involvement in pleasurable activities which have a high potential for painful consequences, e.g., the person engages in unrestrained buying sprees, sexual indiscretions, or foolish business investments.

C. Mood disturbance sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others.

A Manic Episode usually lasts from a few days to a month. [6]

Zoloft is not a treatment for mania but may be used for treatment of the depressed phase of Bipolar Disorder. In this situation, patients are usually stabilized and maintained on a prophylactic medication for bipolar disorder (such as lithium) in order to reduce the risk of mania occurring when the depression is treated. Some patients with Bipolar Disorder will not have experienced a Manic Episode before their first depressive episode (although in Bipolar Disorder, the first episode is usually manic). They may be treated with an antidepressant such as Zoloft for the depression and develop mania during their antidepressant treatment. During pre-marketing testing, mania or hypomania (a less severe form of mania) occurred in approximately 0.4% of Zoloft-treated patients. [7]

Depressive disorder is a highly lethal psychiatric disorder. Approximately 15% of depressed patients die by suicide. [8]

F. <u>Zoloft vs. Prozac</u>

Zoloft and Prozac are in the same class of drugs: selective serotonin reuptake inhibitors, or SSRIs, but Zoloft's chemical structure differs from Prozac's. As a result, there are significant differences between the two medications. For example, Zoloft's 26-hour half life -- that is, the amount of time needed for the body to reduce the level of Zoloft in the blood stream by one half -- is significantly shorter than Prozac's two- to three-day half life. The principal metabolite of Zoloft (that is, the human body's "break-down" product of the active neurochemical that is ingested) has a half-life of two to four days and is significantly less active than its parent compound, while the principal metabolite of Prozac is as potent as its parent compound and has an active half-life of seven to nine days. Furthermore, a study has

shown that many patients who do not tolerate Prozac well because of side effects can be successfully treated with Zoloft. [9]

Prozac has been marketed in the United States since 1988. Because of this, because of its widespread use, and because of allegations of a link between Prozac and violence (made most vociferously by the Citizens' Commission on Human Rights ("CCHR"), a group affiliated with the Church of Scientology), more attention and scientific study has been devoted to Prozac than to Zoloft. It is important to remember that studies regarding Prozac do not necessarily have any bearing on Zoloft, particularly those addressing side effects. A criminal defendant trying to use a "Zoloft defense" will likely point to papers, studies, or other information about Prozac. Most such attempts should be challenged on relevance grounds. You will need to consult an expert psychiatrist and/or pharmacologist to evaluate fully the extent to which any Prozac data might be relevant to a defendant who is attempting to use a "Zoloft defense."

G. Adverse Reactions

As with any drug, a certain proportion of patients taking Zoloft will experience various adverse reactions. During clinical trials, the following adverse reactions were observed in patients treated with Zoloft at a frequency greater than in patients treated with a placebo: nausea, diarrhea or loose stools, dry mouth, insomnia, male sexual dysfunction (primarily ejaculatory delay), somnolence, dizziness, tremor, dyspepsia, and increased sweating. [10] The incidence of side effects such as agitation, anxiety, and nervousness was not significantly different for patients taking Zoloft as compared with patients taking a placebo. [11] The side-

effect profile of Zoloft is considerably different from that of the first-generation antidepressants, tricyclics and MAOIs. [12]

A litigant attempting to invoke his use of Zoloft in defense of a criminal charge or in prosecution of a civil claim may claim that Zoloft causes aggression or suicidal thoughts. As explained more fully below, there is no evidence to support such a claim. In none of the pre-marketing clinical trials was there evidence that the rate of suicide, suicidal ideation (suicidal thoughts), or aggression in patients treated with Zoloft was significantly greater than in patients treated with placebo. The nature of the illness being treated -- depression -- is such that suicide and suicidal ideation are common in the patients being treated, wholly independently of Zoloft. There is no scientifically accepted evidence that Zoloft causes such thoughts or behavior.

II.

HOW A DEFENDANT IS LIKELY TO ATTEMPT TO SUPPORT A "ZOLOFT DEFENSE"

A defendant attempting to invoke a "Zoloft defense" will try to prove that the criminal conduct of which he is accused is a result of Zoloft therapy. As a preliminary matter, a prosecutor must confirm that at the time of the commission of the crime, the defendant was taking Zoloft. Blood tests can determine the presence and level of Zoloft in the blood stream. Because the level of Zoloft in the bloodstream decreases at a steady rate over time, blood levels taken a certain time after a crime can be used to determine blood levels at the time of commission of the crime. The prescribing physician will have information on the dosage level of Zoloft.

In order to invoke a "Zoloft defense" successfully, the defendant will need to demonstrate two elements: general causation (that Zoloft causes persons to act in a criminal manner) and specific causation (that Zoloft caused this particular individual to commit the criminal act). There is no support in the scientific literature for either of these two claims. No currently available data links Zoloft therapy with increased aggression or violence, or with criminal conduct of any sort. Moreover, the effect of Zoloft is to increase the levels of serotonin in the brain. Scientific research indicates that as serotonin levels increase, aggression and hostility decrease. [1,13,14,15]

Given the lack of evidence supporting any sort of "Zoloft defense," the defendant may attempt to rely on data relating to Prozac. This should be challenged because, as stated above, Zoloft is chemically distinct from Prozac, and studies relating to one therefore are not

necessarily relevant to the other. Because defendants are likely to rely on Prozac data, however, it is useful for you to know the history of the controversy that has developed surrounding Prozac.

Prozac was first marketed in the United States in January 1988. It has become the most widely prescribed antidepressant in the United States. The media initially hailed it as a "wonder drug" that was effective in treating various psychological problems.

Allegations about Prozac's inducing aggression, violence, or suicidality first began to gather notoriety in 1989 as the result of one particular incident. In September 1989 a man named Joseph Wesbecker killed seven people and injured 12 in a shooting spree in Louisville, Kentucky. Reports indicated that he was on Prozac at the time. Since 1989, dozens of criminal defendants have unsuccessfully asserted a "Prozac defense," and more than 100 civil lawsuits have been filed against Eli Lilly and Company alleging that Prozac caused violent, aggressive, or suicidal behavior. No plaintiff has succeeded.

The Prozac controversy was fueled in February 1990 when Martin Teicher, M.D., Ph.D., and two colleagues published a paper suggesting an association between Prozac therapy and suicidal ideation. The paper described case histories of six patients who had developed intense, violent suicidal preoccupation after two to seven weeks of treatment with Prozac. The suicidal states of these patients were said to have subsided within three days to three months after discontinuation of Prozac. [16]

The Teicher paper was simply an anecdotal case report of six patients. It did not attempt to compare rates of suicidal ideation between patients given Prozac and patients given

a placebo. Furthermore, the six patients had significant psychiatric histories suggesting that they were predisposed to suicidal ideation. Since the publication of the Teicher paper, numerous other physicians have noted that Teicher's observations do not establish any causal relationship between Prozac and suicidal ideation. [17-24]

Despite the deficiencies of the Teicher paper, it has been relied on heavily by the Citizens Commission on Human Rights and the Public Citizen Health Research Group ("HRG"), an organization affiliated with Ralph Nader. On October 11, 1990, CCHR petitioned the FDA to withdraw marketing approval for Prozac. Among the allegations made by CCHR were that Prozac causes:

- increased suicidality in depressed patients
- obsessive suicidality
- suicidality in non-depressed patients
- excessively violent behavior leading to murder/suicide

In July 1991, the FDA denied CCHR's petition to remove Prozac from the market. [25] The FDA addressed certain accusations made by CCHR as follows:

Suicidality:

The FDA stated that none of the information submitted in the petition, including the Teicher paper, differentiated between suicidality caused by the underlying disease, life events, or drug therapy. Therefore, it could not be concluded that Prozac caused the suicidality. The

FDA also analyzed Eli Lilly & Company clinical data and published clinical studies, none of which reported statistically significant increases in suicidality with Prozac treatment.

Violent Behavior:

The FDA stated that none of the isolated events of supposedly Prozac-related violence presented by CCHR provided persuasive evidence that Prozac causes violent behavior. Regarding pending litigation, the FDA said that, "in spite of repeated attempts to establish a causal relationship between Prozac and violent behavior in judicial proceedings, the petition did not identify a single instance of any court concluding that Prozac causes violent behavior."

In May 1991, HRG petitioned the FDA to revise the approved labeling of Prozac to include a warning of association with suicidal ideation, agitation, and impulsivity. On September 20, 1991, the FDA's Psychopharmacological Drugs Advisory Panel (a panel of 10 independent medical experts) held a public hearing on the issue of whether changes should be made to Prozac's labeling. The panel unanimously concluded that there was no credible evidence of a link between the use of antidepressant drugs, including Prozac, and suicidality or suicidal ideation. A majority of the panel further rejected the call for a change in labeling for Prozac. [26] Numerous mental health groups hailed the FDA's decision. The American Psychiatric Association issued a press release saying that "suicidal thoughts are common among persons with major depression and are specific to the illness, not the treatment." [27] On June 3, 1992, the FDA issued a formal denial of HRG's petition, stating that the evidence

was "not sufficient to reasonably conclude that the use of Prozac is possibly associated with suicidal ideation and behavior (suicidality). . . ." [28]

You should expect that a defendant seeking to use a "Zoloft defense" will attempt to support that claim by reference to the Prozac-related controversy. As stated above, you should challenge the assumption that research or information relating to Prozac is relevant to Zoloft. If a court determines that any of this history or information is relevant, however, you should be prepared to counter it with the FDA findings described above and with the research by reputable experts, as described below.

III.

COUNTERING THE "ZOLOFT DEFENSE"

Defendants invoking the "Zoloft defense" when charged with a violent crime may try to prove one or more of the following:

- Zoloft caused aggressive, violent behavior;
- Zoloft caused akathisia (defined below), which then resulted in violent behavior;
- Zoloft interacted with other drugs or substances (e.g. alcohol) resulting in violent behavior;
- Zoloft caused suicidal ideation, which then resulted in violent behavior.

Each of these allegations is addressed below.

A. Zoloft Has Not Been Medically/Scientifically Linked With Aggression or Violence.

A defendant may allege a relationship between Zoloft therapy and aggressive or violent behavior. Most likely, the defendant will rely on two types of evidence: (1) Evidence relating to Prozac, including the Teicher paper, the accusations by the Church of Scientology, and the history of lawsuits against Prozac; and (2) adverse reaction reports,* filed with the FDA by Pfizer, that report instances of patients who experienced suicidality or suicidal ideation while

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* FDA regulations require a drug manufacturer to report certain instances of an "adverse drug experience." 21 C.F.R. § 314.80(c). "Adverse drug experience" is defined as "any adverse event associated with the use of a drug in humans, whether or not drug related. . . ." 21 C.F.R. § 314.80(a). Because these reports are filed regardless of whether the adverse experience is "drug related," and because many lack trustworthiness for other reasons, including reporter error, they are by no means proof of a causal relationship between the drug and the adverse experience. See Richardson v. Richardson-Merrell, Inc., 649 F. Supp. 799, 801, n. 5 (D.D.C. 1986) (reflecting ruling that adverse reaction reports are inadmissible hearsay and are not reasonably relied upon by experts in the field). The substance of the adverse reaction reports is available to the public from the FDA.

taking Zoloft. For the reasons stated below, this evidence does not support the allegation that Zoloft causes aggressive or violent behavior.

Zoloft was tested in approximately 2,700 patients during pre-marketing clinical studies.* There is no evidence from those studies to support the theory that Zoloft causes aggression. Data from the Zoloft clinical studies reveal no statistically significant difference in the frequency of occurrence of adverse experiences identified as "aggressive reaction" among patients treated with Zoloft, placebo, or a tricyclic. Furthermore, nothing in the post-marketing reports** indicates a causal connection between Zoloft and aggression.

A defendant may attempt to prove a causal relationship by pointing to a few incidents in which a patient taking Zoloft demonstrated aggressive or violent behavior. Such information may be obtained from adverse reaction reports that are required to be filed with the FDA. The defendant may claim that the mere fact that a patient taking Zoloft acts aggressively or violently establishes a link. For the following reasons, the existence of a few individuals who act violently or aggressively while taking Zoloft does not establish a causal link between Zoloft and violence or aggression.

As a preliminary matter, it is worth noting certain facts about violence in the United States. Violence is a widespread phenomenon. According to the FBI, the violent crime rate

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* Pre-marketing clinical studies are studies conducted prior to marketing a new pharmaceutical that are designed to determine its safety and efficacy in humans. In addition, once a prescription drug has been marketed, the manufacturer routinely conducts additional clinical studies to further evaluate the efficacy of the drug.

** Post-marketing reports are reports of adverse effects generated after a drug has been made available to pharmacies and doctors for prescription.

for 1991 was 758 per 100,000 inhabitants, or a total of over 1.9 million offenses. [29] In addition, an estimated 2 million women are battered by their partners each year. Up to 4 million children are physically abused and neglected. [30]

The causes of aggression and violence are far from clear. In the mid-1970's investigators determined that certain kinds of violent outbursts were the result of malfunctions of the limbic system of the brain, believed to be the seat of human emotions. Beyond this demonstrated link, however, the causal relation between brain damage and violence or aggression remains unclear. It is evident that violence is the result of a complex mixture of physiological, social, and behavioral factors. [31]

In light of the difficulty in determining the causes of violence, any claim that a particular incident of violence was caused by a particular medication should be viewed skeptically. This is particularly true because, under scientific principles accepted by the FDA for evaluating the safety and efficacy of drugs, one, or even many, incidents of violence in patients administered a drug do not establish a causal link between a medication and violence.

In order to investigate scientifically whether there is a causal relationship between a medication and violence, one should conduct a study in which the rates of violence are compared between patients receiving placebo and patients receiving the drug. Given the prevalence of violence in society, if large numbers of persons are administered any drug or a placebo, it is likely that some of them will commit a violent act. One could reasonably conclude that there is a relationship between a drug and violence only if, in a properly structured and conducted study, there is a statistically significant increase in the rate of

violence in patients administered the drug compared with patients administered a placebo. In such a study, called a double-blind placebo-controlled study, neither the patients nor the doctors would be informed about which patients were being administered the drug and which were being administered the placebo, thus ensuring unbiased results. Such a study is the best way to determine the existence of a causal relationship.

As stated above, none of the double-blind placebo-controlled studies performed with Zoloft indicates any statistically significant difference in the rates of aggression or violence between Zoloft, placebo, or tricyclic medications. [32] This is much more compelling scientific evidence than are isolated reports of aggression or violence in patients being administered Zoloft.

The absence of any sound scientific evidence to support a claim that Zoloft induces violence is consistent with research regarding the effect of serotonin on human behavior. Zoloft acts by blocking the reuptake of serotonin in the neural synapse and, by so doing, increases the amount of serotonin in the brain. This effect of Zoloft is well-documented in both animal studies and human studies. [1,33] It is also generally agreed that this serotonin-specific increase is Zoloft's primary mechanism of action. [3,10]

It follows, therefore, that a defendant seeking to invoke the "Zoloft defense" is making the following argument: Increasing the level of serotonin in the brain causes people to become aggressive, hostile, or violent. There is no support in the scientific literature for this proposition. Rather, there is overwhelming evidence to the contrary.

Considerable scientific research has been devoted to the study of the biological basis of aggression. There are many scientific papers, known as review articles, summarizing the existing knowledge in the field. [1,2,14,15,34,35,36] This large body of scientific work demonstrates that increasing the level of serotonin in the brain decreases aggression in both animals and humans.

The most common animal model for aggression is that of mouse-killing behavior ("muricidality") in rats. Such behavior is consistently decreased (that is, there is less aggression) by the administration of drugs that increase serotonin levels. [15,37,38] Administration of drugs that activate serotonergic neurotransmission or inhibit serotonin reuptake (i.e., increase the amount of serotonin available in the synapse) have been shown to decrease such muricidal behavior in rats. [39,40]

Furthermore, just as increasing serotonin levels in the brain serves to decrease aggression, studies that decrease serotonin levels consistently increase aggression in animal models. Rats given chemicals to decrease or eliminate serotonin (while leaving other neurotransmitters unaltered) become hyper-aggressive. [39,41] These experiments serve as strong evidence that there is an inverse relationship between brain serotonin levels and aggression.

Another line of research that undermines the thesis of the "Zoloft defense" is the study of the relationship between the level of aggression (as shown by clinical aggression ratings) and serotonin levels (as shown by physiological indices of serotonin in both living human patients and post-mortem analysis). Such research is based upon the following observations:

1. In living patients, serotonin levels can be inferred from levels of a substance called 5-HIAA in the urine or blood plasma. 5-HIAA is the primary metabolite, or biochemical degradation product, of serotonin that makes its way from the brain into the blood and urine. It has been shown that there is an inverse relationship between clinical aggression ratings and levels of urinary or plasma 5-HIAA -- that is, the more aggressive a patient is, the lower the levels of 5-HIAA, and vice-versa. [42-49]

2. In post-mortem studies, it has been shown that victims of violent suicide have lower levels of serotonin in their brain tissue than do victims of non-violent suicide. [50]

Furthermore, recent clinical data based upon studies of human subjects corroborate the animal findings. A recent study undertaken at Harvard Medical School found that anger attacks are "fairly prevalent" in depressed patients. [51] The authors state: "Our results suggest that anger attacks are fairly prevalent among depressed outpatients." These researchers also found that anger attacks dramatically decreased in the majority of patients treated with Prozac which, like Zoloft, increases the serotonin levels in the brain. They sum up the discussion of their report by stating:

> Treatment with fluoxetine [Prozac], a relatively selective inhibitor of serotonin uptake, was clearly followed by a significant reduction in the number of depressed patients with anger attacks.

Similarly, four independent studies show that Prozac administration leads to a decrease in impulsive-aggressive behavior. [52-55] In these studies, patients diagnosed as borderline personality-disordered became less angry, impulsive, and hostile following treatment with Prozac.

Since these scientific studies support the principle that people who demonstrate aggressive, hostile, and violent behavior have below-normal levels of serotonin, it follows that the administration of Zoloft (which increases serotonin) will not lead to an increase in such behavior. Indeed, the scientific evidence strongly suggests that Zoloft should serve as a therapeutic agent to control such behavior, rather than as an agent to exacerbate such behavior.

The studies referred to above are useful because they demonstrate that low serotonin levels in the brain can cause violence and that increasing those levels is beneficial in terms of reducing violence. To the extent that they are used to demonstrate the relationship between serotonin levels and violence, the studies regarding Prozac and other SSRIs are useful. One must bear in mind, however, that Prozac and Zoloft chemically differ from each other. To succeed in using Prozac side effect data in a case against Zoloft, a defendant must demonstrate that because the effects on the serotonin system are similar, the adverse effects must be similar. That theory is refuted by clinical studies that demonstrate that the rates of various adverse reactions differ between the two compounds. [56] The theory is further refuted by a recent study that indicates that many patients who are intolerant to Prozac may be treated successfully with Zoloft. [9]

A defendant might allege that Zoloft induced a Manic Episode, which, in turn, caused him to become violent. In such a case, it will be important to evaluate whether, in fact, the defendant experienced a Manic Episode. As stated above, a Manic Episode usually lasts from a few days to a few months. A defendant who did not experience the symptoms of a Manic Episode either before or after the criminal activity most likely did not experience a Manic

Episode. You will need to investigate the defendant's behavior both before and after the commission of the crime to evaluate an allegation of mania. If the defendant was arrested shortly after the commission of the crime, the arresting and interrogating officers will have important information on this issue. The physician who prescribed Zoloft for the defendant will also be an important source of information.

Even if the defendant did experience a Manic Episode while taking Zoloft, you should not assume that the Zoloft triggered the mania, and that the mania caused the violence. A Manic Episode may have numerous triggering events. Furthermore, a patient experiencing a Manic Episode will not necessarily become violent. These are complex issues about which you will need to consult a psychiatrist for assistance.

B. Akathisia Has Not Been Medically/Scientifically Linked With Violence.

In attempting to establish a causal link between Zoloft and violence, the defendant may try to show that Zoloft causes a condition called akathisia, and that akathisia in turn causes violence. As demonstrated below, no such causal link has been established.

Akathisia (sometimes spelled "akathesia") is a syndrome associated with the use of a different class of drugs -- the antipsychotics, which include Haldol (haloperidol), Thorazine (chlorpromazine), and Mellaril (thioridazine). According to The Pharmacological Basis of Therapeutics:

> Akathesia refers to strong subjective feelings of distress or discomfort, often referred to the legs, as well as to a compelling need to be in constant movement rather than to follow any specific movement pattern. The patient feels that he must get up and walk or continuously move about, and he may be unable to keep this tendency under control. [57]

Another text states: "Akathisia is a motor restlessness in which the patient manifests a great urge to move about and has considerable difficulty in sitting still." [58] Thus, the central feature of the disorder is the patient's felt need to get up and move around.

These sources make the explicit point that akathisia is not to be confused with a psychotic agitation. This distinction is made as follows:

> Akathisias can be confused with psychotic agitation; the patient is driven by motor restlessness and is usually not preoccupied with the psychological content of whatever the agitation is about. The restlessness is primarily motor and cannot be controlled by the patient's will. Unlike psychotic agitation, akathisias are worsened by increasing the antipsychotic dose and are benefited by decreasing the dose. [58]

In practice, the term akathisia is used to define a variety of symptoms, both objective (in the form of a movement disorder) and subjective (in the form of a mental disorder):

> The objective component consists of restless movements of the lower extremities. The subjective component is usually described as a vague sense of inner restlessness and anxiety. "Pseudo-akathisia" has been recently described as the objective motor component without subjective distress.

[59] In fact, "there appears to be no consensus as to the definition of this term." [60] None of the definitions suggests that akathisia leads to uncontrollable aggression, violence, or suicidal behavior. Instead, it is quite clear from these sources that akathisia is not a psychotic episode of general "violence-associated" agitation.

Given the inexactness with which the term "akathisia" may be used, it is important to challenge claims of Zoloft-induced akathisia. It is highly possible that the symptoms and history a defendant alleges may not be true akathisia, but symptoms of his underlying illness. Furthermore, akathisia is not a condition that is likely to appear and disappear suddenly.

Rather, the patient will experience akathisia until the medication that causes it is discontinued (and a certain period of time has elapsed for the medication to be sufficiently removed from the blood stream), or until a different medication is administered to control the akathisia. An expert psychiatrist will be able to assist you in evaluating these issues. If the patient did not actually suffer from akathisia, then any defense relying on medical/scientific research relating to akathisia must fail.

If an expert confirms that the defendant did, in fact, suffer from akathisia, you will then have to evaluate whether Zoloft caused the akathisia. There was no evidence in the pre-marketing clinical studies indicating that Zoloft induces akathisia. There have been a few post-marketing reports of akathisia associated with Zoloft treatment, including two published letters. [61, 62] In most cases, however, other medications that have been associated with akathisia (e.g., antipsychotic medications) were also taken by these patients. In any circumstance in which a defendant claims that Zoloft induced akathisia, you should investigate whether the defendant was taking other medications that might have caused this condition.

The only evidence of any relationship between Zoloft and akathisia are the few reports described above. There have been no scientifically rigorous clinical studies that have demonstrated that such a link exists. You should consult with an expert to prepare to cross-examine a physician who you believe will testify that Zoloft induces akathisia.

In addition to challenging the claim that Zoloft induced akathisia, you also should be prepared to rebut the allegation that akathisia induced violent behavior. There have been a few reports in the psychiatric literature linking akathisia with violence. [59,63,64] However, all of

these reports are anecdotal case studies, in which small populations of patients were studied in an uncontrolled fashion. There have been no large-scale, placebo-controlled studies demonstrating that akathisia leads to violent behavior. In fact, the FDA has gone on record stating that "akathisia is not a cause of unprovoked anger and violence." [25]

C. **There Is No Evidence to Support the Claim That Zoloft, When Taken in Combination with Other Drugs or Substances (for Example, Alcohol) Causes Aggression or Violence.**

The defendant may allege that Zoloft, when taken in combination with other drugs or substances, caused his violent behavior. As demonstrated below, this hypothesis is refuted by evidence developed in the Zoloft pre-marketing clinical trials.

Epidemiological studies have shown that violence is strongly linked to alcohol intake. [65,66,67] Furthermore, laboratory experiments have demonstrated that alcohol intake leads to increased aggression. [68] Thus, it is not surprising that many, if not most, criminal defendants will have consumed alcohol prior to their criminal act.

On the other hand, it also is well known that certain drugs can enhance the sedating effects of alcohol. For example, it is common knowledge that barbiturates (for example, pentobarbital) and anti-anxiety agents (for example, Valium (generic name: dazepan)) for this reason should not be mixed with alcohol.

During Zoloft pre-marketing clinical trials, a study was conducted to evaluate whether Zoloft enhances any of the effects of alcohol. In a double-blind placebo-controlled study, volunteers were administered alcohol 12 hours after the final dose of Zoloft or placebo. Psychomotor tests and tests designed to determine mood and mental alertness were later

administered to the volunteers. The study results indicated that Zoloft alone and in combination with alcohol did not affect psychomotor performance and assessments of mood and well-being (alertness and calmness). [69]

This study shows that Zoloft does not enhance the effects, either cognitive or psychomotor, of alcohol in normal subjects. Therefore, there is no scientific evidence to support the allegation that a defendant's violent behavior could result from the interaction of Zoloft with alcohol.*

Other studies have evaluated the effects of Zoloft when taken in combination with each of several other medications. In none of these studies has it been shown that Zoloft enhances any cognitive or psychomotor effect of the other medications. [72]

D. <u>There Is No Evidence That Zoloft Causes Suicidal Ideation, Nor Is There Evidence That Suicidal Ideation Leads to Violence Directed at Others</u>.

A defendant may allege that Zoloft caused him to experience severe suicidal thoughts ("suicidal ideation"), and that these thoughts caused him to act violently toward someone else. This hypothesis is contradicted by the results of the Zoloft pre-marketing clinical studies.

It is important to bear in mind that suicidal ideation and acts of suicide are inherent in the natural course of depressive illness. Depression comprises the largest single diagnostic group that is associated with suicide. [73] In depressed patients, suicide has been shown to account for 15 per cent of all deaths. [8] Furthermore, 20 to 40 per cent of depressed patients have been estimated to have had suicidal thoughts at least one time. [74] Finally, the overall

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* Clinical studies of the effects of Zoloft on voluntary alcohol consumption in rats have shown that the drug actually suppresses the consumption of alcohol. [70,71]

suicide rate in patients suffering from depression has been reported to be 8 times that found among persons with non-depressive illness and 79 times the rate among persons with no psychiatric diagnoses. [75] Suicidal thoughts and behavior may occur and intensify in depressed patients both during the early phase of treatment, including during therapy with antidepressants, and later during follow-up.

It is clear that depressed patients are at significant risk for suicide. Nevertheless, in the pre-marketing clinical trials for Zoloft, the occurrence of suicidal ideation and suicidal attempts was uncommon. The database for Zoloft demonstrated no statistically significant difference in the occurrence of suicide attempts among patients treated with Zoloft versus patients treated with placebo or a tricyclic antidepressant. Furthermore, the occurrence of suicidal ideation was neither numerically nor statistically greater in Zoloft-treated patients than in patients treated with a tricyclic.* In fact, the scientific evidence indicates that Zoloft has a beneficial effect on suicide and suicidal ideation. In a multicenter clinical trial of 5684 Zoloft-treated patients, 1055 placebo-treated patients, and 1030 patients treated with tricyclic antidepressants, Zoloft ameliorated suicidal ideation significantly better than did placebo and as well as did the tricyclic antidepressants. [76]

The results of the Zoloft clinical trials are consistent with the findings of the FDA's Psychopharmacological Drugs Advisory Committee. At its hearing on September 20, 1991,

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* Suicidal ideation was measured by patient scores and changes in patient scores in Item #3 (the suicide item) of the Hamilton Rating Scale for Depression (HAMD).

the Committee unanimously agreed that there was no credible evidence of a causal link between the use of the antidepressant drugs and suicidality or violent behavior.*

A consensus statement on suicidal behavior and psychotropic medication prepared by the American College of Neuropsychopharmacology concludes that emergent suicidality during antidepressant medication treatment "is not specific to any one type of antidepressant and may therefore be largely a manifestation of the natural course of the illness." It further states that there is no evidence that antidepressants such as the SSRIs "trigger emergent suicidal ideation over and above rates that may be associated with depression and other antidepressants." [77]

A defendant may try to use adverse reaction reports from the FDA as support for his claim that Zoloft induces suicidal ideation or suicide. As explained above, the fact that certain patients taking Zoloft have committed or attempted suicide does not establish any causal relationship between the medicine and the behavior. Given the patient population that receives Zoloft, and given the large number of prescriptions that have been written for the medicine, it is not surprising that some suicides and attempted suicides have been reported to the FDA.

A defendant also may try to cite particular instances of attempted suicide as support for his claim. For example, a defendant may try to show that a particular individual developed suicidal thoughts shortly after initiating Zoloft therapy and that those thoughts subsided after the patient stopped taking the drug. As explained above, this is not the sort of evidence that is

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* At the time of the hearing, Zoloft had not yet been approved for sale in the United States, and therefore the Committee did not review Zoloft-related information. [24] Nothing in the Zoloft clinical studies or elsewhere, however, suggests that the Committee's findings might have been different had it considered Zoloft-related information. In fact, the studies referred to in the text indicate precisely the opposite -- namely, that Zoloft has a beneficial effect on suicidal ideation among depressed patients.

accepted in the scientific community as demonstrating a causal link between a medication and an adverse effect. Standard scientific procedure for evaluating a claimed link between a drug and an event is to use a controlled clinical study, comparing the incidence of the event in patients administered the drug and patients administered a placebo. In a properly controlled study, if the incidence of the event is significantly higher in patients administered the drug than in patients administered placebo, a causal relationship is demonstrated.

The mere fact that a patient experienced suicidal ideation while on the drug and not after administration was stopped does not establish a causal relationship. Suicidal ideation may have been present before treatment with the drug, or it may emerge spontaneously without being caused by the drug. Suicidal ideation is a symptom of the underlying illness, and its emergence may indicate simply that the patient is not responding to treatment. This is particularly likely if, for example, the patient has tried other medications without success, and experiences significant hopelessness when believing that Zoloft therapy is similarly unsuccessful.

Accordingly, it is particularly important that you fully investigate the defendant's prior pharmacological history, treatment history, other psychiatric diagnoses (such as severe personality disorders and bipolar disorder) and history of suicidality, suicidal ideation, and acts of aggression and violence. Other factors that should be investigated are organic mental disorders, alcohol consumption, psychosis, use of controlled substances, perinatal factors, low neuroleptic blood levels, and military combat experience. If present, each of these factors should be discussed with your expert witnesses.

IV.

ZOLOFT PRODUCT LITERATURE

Attached hereto is a copy of the product literature for Zoloft (February 1993 version). This document is sometimes referred to as the "package literature" or "package insert." It is also considered to be the medicine's "labeling," as that term is broadly defined by the federal Food Drug and Cosmetic Act.

Zoloft's product literature is available in various formats. Accordingly, you may see it in the attached form, or in "booklet" form, or as an entry in the Physician's Desk Reference. The substance of the literature is the same, irrespective of the format by which the information is delivered. The content of the product literature has changed slightly since Zoloft was first marketed. These changes are of little relevance to attorneys.

Several comments about the package insert are in order. First, it is written for, and made available to, physicians and pharmacists, not consumers. The package insert does not typically accompany the medicine as it is dispensed to the patient. It is also written in compliance with federal regulations. This fact is significant, because federal law prescribes the headings that must be used, as well as some types of information that must be included. Because of these facts -- in particular because this information is written for and provided to sophisticated health care providers -- attorneys for a criminal defendant or civil claimant can misuse this literature by attempting to oversimplify its language, taking phrases or entire sections out of context, or otherwise seeking to create false impressions with parts of the document.

The package insert must be read with care, in its entirety, and with some understanding of the information it imparts to physicians and other health care providers. Experts whom you intend to call at trial should also review it carefully, as it is often used as a cross-examination tool.

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