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Margaret A. Hamburg  
Commissioner  
Food and Drug Administration

through

Division of Dockets Management  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
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### **Citizen Petition**

Five leading nonprofit consumer, research and medical organizations identified below petition the Food and Drug Administration (FDA) pursuant to the Food, Drug, and Cosmetic Act 21 USC 352, 505(o)(4), and 21 CFR 10.30 to take action to improve the safety information included in the label for CHANTIX® (varenicline) tablets, a smoking cessation aid approved under NDA 021-928.

The petitioners are the Institute for Safe Medication Practices, a nonprofit organization devoted entirely to medication error prevention and safe medication use; Consumer Reports, which serves consumers through unbiased product testing and ratings, research, public education and advocacy; National Center for Health Research, a nonprofit think tank that scrutinizes scientific and medical research with public health implications; National Physicians Alliance, a non-profit organization that promotes health and fosters physicians' active engagement with their communities to achieve high quality affordable health care for all; and Public Citizen, a consumer advocacy organization with more than 350,000 members and supporters.

#### **A. Action Requested**

The petitioners request that FDA amend the Boxed Warning and Indications sections of the label for CHANTIX® (varenicline) Tablets [1] to reflect new scientific information that has become available since the agency required a Boxed Warning in July 2009. We request specifically the following:

1. Clarify and expand the scope of reported serious neuropsychiatric adverse effects in the Highlights and main Boxed Warning to include the full spectrum of events now known: suicidal behavior, aggression/violence, psychosis, and depression.
2. Add language to the Boxed Warnings describing the risk of blackouts, convulsions, and impaired vision, adverse effects that could also endanger others in some settings such as operating aircraft, driving ambulances or large trucks.
3. Add to the Indications section restrictions against use in persons in sensitive or hazardous occupations such as pilots, air traffic controllers, military missile crews, police, fire fighters, and emergency medical workers. Existing actions by the FAA, the Department of Transportation, and the Department of Defense should be expanded by a clear and uniform label restriction that would include non-federal workers.
4. Remove inappropriate promotional material about CHANTIX benefits from paragraph 3 of the Highlights section Boxed Warning. A survey of Boxed Warnings for 10 classes of drugs showed no other Boxed Warning containing extraneous promotional statements about benefit.
5. Delete recently-approved but misleading description of meta-analyses about the neuropsychiatric adverse effects of CHANTIX from the Warnings and Precautions section.

## **B. Grounds**

### **Compelling Scientific Evidence**

The scientific evidence that CHANTIX (varenicline tartrate) increases the likelihood of suicidal thoughts and behavior, aggression/violence, psychosis, accidents, and depression is compelling and thoroughly documented. The adverse effects can be catastrophic, resulting in death, disability, and disruption of marriage, family relationships, and jobs. Severe symptoms can begin with the first doses even before stopping smoking, and many resolve soon after treatment is stopped. In some cases, symptoms reappear if treatment is resumed. The adverse effects of CHANTIX have been documented in three special studies by the FDA Office of Surveillance and Epidemiology (OSE),[2–4] by six studies in the peer reviewed literature,[5–10] and six reviews in *QuarterWatch*, a scientific publication about adverse drug events.[11–16] Psychiatric

adverse effects of CHANTIX have also been observed worldwide and publicly reported in Canada,[17] France,[9] New Zealand,[5] and Australia.[18] The psychiatric adverse effects of CHANTIX have been reported to the FDA steadily and continuously over the eight years since the drug was approved, and have been roughly proportional to patient exposure.[14,16]

### **Why Clear Warnings Are Essential**

Prominent warnings about the psychiatric and other adverse effects of CHANTIX provide important safety benefits to patients and the public. In many cases symptoms appear early, often in the first week, before stopping smoking. Effective patient and physician warnings to stop treatment immediately can prevent tragic events such as suicide and assault. In addition, two kinds of CHANTIX adverse effects—aggression/violence and impaired consciousness/vision—can and have caused injury to others. The highest public health duty to warn involves emphasizing potential serious harm to innocent persons that can be prevented with early and appropriate action.

### **An Estimated 2,500 CHANTIX Victims Compensated**

An exhaustive scientific evaluation of CHANTIX took place over four years in United States District Court, and involved thousands of cases of alleged injury caused by CHANTIX. Millions of pages of scientific data, analysis, and other records were available under seal to batteries of qualified scientific experts representing both the victims and the manufacturer. This mass of evidence was distilled into expert reports that were subject to rigorous legal criteria monitored by a federal judge to ensure that the judgments therein were reliable and met accepted scientific standards. The result of this exhaustive process was that Pfizer, the manufacturer, paid approximately \$300 million in damages to an estimated 2,500 CHANTIX victims.[19] Thousands of other CHANTIX victims were not eligible for compensation because the judge barred payment if the injuries occurred after the July 2009 Boxed Warning.

### **The Need to Update 2009 Warnings**

It is important for the FDA to revisit the Boxed Warnings because its 2008 assessments, through no fault of the agency, substantially underestimated the psychiatric adverse effects and accident risks of CHANTIX. It was not until July 2010 that the FDA learned that Pfizer had failed to properly submit 26,000 adverse event reports, including 589 serious cases, 150 completed suicides, 102 cases of hostility/aggression, and 56 cases of psychosis.[15] In addition, later peer reviewed studies provide important new insights into CHANTIX cases involving aggression/violence, as well as comparisons with other smoking cessation treatments.

## **Information Adverse to Petition**

21 CFR 10.30 requires citizen petitioners to consider and report information adverse to the petition request. Safety concerns have contributed to a 73% decline in CHANTIX patient exposure since 2008, lessening its use in smoking cessation treatment.[16] Clearer warnings might further reduce smoking cessation treatment using CHANTIX. However, safer alternatives of approximately comparable long-term effectiveness are available.

The two Pfizer-sponsored meta-analyses of its clinical trials that were recently added to the product label did not identify psychiatric adverse effects described in the current or proposed expanded Boxed Warning.[1] However, the clinical trials included in the meta analyses were inadequate in methodological design, including patient selection, adverse event ascertainment, and statistical power, to identify the infrequent but serious psychiatric adverse effects now known.

The FDA also conducted an observational study in electronic health records of the Departments of Defense and Veterans Affairs. It reported no difference in the rate of psychiatric hospitalization in the first 60 days after initiating treatment with CHANTIX or the nicotine patch.[20,21] However, those studies can not be considered conclusive because neither the underlying diagnosis codes nor the hospitalization endpoint was validated for regulatory purposes or previously used in a peer reviewed publication. In addition, the psychiatric hospitalization endpoint omits the 85% of reported psychiatric adverse events that do not result in hospitalization.[22] Additional studies and analysis on this topic appear in the **Detailed scientific documentation** section of this document.

### **C. Environmental Impact**

Granting the actions requested in this petition would have no identifiable environmental impact.

### **D. Economic impact**

The economic impact of this petition cannot be determined in absence of adequate data to assess the costs of reduced injuries resulting from more effective and accurate safety warnings.

### **E. Certification**

Signature pages and certification appear at the end of this petition.

## **F. Detailed Scientific Documentation**

### **Part 1: Four Psychiatric Adverse Effects of CHANTIX: the Evidence**

### **Part 2: Impairment in Sensitive/Hazardous Occupations**

### **Part 3: Inappropriate Promotional Material in Boxed Warning**

### **Part 4: Meta-Analysis and Observational Studies**

### **Part 5: References**

## **Section F: Detailed Scientific Documentation**

### **Part 1: Four Psychiatric Adverse Effects of CHANTIX: the Evidence**

The psychiatric adverse effects of CHANTIX fall into these four psychiatric diagnostic categories: suicidal behavior, aggression/violence, psychosis, and depression. The primary scientific evidence in this section is shown in Table 1.

<b>Table 1. Key studies of CHANTIX side effects</b>	
<b>Short Description</b>	<b>Type</b>
CHANTIX Aggression/Violence Case Series	Case series
Aggression/Violence PRR Study	Disproportionality analysis
Suicidality/Depression in Smoking Cessation	Disproportionality analysis
British Adverse Event Summary	Adverse event comparison
French Pharmacovigilance Study	Case/non-case analysis
FDA suicidal behavior study	FDA OSE Review
FDA Other Psychiatric events	FDA OSE Review
FDA Road Traffic Accidents	FDA OSE Review

Abbreviations: OSE = Office of Surveillance and Epidemiology

Many CHANTIX psychiatric episodes share distinctive features and overlap these four analytical categories: An episode of paranoia may lead to or involve violence. Aggression and rage are rechanneled and result in self-harm. Depression may lead to suicidal behavior. Sleep disturbances may border on exceptionally vivid dreams that resemble psychotic hallucinations. Sleep disruptions have erupted in violence.

This analysis focuses on the most clearly researched common features that include early onset, often before stopping smoking; remission on discontinuation; a senseless act in patients with no previous psychiatric history; and rechallenge, the reappearance of symptoms if the medication is restarted. There is less published scientific information

available for two additional subsets of psychiatric cases: a) Cases that begin on discontinuation; b) Cases where the adverse effects are persistent. These cases require further research.

### **Suicidal Behaviors**

Suicidal and self-injurious thoughts and acts are a prominent and established side effect of many therapeutic drugs, with at least 58 drugs currently carrying some form of warning on the product labels.[10] For CHANTIX, suicidal ideation, attempted suicide, and completed suicide carry the most prominent label warning language and have been documented through multiple sources. The 2008 FDA OSE Suicidal Behavior Study of adverse event data [3] had only limited cases available but concluded:

*“The AERS data suggest a possible association between suicidal events and use of varenicline and bupropion, given that there were postmarketing cases of positive dechallenge/rechallenge, close temporal relationship between the event and drug use, and the occurrence of suicidal events in patients without any psychiatric history.”*

This report was a primary source in the FDA decision to mandate a boxed warning in 2009.

A peer-reviewed survey of British adverse event data found a disproportionate number of cases of suicidal behaviors for CHANTIX, notably fewer cases for bupropion, and few or none for nicotine replacement products. For completed suicides, for example, there were 22 reported for CHANTIX, 6 reported for bupropion, and none for nicotine products. For suicidal ideation, there were 377 cases reported for CHANTIX, 131 for bupropion for all indications, and 2 for nicotine.[8] Exposure to nicotine replacement products was 7 times larger than varenicline, but bupropion exposure for smoking cessation could not be assessed because of its multiple indications.

A larger and more formal disproportionality analysis reported similar results in a peer-reviewed study.[10] When CHANTIX was compared to nicotine replacement products for suicidal/self injury, the odds ratio (OR) was 8.4, (95% CI 6.8-10.4). For CHANTIX compared to bupropion the results were: OR = 2.9 (95% CI 2.3-3.7). The large number of CHANTIX reported cases also adds scientific weight to the findings. In the Suicidality/Depression in Smoking Cessation study, CHANTIX accounted for 1,818 reported cases of suicidal thoughts or behavior compared to just 50 for nicotine products, even though patient exposure to nicotine replacement products was much greater and measured over a longer period of time. [10]

Suicidal behaviors were also prominently featured in regulatory agency reports of adverse events in Canada [23] and Australia,[18] and in the New Zealand patient monitoring study.[5]

**Aggression/Violence**

Thoughts and acts of aggression/violence associated with drugs are quite familiar (such as domestic violence associated with alcohol intoxication), but the association with correctly administered therapeutic drugs (involuntary intoxication) has not been well studied in systematic scientific research.

CHANTIX, however, has proved a valuable research topic because adverse event reports were so numerous, and they occurred in a diverse smoking cessation population (most often women of middle years) where fewer alternative causes of violence were likely confounding variables.

The FDA’s OSE studied five report terms describing aggression and violence using a Bayesian statistical technique applied to a small early subset of CHANTIX adverse event data.[4] The primary measure—Empirical Bayes Geometric Mean (EBGM)—returned a relative risk equivalent compared to all other drugs that ranged from 17.1 for homicidal ideation to 5.4 for hostility. In comparison, bupropion had an EBGM of 4.4 for homicidal ideation and no reported cases of hostility.

A peer-reviewed study of violent thoughts and acts reported for all evaluable drugs used a different statistical technique to measure disproportionality—the Proportional Reporting Ratio (PRR)—and a much larger universe of all case reports from all drugs from 2004 through the third quarter of 2009.[6]

**Table 2.** Drugs prescribed for smoking cessation.

Drug Name	PRR*	$\chi^2$	P Value	Violence Cases	All Cases
VARENICLINE	18.0	5172	p<0.01	408	11393
BUPROPION**	3.9	70.6	p<0.01	35	3689
NICOTINE	1.9	3.6	p=0.059	11	2383

\*Proportional Reporting Ratio.  
 \*\*All indications of this antidepressant drug.  
 doi:10.1371/journal.pone.0015337.t002

This Aggression/Violence PRR study identified 31 drugs associated with thoughts and acts of violence and ranked them by PRR (a relative risk concept). The study compared the proportion of aggression/violence events for each drug, to the proportion for all other drugs, thereby adjusting for differences in the total number of reports. CHANTIX accounted for more thoughts/acts of violence than any other therapeutic drug by all measures in the study.

Table 2 shows that CHANTIX accounted for 18 times as many reports of violent thoughts and acts as would be expected given the total number of reports for that drug (PRR = 18), and compares it to two other smoking cessation treatments. CHANTIX accounted for 408 cases in total, more than any other therapeutic drug, even though it was only marketed for 14 of the 23 calendar quarters in the study. Bupropion also indicated increased risk but to a lesser degree.

A French pharmacovigilance research team performed a related case/non-case study in the French Pharmacovigilance Database.[9] Although the French data universe was substantially smaller, the Reporting Odds Ratio (ROR) for CHANTIX was 29.2 (95% CI 10.8-78.9). Note that the CHANTIX PRR of 18 in the U.S. study overlaps the broad confidence intervals in the French study.

**Table 3. Leading suspect drugs in homicidal ideation cases, 2007-2013 Q3\***

Rank	Drug name	Number, pct
1	Varenicline	306 (24.3)
2	Quetiapine	59 (4.7)
3	Montelukast	51 (4.0)
4	Duloxetine	48 (3.8)
5	Interferon beta	43 (3.4)
6	Sertraline	38 (3.0)
7	Paroxetine	35 (2.8)
8	Venlafaxine	31 (2.5)
9	Atomoxetine	28 (2.2)
10	Pregabalin	26 (2.1)

An additional study in *QuarterWatch* examined all reports of homicidal thoughts for all drugs, but focused on all the adverse event data from 2007 through the third quarter of 2013, essentially capturing the entire period CHANTIX was marketed. An unadjusted ranking is shown in Table 3.[16]

These data show that CHANTIX accounted for more reports of homicidal ideation than any other therapeutic drug over a 75-month period. The number of cases was 5-times larger than second-ranked quetiapine, and 12-times larger than pregabalin. In 2013 Q3 all the other drugs on the list of 10 most frequently reported drugs had greater patient exposure than CHANTIX, except for interferon beta, where exposure was unknown and the patient population is smaller.

## Psychosis

Psychosis may involve auditory or visual hallucinations, paranoia, delusions, or disorganized speech. These may involve acts of violence related to the delusions or paranoia. These are not typical symptoms of smoking cessation.

Psychotic behaviors have been identified in CHANTIX patients in clinical studies [24], the Pfizer-Tonstad meta-analysis [25], an FDA OSE report[4], and in *QuarterWatch* assessments [11].

The 2008 FDA OSE report identified 98 cases of psychosis for CHANTIX with 3.5 times as many cases as bupropion, adjusted for prescription volume. The OSE disproportionality analysis compared CHANTIX to all other drugs and showed an

unexpectedly large number of reports for eight different symptoms ranging from an EBGM of 7.7 for paranoia to 3.5 for hallucinations. In these OSE data, psychosis reports (n = 98) were more numerous than and disproportional to those categorized as aggression (n = 48). The report also quoted Pfizer as stating two cases were seen in preapproval clinical studies. In the Pfizer-Tonstad meta-analysis of selected clinical trial data, “Disturbances in thinking and perception” were reported more frequently with CHANTIX than placebo (13 vs 2 cases, RR = 3.29, p = not significant).

The New Zealand Prescription Event Monitoring Program [5] provided additional insights because despite a relatively small population of 3,415 patients, it had access to medical and other records, which provides an improved follow-up compared to adverse event reports. It also conducted case causality assessments. This report identified three cases of hospitalization for psychosis; all occurred within 2 weeks of starting CHANTIX and all resolved on discontinuation of CHANTIX.

A small Pfizer-supported clinical trial [26] in patients with previous mental illness compared 208 patients on CHANTIX with 204 taking nicotine replacement therapy. It reported one CHANTIX case as “a severe psychological reaction likened to a ‘bad LSD trip’, including anxiety, paranoia, confusion and impaired motor control.” It was not reported whether symptoms resolved on discontinuation and no case was reported in the comparison group.

In the initial 2008 *QuarterWatch* report on CHANTIX adverse events, reports of psychosis/psychotic disorders (n = 397) outnumbered those of suicide/self-injury (n = 227).[11]

In the most recent FDA adverse event data for the 12 months ending 2013 Q3, report totals for the two kinds of injury were similar: Psychosis (n = 102) and suicide/self-injury (n = 123). In both comparisons, however, a case could include symptoms in both categories.[16]

## **Depression**

Depression raises measurement and identification issues because it varies in severity and waxes and wanes, rather than being a single dramatic episode such as completed suicide or psychotic break, and has much higher prevalence. In addition, although it was prominent in the 2009 Boxed Warning, a specific FDA OSE report supporting the regulatory action was not identified. However, strong evidence that CHANTIX causes or exacerbates depression can be seen in numerous other reports.

In the Suicide/Depression Smoking Cessation Study [10], the depression odds ratio for CHANTIX compared to nicotine replacement products was similar to the suicidal behaviors: OR = 8.5 (95% CI 6.5-11.0). As with suicidal behavior, the volume of cases

adds scientific weight. CHANTIX accounted for 2,000 reported cases of depression assessed as serious, compared to 58 for nicotine replacement products.

In the initial 2008 *QuarterWatch* report on CHANTIX, reports of depression (n = 287) were second only to nausea, the most frequent side effect in clinical studies. In the Pfizer-Tonstad meta-analysis, depression was the second most frequently reported psychiatric side effect.

Reports of depression have continued for many years. In the FDA adverse event data 12 months ending 2013 Q3, “Depression” was the single most frequent adverse event term for the drug (n = 93).

### **Distinctive Features of CHANTIX Reactions**

While the four psychiatric event categories in this petition—suicidal ideation and behavior, aggression/violence, psychosis, and depression—capture the spectrum of CHANTIX adverse effects, they do not fully portray the unique character that distinguishes many CHANTIX events. Examining individual cases and case series provides insight into CHANTIX events and show how to identify and prevent them.

#### **Case # 1: Assault**

*By the third day of taking Chantix I was completely out of control. I woke my boyfriend up in the middle of the night and started physically beating him. I contemplated suicide about 5 times a day and contemplated homicide about 3 times a day.*

This case shows early onset prior to smoking cessation, sleep disturbance, homicidal ideation, suicidal ideation, and later but not shown here, attempted suicide. Female, age 24, (ISR 5742066\*)

#### **Case #2: Terrifying Nightmares**

*She had a nightmare on 23Dec2007 that she was lying in prison laying on a cold wet floor shackled to a corpse. On 26Dec2007 she wanted to get the key to the gun cabinet and shoot her husband.” She stopped taking Chantix and “everything setting her off resolved on 28Dec2007.”*

This case shows a sleep disturbance so vivid it approaches a hallucination, and is followed by an apparently unrelated episode of homicidal ideation and dechallenge. Female, age 43 (ISR 5587336)

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\* ISR = FDA Individual Safety Report number

### **Case # 3: Anger/Aggression**

*She swung at her mother (who was in her late 90's) due to the extreme rage as she almost struck her and missed. She went out in the back yard and broke a weed wacker, a couple of glasses, the frame work on a couple of lamps, she threw concrete in the backyard and she began stabbing chunks of wood with the garden tools to get her rage out.*

In this case report reviewed by FDA OSE the index event was suicidal ideation, but the narrative excerpt portrays uncontrolled aggression/anger and senseless violence.[4]

### **Case #4: Screaming and Crying**

*On Saturday while at home she got into a verbal argument with her mom over a minor issue and reports now that she was 'totally out of hand' and she was unable to control her impulses and was yelling and screaming and crying. She acutely became suicidal and also became homicidal threatening her mother with a shotgun. Her mother fled the house and called police. She locked herself in the bathroom and eventually calmed down.*

Suicidal behavior and senseless aggressive acts occur together. Female, age 21 (ISR 5821157)

### **Case #5: Suicide Attempt**

*After 2 weeks of taking Chantix, I flew into a fit of uncontrollable rage after consuming alcohol one evening – resulting in me beating my boyfriend, followed by an attempt to take my own life. An overnight stay in the ER followed.*

Senseless aggression and suicide attempt. Symptoms resolved on discontinuation. Female, age 28 (ISR 5626093)

### **Case #6: Homicide**

*Appellant was nineteen years old and had been in the service for approximately a year. Prior to enlisting, Appellant was an active member of his community and led various volunteering and mentoring projects as an Eagle Scout. Upon turning eighteen, both Appellant and his twin brother enlisted in the United States Army. After successfully completing Infantry Training and the Airborne Course, they were both selected for an appointment to the United States Military Academy Preparatory School (USMAPS), class of 2009. [Was temporarily assigned to a supply room at Fort Benning and prescribed Chantix ].*

*Appellant had been experiencing “new and strange thoughts” including a “person [was] telling me . . . dangerous things that aren't [sic] me.” These included violent thoughts of killing someone. On May 18, 2008, one month after the Army doctor prescribed Chantix, Appellant fatally attacked Private (PVT)*

*Bulmer while he was sleeping, stabbing him to death. Prior to this attack, Appellant did not know nor had he ever interacted with PVT Bulmer.*

This case includes nightmares, psychosis, homicidal ideation, senseless act, and homicide. Male, age 19. Extracted from appeals court judgment reversing his murder conviction because the judge did not allow a CHANTIX defense of involuntary intoxication.[28]

### Published Case Series

Based on a peer reviewed case series analysis of 26 cases involving thoughts and acts of aggression/violence in association with CHANTIX [7], the distinctive characteristics of these events are described in Table 2, reproduced below from the published study. This is one of the first studies that examined the characteristics of cases of violence associated with involuntary drug intoxication.

Characteristic	Cases/ Observed, n (%)
Inexplicable and unprovoked act	26/26 (100)
Victim anyone nearby	26/26 (100)
Symptoms within first week of treatment	16/18 (89)
No prior history	24/26 (92)
Resolved on discontinuation	13/14 (93)
Nightmares, sleep disturbances	17/26 (65)
Uncontrollable rage explicitly stated	16/26 (62)
Aggression/violence to both self and others	11/26 (42)

### Findings Are Robust

The scientific evidence that CHANTIX causes four types of psychiatric adverse effects is robust. The numbers of reported cases are so large it would be illogical to conclude that thousands of trained medical professionals who observed these cases were always wrong. It would be illogical to discount the reports of thousands of consumers who told of frightening or destructive experiences with CHANTIX that had never occurred before. This disproportional reporting of CHANTIX psychiatric adverse effects was established using three different statistical methods: Proportional Reporting Ratio, Reporting Odds Ratio, and a Bayesian method, the Empirical Bayes Geometric Mean (EBGM). Consistent results were seen by different research teams in the United States, France, and New Zealand. Many cases were confirmed using case-causality tools. They showed events occurring in patients with no previous history of psychiatric illness in which symptoms began soon after starting treatment, often prior to quitting smoking. In most—but not all—episodes, symptoms resolved on discontinuation. In addition, cases from multiple sources documented that symptoms resumed if treatment started again.

## **Limitations**

Although reports are numerous, worldwide, and extend over many years, they do not provide a reliable estimate of the incidence of serious psychiatric adverse events in CHANTIX patients. The observational studies and meta-analysis studies below suggest that such cases, although catastrophic and distinctive, are comparatively rare. This is a characteristic shared by many well-documented serious adverse effects such as Stevens-Johnson syndrome, rhabdomyolysis, osteonecrosis of the jaw, and progressive multifocal leukoencephalopathy (PML). All these adverse effects are rare and are seldom identified in clinical trials. Further, while many of the adverse event cases described above included specific causality assessments, the statistical studies were based on all submitted reports. However, these limitations would apply to all of the comparison drugs; there is no evidence that the CHANTIX reports were uniquely defective.

## **Part 1 Conclusion**

Studies from multiple sources using varying scientific approaches demonstrate that CHANTIX causes serious psychiatric adverse effects. The first paragraph of the Boxed Warning Highlights should state:

**Serious neuropsychiatric events have been reported in patients taking CHANTIX, including suicidal behavior, aggression/violence, psychosis, and depression.**

These same four adverse effects should also be delineated more clearly in the longer Boxed Warning in the main section of the product label.

## **Part 2: Impairment in Sensitive Occupations**

It is self-evident that a drug capable of inducing episodes of anger, rage, psychosis, and hostility should be banned in sensitive occupations such as pilot, air traffic controller, military crews, police, and many other military personnel. The CHANTIX accident risk also extends to a series of neurological (or possibly cardiac) effects that include blackout/syncope, convulsions, and impaired vision. Less severe forms of impairment include dizziness and somnolence.

### **Evidence**

Concerns about the use of CHANTIX in sensitive or hazardous occupations were published as early as May 2008.[11] Of particular concern were reports of accidents and injuries (n = 173) and in particular 28 road traffic accidents. Another 148 case reports indicated vision disturbances with the potential to cause accidents.

The FDA OSE followed up on those published findings with its own assessment in October 2008, “Varenicline and automobile accidents.”[29] By this later date, the FDA knew about 441 cases of accidents and injuries, including 68 road traffic accidents. The FDA analyzed 39 cases and listed contributing factors, in order of frequency, as anxiety-related, abnormal behavior, memory impairment, visual disturbance, dizziness-related, and loss of consciousness.

That 2008 FDA report was the first and possibly only assessment to examine event onset, and the results raised an additional safety concern. Unlike many psychiatric adverse effects where onset appeared to be quite early, that was not necessarily the case for these adverse effects. It showed that in 7/35 (20%) of cases the impairment/accident occurred between 60 and 140 days after initiating treatment. Given a recommended initial treatment period of 12 weeks (84 days) this means that his adverse effect could appear at any time during treatment despite no serious initial reactions.

The accident/ impairment risks are also supported by the clinical trials data.[1] In the current product label description of clinical trials experience, these are *frequent* neurological adverse effects: disturbance in attention, dizziness, sensory disturbance. *Infrequent* events included amnesia, syncope, tremor, and psychomotor hyperactivity.

### **Actions Taken**

Currently, the Federal Aviation Administration has banned the use of CHANTIX by pilots and air traffic controllers.[30] The Department of Defense has banned it for pilots, missile crews, and possibly other military personnel.[31] The Department of Veterans Affairs has restricted CHANTIX only to patients who have failed alternative smoking cessation treatments, and requires psychiatric screening before use and weekly

monitoring.[32] We do not know whether state or local entities have restricted CHANTIX in other sensitive occupations such as police, fire fighters, ambulance drivers, nuclear power plant operators, and construction crane operators.

The FDA required a specific label warning for accident risk, noting reports but stating “Advise patients to use caution driving or operating machinery or engaging in other potentially hazardous occupations until they know how CHANTIX may affect them.”

## **Part 2 Conclusion and Actions Requested**

The Indications section of the label should contain a clear and unambiguous restriction on the use of CHANTIX in hazardous or sensitive occupations. The list should include as examples specific occupations such as airline pilot, military missile crew, nuclear power plant operator, and police officers who carry weapons in the field.

Deficiencies in the current warning increase safety risks because the vague phrase “*until they know how CHANTIX may affect them*” implies that in the absence of early symptoms there is no further risk. On the contrary, neurological or cardiac impairment can occur at any time during treatment. This vague statement increases risk of accidental injury and should be removed without delay.

### Part 3: Inappropriate Promotional Material in Boxed Warning

The Highlights section Boxed Warning may be unique in FDA regulation because in addition to the warning, it contains promotional material about the benefits of smoking cessation. Here is the passage, which FDA documents show was inserted at the request of Pfizer.

*Weigh the risks of CHANTIX against benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.*

The benefits of quitting smoking are well known. The petitioners request that this promotional language be removed for two reasons: a) The force and clarity of the FDA’s most important warning format should not be diluted with extraneous benefits information; b) The specific promotional language is misleading and not an accurate summary of CHANTIX benefits.

#### Diluting Warnings

Because it was not feasible to screen more than 60,000 product labels on the FDA/National Library of Medicine web site, the petitioners inspected Boxed Warnings for a diverse sample of drugs in 10 different therapeutic classes. The following table shows the drugs and type of adverse effects identified for this most prominent FDA warning type.

Table 3 shows that the types of risks described are all appropriate for a Boxed Warning and of roughly the same severity or clinical importance as the psychiatric adverse effects of CHANTIX. However, not one of the 10 Boxed Warnings contained even a

<b>Drug</b>	<b>Class</b>	<b>First listed risk</b>
Etanercept	Anti-TNF	Serious infections
Fentanyl	Synthetic opioid	Addiction, abuse
Natalizumab	Multiple sclerosis	Fatal brain infection
Methotrexate	Anti-neoplastic	Bone marrow suppression
Duloxetine	Antidepressant	Suicidal behavior
Testosterone	Sex hormone	Virilization of children
Risperidone	Anti-psychotic	Increased deaths in elderly
Drispirenone	Sex hormone	Blood clot risk
Lamotrigine	Anti-epileptic	Serious skin rashes
Isotretinoin	Acne medication	Birth defects

sentence or phrase about treatment benefits. In fact it would be quite odd for an anti-neoplastic drug to contain language about the importance of treating cancer in the warning section.

## **Specific Misleading Content**

The sentence “*The health benefits of quitting smoking are immediate and substantial*” is misleading because none of the clinical trials of CHANTIX have demonstrated an “immediate” or “substantial” health benefit. In smoking cessation literature, that passage normally refers to the fact that while pulmonary toxicity of tobacco products takes years to resolve, reduced cardiovascular risk is the most important immediate benefit of quitting. In the case of CHANTIX the opposite is true. Meta-analysis has shown 30% increased cardiovascular risks [33] over 52 weeks of treatment rather than the lower risks predicted by other smoking cessation studies. Thus, for CHANTIX this statement is at best unproven, and probably false.

The sentence “*CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo*” is vague and could be misunderstood. The placebo group was an unusual and unique comparison group. Enrolled patients were informed they might be given medication that investigators believed could reduce their tobacco craving, but instead, by getting a placebo, many subjects underwent abrupt nicotine withdrawal symptoms. Typically in clinical trials, most placebo controls are not subject to harmful effects. The Boxed Warning statement also might lead to an overestimation of the likely results of CHANTIX smoking cessation treatment. Clinical trials with 52-week follow up showed confirmed abstinence rates that ranged from approximately 21% for CHANTIX compared to 14% for bupropion and 10% for “placebo.[1]” In addition, the current label omits the most relevant efficacy study, which compared CHANTIX to the nicotine patch. In that study, at 52 weeks there was no statistically significant difference between CHANTIX and nicotine replacement in 7 day point prevalence of abstinence (34.8% vs 31.4%,  $p = 0.285$ ) and a small difference in continuous abstinence rate (25.9% vs 19.8%,  $p = 0.04$ ). Moreover, the analysis of efficacy belongs in Section 14, the Clinical Studies section of the label.

## **Part 3 Conclusion**

The entire paragraph of misleading promotional information should be removed from the CHANTIX label Boxed Warning. The agency’s most important warning statements should be brief and focused to maximize their impact to promote drug safety, not diluted with other material.

## Part 4: Meta-Analysis and Observational Studies

Sound drug risk analysis should be based on the full scope of scientific information available, including mechanism of action, case reports in clinical studies, spontaneous adverse event reports, meta-analysis of clinical studies, and observational studies.

On September 17, 2014, the FDA approved a new version of the CHANTIX label that described two new meta-analyses (unpublished) and four observational studies.[1] The studies are shown in Table 4. The first two observational studies shown in the Table 4 as “FDA DoD Hospitalization” and “FDA VA Hospitalization” are very similar, were led by the same FDA OSE team using the same endpoint in two different databases, and were reported together in the same Drug Safety Communication. [20]

<b>Name</b>	<b>Type</b>	<b>Status</b>
Suicidal Ideation/Behavior	Meta-analysis	Unpublished
Psychiatric Adverse Events	Meta-analysis	Unpublished
FDA DoD Hospitalization	Observational	Published
FDA VA Hospitalization	Observational	Unpublished
British Medical Records Study	Observational	Published
Danish Health Records Study	Observational	Published
Source: CHANTIX 9-17-14 label		

### Key Scientific Questions

The scientific question is whether studies with no statistically significant difference with a comparison group provide an assurance of safety (since no increased risk was seen) or whether the methodologies were simply incapable of detecting a difference if one existed. Did these studies have an appropriate sample, validated outcome measures, and adequate control groups to demonstrate whether or not CHANTIX increases the risk of psychiatric adverse effects? Finally a pivotal regulatory question is whether these studies are so well done and compelling that they should persuade the scientific community to disregard or discount all the other evidence gathered through other methods.

All six studies detected no statistically significant differences in selected psychiatric adverse effects between CHANTIX and various comparators. All six studies share the methodological flaw that they could only assess a small fraction of the four serious CHANTIX psychiatric side effects, suicidal behavior, aggression/violence, psychosis, and depression. This is a critical drawback in assessing serious psychiatric adverse effects known to be rare.

- The Suicidal Ideation/Behavior meta-analysis included only five studies and did not assess hostility/aggression, depression or psychosis. In addition, the meta

analysis excluded a majority of 14 or more trials that monitored psychiatric adverse effects.[25] Moreover, one of the five studies was of smokers with a history of schizophrenia; no explanation was given for including that study in a meta analysis with 4 studies of non-schizophrenic smokers. The meta-analysis has not been published in the peer reviewed literature and no justification for the inclusion or exclusion criteria is provided on the label. With so much data excluded without explanation, the results of this meta analysis are questionable and should be excluded from the label.

- The Psychiatric Adverse Events meta-analysis excluded both the most common psychiatric side effects (nightmares/ sleep disturbances), and all of the rarest side effects (a 1% threshold). There is no justification for these exclusions, which bias the results.
- Two FDA OSE observational studies were limited to psychiatric hospitalizations, even though 85% of the four serious psychiatric side effects seen in adverse event data did not result in hospitalization.[22]
- The British Medical Records Study examined only suicidal behaviors and depression, and had limited capability to detect depression because nearly 47% of the study population had present or previous use of antidepressant medication, and was excluded from this calculation.[34]
- The Danish Medical Records study [35] only captured hospitalization and emergency room visits for the first 30 days after CHANTIX use was initiated.
- None of the six studies reported investigating whether the psychiatric adverse effects remitted on discontinuation of treatment.

None of the six studies reported a statistically significant difference between CHANTIX and comparators for any adverse endpoints. However, it is impossible to determine whether this lack of a statistically significant difference was because of a weak design that did not capture all psychiatric side effects or whether it indicates safety. The two FDA OSE studies were based on diagnostic codes in electronic health records that had not been validated. The Danish Medical Record study only compared CHANTIX to bupropion, which also has labeled psychiatric side effects, and only assessed the first 30 days of treatment. None of the studies reported assessing violence/aggression, a problematic endpoint in medical records based studies but one of the most commonly reported.

## **Incidence Evaluated**

Clinical trials and observational studies provide limited basic information about incidence, which is problematic in adverse drug event reporting. In the CHANTIX New Drug Application (n = 3,490 on active drug), clinical studies were conducted in a selected patient population that excluded persons with a mental disorder (including current depression) and those taking nearly any psychoactive or stimulant drug, including the cold medication pseudoephedrine.[24] The sponsor reported 1 CHANTIX suicide and 2 CHANTIX psychosis cases, versus none in comparators. However, this was a very limited study population that is not generalizable to most smokers. CDC estimates that approximately 25% of the public reports having a mental illness in the past year, and that smoking rates are 76% higher among those with current mental illness (36% vs 21%).[36,37]

The Danish Medical Records study reported an incidence of the emergency room/hospitalization events of approximately 2 per 1,000 prescription starts. However, this study could not capture the many psychiatric side effects that would not result in emergency medical treatment or hospitalization.

The New Zealand patient monitoring study used case causality assessment and reported new onset depression in 26 of 3415 patients or approximately 7 per 1000 starts and psychosis in 3 cases.[5]

It is difficult to evaluate acute psychiatric adverse reactions in large studies because of limitations in the availability of those data; most patients are not hospitalized and many such episodes are not included in medical records. The data from these studies therefore provide limited assurance that serious adverse reactions are probably rare, but unfortunately the studies are not adequate to determine the incidence of these adverse reactions because of the aforementioned substantial methodological shortcomings of each of these studies.

## **Part 4 Conclusion**

The meta-analysis and observational study results establish that the four serious psychiatric side effects of CHANTIX may be uncommon. However, none of the studies are of sufficient quality to establish a convincing estimate of incidence, provide a valid comparison to other treatments, or have the scientific weight to refute evidence from other scientific methods.

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**B. Certification and signature pages follow in official filed document**

**Disclosure of Competing Interests**

Report coauthors Moore and Furberg who are associated with ISMP were experts for the plaintiffs in the federal litigation that resulted in Pfizer paying approximately \$300 million to an estimated 2,500 CHANTIX victims. Moore was also an expert consultant to the United States Army Trial Defense Service in the criminal case described herein.