FACSIMILE COVER SHEET

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Regulatory Policy
Divisions of Regulatory Policy I, II, III and IV
10903 New Hampshire Ave., Building 51, 6th Floor
Silver Spring, MD 20993-0002
Phone: (301) 796-3601 or 796-3602
Fax: (301) 847-8437

DATE: 12/16/16

TO: Thomas J. Moore
Michael R. Cohen

FAX #: 215-914-1492

FROM: Tyra Sellman

PAGES: (Including Cover Sheet) 16

COMMENTS:

U.S. FOOD & DRUG ADMINISTRATION

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Thomas J. Moore
Institute for Safe Medication Practices
101 North Columbus St., Ste. 410
Alexandria, VA 22314

Sammy Almashat, MD, MPH
Public Citizen's Health Research Group
1600 20th St., NW
Washington, DC 20009

Michael R. Cohen, RPh, MS, ScD
Institute for Safe Medication Practices
200 Lakeside Dr., Ste. 200
Horsham, PA 19044

Doris Peter
Consumer Reports' Health Ratings Center
101 Truman Ave.
Yonkers, NY 10703-1057

Jean Silver-Isenstadt
National Physicians Alliance
888 16th St., NW, Ste. 800
PMB 835
Washington, DC 20006

Diana Zuckerman
National Center for Health Research
1001 Connecticut Ave., NW, Ste. 1100
Washington, DC 20036

Curt D. Furberg
Wake Forest University
School of Medicine
103 St. George Pl.
Advance, NC 27006

Re: Docket No. FDA-2014-P-1562

Dear Petitioners:

This letter responds to your citizen petition received on October 8, 2014 (Petition), requesting that the Food and Drug Administration (FDA or the Agency) amend the boxed warning and the INDICATIONS AND USAGE and WARNINGS AND PRECAUTIONS sections of the FDA-approved labeling for Chantix (varenicline) tablets. You state that you are seeking these changes to the labeling to reflect new scientific information that has become available since the Agency required a boxed warning for Chantix in July 2009. Specifically, your Petition requests that the labeling for Chantix be revised:

(1) To clarify and expand the scope of reported serious neuropsychiatric adverse effects — in the boxed warning that appears in both the Highlights of Prescribing Information (Highlights) and the Full Prescribing Information parts of the labeling — to include what you characterize as "the full spectrum of events now known: suicidal behavior, aggression/violence, psychosis, and depression"

(2) To add language to the boxed warning in the labeling that describe the risk of blackouts, convulsions, and impaired vision as adverse events that could also endanger others in some settings

(3) To add to the INDICATIONS AND USAGE section of the labeling 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

(4) To remove what you characterize as inappropriate promotional material about the benefits of Chantix from the boxed warning in the Highlights part of the labeling

(5) To delete from the WARNINGS AND PRECAUTIONS section of the Chantix labeling a description of meta-analyses and observational studies about the neuropsychiatric adverse effects of Chantix.

We have carefully considered the issues raised in your Petition. For the reasons stated below, your Petition is denied in part and granted in part.

I. CHANTIX (VARENICLINE) SAFETY AND LABELING BACKGROUND

On May 10, 2006, FDA approved new drug application (NDA) 021928 for Chantix (varenicline), submitted by Pfizer Inc. (Pfizer). Chantix is available in 0.5-milligram (mg) and 1-mg tablets and is indicated for use as an aid to smoking cessation treatment.

The risk of serious neuropsychiatric adverse events associated with varenicline has received FDA's attention since 2007, when FDA first learned about reports of suicidal thoughts and aggressive behavior in patients who had taken Chantix.[1]

In 2008, using the postmarket safety authorities included in the Food and Drug Administration Amendments Act of 2007 (FDAAA), FDA imposed a postmarket requirement (PMR) for Pfizer and GSK, the sponsors of Chantix and Zyban (bupropion

[1] See the November 20, 2007, FDA bulletin, *Early Communication About an Ongoing Safety Review of Varenicline (marketed as Chantix)*, available as archived content on FDA's Web site (http://www.fda.gov/).

hydrochloride (HCl)), respectively; Zyban is another smoking cessation drug product. FDA required Pfizer and GSK to conduct a placebo-controlled postmarket safety outcome trial to further characterize the risk of neuropsychiatric adverse events and to evaluate whether a prior history of psychiatric illness was a risk modifier.[2] Because patients with a history of psychiatric illness did not participate in the initial clinical efficacy trials that supported approval of the NDA, finding out whether the medications were effective in these patients was also important, to understand the balance of risks and benefits. An active comparator of transdermal nicotine was included in the clinical trial design to determine whether nicotine replacement, another pharmacologic option for treating tobacco dependence, offers any advantage or disadvantage with respect to neuropsychiatric effects.

In 2009, after an FDA review of adverse events reported to FDA's Adverse Event Reporting System (FAERS), FDA added a boxed warning for serious neuropsychiatric adverse events, including suicide, to the approved labeling for Chantix and approved a Risk Evaluation and Mitigation Strategy (REMS) for Chantix.[3,4] The REMS required the distribution of a Medication Guide to patients with each Chantix prescription. The goal of the REMS was (and is) to inform patients about the potential serious risk of neuropsychiatric adverse events associated with the use of Chantix.

In September 2014, FDA approved new warnings for the Chantix labeling concerning reports of seizures in patients treated with Chantix and reports of patients experiencing increased intoxicating effects of alcohol while taking Chantix. These new warnings were also included in the patient Medication Guide. In addition, the existing warning about serious neuropsychiatric adverse events was updated to include information about several studies that investigated the risk of neuropsychiatric side effects on mood, behavior, or thinking occurring with Chantix. These included observational studies, as well as Pfizer-conducted analyses of their randomized controlled clinical trial data. The labeling revisions approved in September 2014 also included information about the limitations of the observational studies and about an appropriate interpretation of the findings of these studies. Information about the observational studies and meta-analyses, as well as their limitations, was also included in a Drug Safety Communication issued on March 9,

[2] Pfizer and GSK were encouraged to collaborate on this PMR trial. Pfizer took the lead on designing and conducting the PMR trial, and GSK provided financial support and study drug.

[3] A REMS is a risk mitigation strategy that may be required if FDA determines it is necessary in order to ensure that the benefits of a drug outweigh its risks (see section 505-1 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355-1). A REMS may be required by FDA as part of the approval of a new product, or for an approved product when new safety information arises following approval.

[4] The same boxed warning and REMS was also required for Zyban.

2015.[5]

On October 16, 2014, experts at a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee (2014 AC Meeting)[6] considered whether the boxed warning for neuropsychiatric adverse events should be removed from Chantix's labeling. This examination took place because, based on a reanalysis of clinical trial data and observational studies, Pfizer had requested that the boxed warning be removed. The advisory committee members largely disagreed with Pfizer, with only one member voting for removal. The members who advocated retaining the boxed warning believed that the available information at that time did not warrant removal of the boxed warning. Additionally, the advisory committee members were aware that the required postmarket safety outcome trial was nearing completion, and they sought the results of that trial prior to opining on whether the boxed warning should be removed.

At the end of 2015, Pfizer and GSK completed the postmarket safety outcome trial that assessed the serious risk of neuropsychiatric adverse events with three smoking cessation therapies. The trial was a large randomized, double-blind, active- and placebo-controlled, multicenter study that evaluated the neuropsychiatric safety of varenicline, bupropion HCl, and the nicotine patch for smoking cessation in subjects with and without a history of psychiatric disorders.[7] Efficacy of the smoking cessation products was also measured.

To support FDA's evaluation of the postmarket safety outcome trial, the Agency held a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on September 14, 2016 (2016 AC Meeting), to discuss the completed trial, along with relevant published observational studies, to determine whether these new data supported changes to smoking cessation product labeling.[8] The majority (10 of 19 committee members) voted to remove the

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[5] See the March 9, 2015, Safety Announcement, *FDA updates label for stop smoking drug Chantix (varenicline) to include potential alcohol interaction, rare risk of seizures, and studies of side effects on mood, behavior, or thinking* (March 2015 Drug Safety Communication), available at http://www.fda.gov/downloads/drugs/drugsafety/ucm436960.pdf.

[6] The transcript for the 2014 AC Meeting can be found at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM434007.pdf.

[7] Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomized, placebo-controlled clinical trial. Lancet 2016 Jun 18;387(10037):2507-2520.

[8] The minutes for the 2016 AC meeting can be found at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM524402.pdf.

boxed warning for serious neuropsychiatric events. The committee also agreed with FDA's assessment that data from the available observational studies were insufficient to either confirm or refute an increased neuropsychiatric risk associated with varenicline, due to several methodological limitations.[9] The committee concluded that observational data did not contribute additional insight beyond the findings of the postmarket safety outcome trial.

As discussed in further detail below, based on the results of the postmarket safety outcome trial and input from the advisory committee, FDA has determined that it is appropriate to remove the boxed warning for serious neuropsychiatric events from Chantix labeling.[10] The Warnings and Precautions statement for serious neuropsychiatric adverse events (section 5.1) will remain and will be updated with the postmarket safety outcome trial data. The *Analyses of Clinical Trials* and *Observational Studies* subsections in Section 5.1 will be removed due to the availability of the postmarket safety outcome trial data. It is important to point out that the Medication Guide alerting patients and practitioners about the potential for neuropsychiatric adverse events will be maintained; however, the REMS requirement will be removed. This removal of the boxed warning and related issues are discussed in an FDA Drug Safety Communication issued today, December 16, 2016.[11]

II. DISCUSSION

A. Psychiatric Adverse Effects

You ask FDA to "clarify and expand the scope of reported serious neurological adverse effects" in the two boxed warnings in the Chantix label — the smaller boxed warning in the Highlights section and the complete boxed warning in the Full Prescribing Information. More specifically, you refer to the full spectrum of neuropsychiatric adverse effects associated with Chantix as including (1) suicidal behavior, (2) aggression/violence, (3) psychosis, and (4) depression. You ask that all four be added to the two boxed warnings.

You claim that many psychiatric episodes associated with Chantix share distinctive features and may involve effects from more than one of these categories, such as an

[9] FDA Epidemiology Review (Attachment 1 of the FDA briefing material for the 2016 AC Meeting), available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM520103.pdf.

[10] The boxed warning will also be removed from the Zyban labeling.

[11] See the December 15, 2016, Safety Announcement, www.fda.gov/Drugs/DrugSafety/ucm532221.htm.

episode of paranoia leading to or involving violence (Petition at 5). In support of this claim, you cite various studies, trials, and information developed by FDA's Office of Surveillance and Epidemiology (OSE) (Petition at 6-12). You assert that the scientific evidence supporting these four types of psychiatric adverse events is robust, and that the numbers of reported cases are so large that it would be "illogical to conclude that [the] thousands of medical professionals who have observed these [events were mistaken]" (Petition at 12).

Based on the cases reported to the FDA Adverse Event Reporting System, we agree that suicidal behavior, aggression/violence, psychosis, and depression are adverse events associated with Chantix and that these events can overlap in a given patient.[12] We also agree that these risks should be described in Chantix's labeling. However, as evidenced by the recent postmarket safety outcome trial examining neuropsychiatric adverse events with smoking cessation drugs, changes in mood, behavior, or thinking occurred in patients taking *any* of the smoking cessation treatments (including varenicline, bupropion HCl, nicotine replacement therapies (NRT)) and placebo. It appears that these types of events can occur when patients quit smoking, regardless of whether they used medicines to help them. However, most patients who had changes in mood, behavior, or thinking did not have severe consequences that required hospitalization. The risk of these symptoms was higher in patients who already had mental health conditions, and in those patients, using Chantix and Zyban could increase the risk modestly.

When we made our initial assessment of the neuropsychiatric adverse events with Chantix and Zyban that resulted in the boxed warning, the only information we had was from spontaneous reports of adverse events. Estimating the incidence of an adverse event using spontaneous reports is difficult and often not possible. Because the neuropsychiatric adverse events described in the spontaneous reports were of a serious nature, we decided at that time to require a boxed warning in the labeling. It is not

[12] Association does not equate with causality, however, and FDA does not agree with your reliance on disproportionality analyses or on the total numbers of safety reports to establish causality between Chantix and these adverse events. Disproportionality methods are generally used to identify statistical associations between products and events in their respective databases of safety reports. Such methods compare the observed count for a product-event combination with an expected count. Unexpectedly high reporting associations signal that there may be a causal association between the particular adverse event and the product. Such analyses must be followed by further assessment and should not serve as the basis for establishing causality on their own. Likewise, making inferences regarding causality based on the total number of spontaneous reports is not appropriate, because many factors can affect reporting other than the underlying incidence rate. For example, media coverage and legal actions are known to substantially stimulate adverse event reporting even if the adverse event is not causally related to the drug. Therefore, a careful review of all details in case reports is required to make informed assessments, and neither the number of reports nor disproportionality measures alone should be used to assign causality.

unusual for FDA to require strong warnings in product labeling based on our review of serious adverse events in spontaneous reports At that time, FDA recognized that although spontaneous reports had described serious neuropsychiatric adverse events in patients taking Chantix, the Agency needed a randomized, placebo- and active- controlled clinical trial to systematically evaluate the risk of neuropsychiatric adverse events in a population of smoking cessation patients broader than that included in the premarket clinical trials. As a result, we required Pfizer and GSK, the sponsors of Chantix and Zyban, respectively, to conduct a clinical trial to assess the serious risk of neuropsychiatric adverse events.

Consequently, the sponsors of Chantix and Zyban conducted a large randomized, double-blind, active- and placebo-controlled trial, with the following treatment arms: varenicline, bupropion, NRT, and placebo. The trial needed to compare the risk of clinically significant neuropsychiatric adverse events, including, but not limited to, suicidality, and also determine whether individuals with prior history of psychiatric disorders are at greater risk for such adverse events compared to individuals without prior history of psychiatric disorders. Finally, the trial needed to be sufficiently powered to adequately detect clinically significant neuropsychiatric events with each treatment and in both of the two subgroups (those without and with a history of psychiatric disorder).

FDA received the results of the postmarket safety outcome trial at the end of 2015. FDA's review of the trial data revealed several issues limiting our confidence in the sponsors' reported frequencies of primary neuropsychiatric events. However, a variety of sensitivity analyses performed to address the trial conduct issues did not change the overall conclusion of the primary analysis which showed that (1) none of the smoking cessation treatments appeared to increase the risk of neuropsychiatric events in patients without a history of psychiatric disorders, and (2) in patients with a history of psychiatric disorders or current illness, both varenicline and bupropion HCl had numerically higher frequencies of events in all analyses.[13] In addition, FDA was able to confirm the sponsors' finding that all three of the smoking cessation medications are effective both in patients with and without a history of psychiatric disorders. Furthermore, performing sensitivity analyses that excluded patients with previous experience with the study drugs, as well as using a different approach to imputation of missing data, all confirmed the efficacy of the three studied products.[14]

[13] Some of the bupropion-related events appeared to involve precipitation of mania in patients with a known affective disorder, which is a labeled risk of bupropion.

[14] See FDA Briefing Document, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM520103.pdf

The results of the postmarket safety outcome trial, as well as updated FDA reviews of observational studies, were discussed at the 2016 AC Meeting. Because of the specific concerns to be discussed, special government employees with a variety of backgrounds were also added as voting members for this meeting, including individuals with general internal medicine background, clinicians involved in treating smoking addiction and smoking cessation research, and some of the experts involved in the 2014 AC Meeting.

The principal issues that were discussed at the 2016 AC Meeting included the following topics:

- The strengths and weaknesses of the completed postmarket safety outcome trial with regard to the study design, including the novel primary endpoint
- The potential impact of the variability in data collection, adverse event coding, and case definition on the primary endpoint
- Which analyses and results most appropriately described the effect of the smoking cessation therapies on neuropsychiatric events
- The contribution of the evidence from observational studies added to the Chantix labeling in September 2014 when evaluating the risk of serious neuropsychiatric adverse events in patients taking smoking cessation products
- The impact of psychiatric history on the occurrence of neuropsychiatric adverse events during smoking cessation therapy
- Whether the boxed warning should be removed, modified, or retained, and whether any additional labeling changes should be made

Overall, panel members appreciated the completion of a randomized controlled trial to add to prior studies. There were concerns about the difficulty with data monitoring and control across so many trial sites located in several countries with different languages, cultures, and investigators. The committee members also expressed concerns with the lack of statistical power to detect suicidal events. In addition, some of the committee members expressed concerns regarding the inclusion of patients who were not naive to treatment with the drugs under study, which may have enriched the population for individuals able to tolerate the drugs. However, following the 2016 AC Meeting, FDA performed an analysis that confirmed that exclusion of patients who had prior exposure to the study drugs did not change the results of the primary endpoint analysis.

Most committee members did not have specific recommendations regarding which of the analyses best represented the data, although there was support for using an expanded outcome definition and for using the alternate statistical approach employed by the FDA

team. The potential impact of the variability of data collection practices and coding of adverse events was discussed, but some committee members noted that they did not expect that the variability would affect the adverse event data differentially across treatment arms. With respect to the observational studies, the committee concluded that the studies did not contribute additional insight beyond the findings of the postmarket safety outcome trial. We also note that committee members recognized the increased risk for neuropsychiatric events in the population with a psychiatric history. Several committee members who recognized this difference recommended that this information be described in product labeling.

After the presentations by FDA, the presentations by the sponsor of Chantix and the opportunity for public comment, the committee members voted for one of the following options:

(1) Remove the boxed warning regarding risk of serious neuropsychiatric adverse events - 10 members voted in favor of this option
(2) Modify the language in the boxed warning - 4 members voted for this option
(3) Keep the current boxed warning - 5 members voted for this option

Some committee members who voted to remove the boxed warning noted that the decision was difficult due to their concerns with the limitations from the study results presented. Several members emphasized the public health importance of effective smoking cessation therapies being available for patients who need smoking cessation aids, especially those with psychiatric illness. Several members who voted to retain or modify the boxed warning reported that they did so not because of the results of the study, but due to a concern that removing a boxed warning would be misinterpreted as communicating a complete absence of risk or the potential precedent-setting nature of removing the boxed warning for other products in the future. Those who voted to keep the boxed warning cited concerns about the study endpoint, study conduct, and the inadequate statistical power to detect more rare events, or simply noted that they were unconvinced by the study.

Based on FDA's review and analysis, including sensitivity analyses, and the discussion at the 2016 advisory committee meeting, FDA has determined that it is appropriate to remove the boxed warning for serious neuropsychiatric adverse events. Therefore, on the day of issuance of this response to your Citizen Petition, revised labeling for Chantix will be approved; in addition to the removal of the boxed warning, the Warnings and Precautions section will be revised to include the results of the postmarket safety outcome trial, including the frequencies of the neuropsychiatric adverse events and the efficacy results, and to remove the discussion of the meta-analyses and observational studies from

the labeling. The patient Medication Guide is being maintained, but the REMS requirement will be removed.[15] The neuropsychiatric events described in the Warnings and Precautions section will continue to include not only the four types specified in your Petition (suicide, aggression, psychosis, and depression), but also other events including mania, hallucinations, paranoia, delusions, anxiety, and panic.

B. Hazardous or Sensitive Occupations

You state that a drug capable of inducing episodes of anger, rage, psychosis, and hostility should be banned in sensitive occupations such as pilots, air traffic controllers, military crews, police, and other military personnel (Petition at 13). You also mention that the Chantix accident risk extends to neurological or possible cardiac effects that include the risk of blackouts, convulsions, and impaired vision (Petition at 14). You cite OSE findings regarding Chantix and automobile accidents and cite actions taken by the Federal Aviation Administration (FAA) and the Department of Defense banning the use of Chantix by pilots and air traffic controllers (Petition at 14). As a result, you request to have the Indications section of the Chantix label changed to contain a "clear and unambiguous restriction on the use of Chantix in hazardous or sensitive occupations." You suggest that the list include as examples specific occupations such as airline pilots, military missile crew, nuclear power plant operators, and police officers who carry weapons in the field. In addition, you request what you characterize as a vague phrase "until they know how CHANTIX may affect them" be removed from the labeling because it implies that in the absence of early symptoms, there is no further risk (Petition at 15).

Regulating the types of medications certain occupations can or cannot take would require an understanding of the demands of various occupations and how they might be affected by medications and is outside of FDA's area of expertise. Under 21 CFR 201.57(c)(2), the Indications and Usage section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or manifestation of such disease or condition, or for the relief of associated symptoms. It also requires inclusion of information on certain limitations of use, such as when a drug is indicated for use only in conjunction with a primary mode of therapy, or evidence is

[15] It is important to point out another example of an FDA action to remove a REMS once more information on the adverse events became available. In November 2013, restrictions on the use of the diabetes drug rosiglitazone (Avandia) were removed after the results of a major clinical trial were readjudicated and discussed with an FDA advisory committee. In that case, after the clinical trial was readjudicated, showing no increased risk in heart attack or death in patients treated with rosiglitazone as compared to standard-of-care diabetes drugs, a restrictive REMS requiring physician registration to prescribe rosiglitazone was removed, and the second line indication status was removed, aligning the indication with other diabetes drugs. In addition, a postmarket randomized controlled trial was no longer required by the Agency.

available to support safety or effectiveness of the drug only in selected subgroups of the population (e.g., patients with mild disease or in a special age group). These examples of limitations on use generally involve clinical conditions or clinical subpopulations; a limitation based on occupation, which is neither a clinical condition nor a clinical subpopulation, is not relevant to the Indications and Usage section of labeling. Other regulatory bodies with specific expertise in the demands, requirements, and risks of specific occupations are better able to determine what is appropriate for individuals engaged in those occupations. For example, the FAA regulates the types of medications allowed to be used by airline pilots. In May 2007, the FAA banned the use of Chantix by pilots and air traffic controllers when it learned of the safety problems associated with this product. [16]

The phrase "until they know how Chantix may affect them" was included in the labeling because individuals may have different reactions to Chantix, and we believe that the current labeling is adequate. We believe that it is prudent for patients to assess what side effects the medication may have on them before making the decision to drive or operate heavy machinery.

With respect to the incidence of blackouts, convulsions, and impaired vision, we agree that patients experiencing these events while taking Chantix could endanger other people in certain occupational settings. However, we do not agree that these risks should be added to a boxed warning; rather, we believe they are adequately described in the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the Chantix labeling. Additionally, we do not agree that additional specific occupations should be added to this warning statement in the labeling. The current labeling broadly warns those who "drive or operate machinery," and is not intended to be a complete list of all at-risk occupations. Consequently, your request to change the Indications and Usage section to restrict this drug product for hazardous or sensitive occupations and to add language regarding risks posed to other people in certain occupational settings is denied.

C. Boxed Warning and Promotional Material

You state that the boxed warning in the Highlights part of the labeling may be unique for drug product labeling because it includes what you characterize as promotional information about the benefits of smoking cessation (Petition at 16). You cite the following passage from the boxed warning (emphasis removed) and state that FDA documents show that this passage was inserted at the request of Pfizer:

[16] See Anti-Smoking Medicine Chantix Banned, FAA News & Updates, available at http://www.faa.gov/news/updates/?newsId=56363.

> 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.

You provide the following reasons to support your request that this language be removed: (1) inclusion of a statement of benefit in a boxed warning is unusual; (2) the statement is misleading and an inaccurate summary of Chantix benefits; (3) the statement is vague and could be misunderstood; and (4) the statement might lead to an overestimation of the likely results of Chantix smoking cessation treatment (Petition at 16-17).

First, while inclusion of a statement about a drug's benefit in a boxed warning may be unusual, this information was included to emphasize that the potential benefits of the drug continue to outweigh its risks. The Agency determined it was important to convey this message because of concerns that smokers ready to attempt cessation could be dissuaded by a description of the risks in the labeling and may therefore not appreciate the potential benefits of smoking cessation. You note that "it would be quite odd for an anti-neoplastic drug to contain language about the importance of treating cancer in the warning section" (Petition at 16). Although the importance of treating cancer would not normally be found in the boxed warning of an anti-cancer product's labeling, patients with cancer are typically highly motivated to seek treatment, whereas patients with addictions are often ambivalent about or unready for treatment. Having a prominent statement explaining the importance of weighing the benefits of the treatment against its risks may particularly be useful for patients with addictions.

Second, you contend that the statement of health benefits is misleading and inaccurate because you believe that none of the clinical trials for Chantix has demonstrated an immediate or substantial health benefit (Petition at 17). You assert that reduced cardiovascular risk is the most important immediate benefit of quitting smoking and note that Chantix is not associated with a reduction in cardiovascular risks (Id.). You are correct in stating that the Chantix clinical trials have not demonstrated health benefits; however, none of the potential health benefits of Chantix was measured in these trials because the benefits of attaining and sustaining abstinence from cigarette smoking have been well established. In fact, the specific language in the labeling — that is, that "[t]he health benefits of quitting smoking are immediate and substantial" — is quoted in the preface to the Surgeon General's 1990 report on the health benefits of quitting smoking.[17] Even if a question remains about the cardiovascular effects of quitting smoking while using Chantix, the respiratory system benefits of quitting smoking from using Chantix are

[17] CDC, 1990, The Health Benefits of Smoking Cessation: A Report of the Surgeon General, available at http://profiles.nlm.nih.gov/ps/access/NNBBCT.pdf.

known to be immediate (accruing as soon as 2 weeks after use of the last cigarette).[18]

Third, you claim that the statement "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 (Petition at 17). You note that the placebo group used in the Chantix trials was unusual and unique because, although "most placebo controls are not subject to harmful effects," this placebo group experienced the symptoms of untreated nicotine withdrawal even though they "were informed [that] they might be given medication that investigators believed could reduce their tobacco craving" (Id.). This assertion is difficult to understand: participants in placebo-controlled clinical trials are informed that they might receive a placebo; moreover, in many clinical trials involving symptomatic conditions, subjects who are randomized to receive a placebo experience either some exacerbation of symptoms or at least a transient lack of relief of presenting complaints.

Fourth, you caution that the "placebo" statement "might lead to an overestimation of the likely results of Chantix smoking cessation treatment" (Id.). However, as illustrated in the CLINICAL STUDIES section (section 14) of the labeling, the clinical trial results demonstrate that 21% of patients who had received Chantix for 12 weeks abstained continuously from cigarette smoking from their quit day to their 52-week follow-up; in patients receiving a 12-week course of the placebo, this rate was 10%. You also describe a study (no citation provided) that was not included in the NDA, in which Chantix was compared to transdermal nicotine. You state that Chantix was superior to transdermal nicotine in continuous abstinence at a 52-week follow-up (25.9% versus 19.8%, p=0.04) but focus on the study's lack of a statistically significant difference between Chantix and transdermal nicotine in its 7-day point prevalence (34.8% versus 31.4%). The Agency has not customarily emphasized findings involving transient abstinence and would view continuous abstinence at 52 weeks as a better predictor of clinical benefit, as well as of future sustained abstinence. As such, we do not find the statement regarding the efficacy of Chantix to be misleading.

The postmarket safety outcome trial also measured the efficacy of the smoking cessation aids. The trial evaluated efficacy by comparing smoking abstinence rates of Chantix and Zyban relative to placebo for the last 4 weeks of the 12-week treatment and continuously through week 24, as measured by carbon monoxide (CO)-confirmed continuous abstinence rate. In both cohorts, subjects treated with Chantix, Zyban, or NRT had a superior rate of CO-confirmed abstinence during weeks 9 through 12, and 9 through 24 compared to subjects treated with placebo.

[18] National Cancer Institute, 2014, Harms of Cigarette Smoking and Health Benefits of Quitting, available at https://www.cancer.gov/about-cancer/causes-prevention/risk/tobacco/cessation-fact-sheet.

Because the boxed warning is being removed for the reasons discussed above, the health benefits statement in question will be removed as well. However, we note that the postmarket safety outcome trial established that Chantix is statistically significantly more efficacious than bupropion and NRT, and that finding was observed in both patients without and with a history of psychiatric disorders.

D. Meta-Analysis and Observational Study Results

The Petition states that on September 17, 2014, FDA approved a new version of the Chantix labeling that described two new (unpublished) meta-analyses and four observational studies (Petition at 18). The Petition requests that FDA delete this recently approved description of meta-analyses and observational studies about the neuropsychiatric adverse effects of Chantix from the WARNINGS AND PRECAUTIONS section of the labeling. The Petition claims that the meta-analysis and observational study results establish that the four serious psychiatric side effects of Chantix (i.e., suicidal behavior, aggression/violence, psychosis, and depression) may be uncommon; however, the Petition asserts that none of these studies is of sufficient quality to establish a convincing estimate of incidence, to provide a valid comparison to other treatments, or to refute evidence from other scientific methods (Petition at 20).

Based on FDA's 2014 review of the meta-analyses and observational studies submitted by Pfizer, we determined that some information about these data could be included in the Chantix labeling so that prescribers could have a fuller picture of what analyses and studies have been conducted to enhance their understanding of varenicline-associated serious neuropsychiatric adverse events. We agree that the observational studies were not of sufficient quality to establish a convincing estimate of the incidence of varenicline's neuropsychiatric risk. However, because the published reports on those observational studies were publicly available, FDA decided that it was important to inform the public that we had reviewed those papers and identified important shortcomings that should be noted when interpreting the studies' results. Therefore, FDA revised the label to include information about the limitations of those studies and an appropriate interpretation of their findings. The limitations and our interpretation were also disseminated in the March 2015 Drug Safety Communication.

Because of the recent results of the postmarket safety outcome trial, FDA reevaluated the inclusion of the meta-analyses and observational studies in the Chantix labeling. At the 2016 AC meeting, FDA presented its review of the observational studies published about neuropsychiatric adverse events with smoking cessation drugs. We concluded that existing observational data alone are insufficient to either confirm or refute an increased

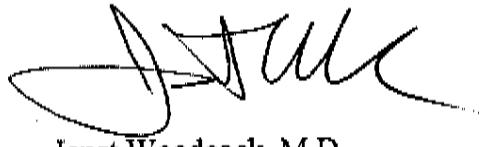
neuropsychiatric risk associated with either varenicline or bupropion HCl use among patients with or without a psychiatric history. In general, the advisory committee concluded that the meta-analyses and observational studies did not contribute additional insight beyond the findings of the postmarket safety outcome trial.

Because the Warnings and Precautions statement regarding serious neuropsychiatric adverse events is being revised to include the results of the postmarket safety outcome trial, and we find that the observational data do not provide additional information, this information will be deleted from the Chantix labeling.

III. CONCLUSION

For the reasons explained above, your Petition is denied in part and granted in part, with respect to the removal of the meta-analyses and observational studies from the Chantix labeling. The recent results of the postmarket safety outcome trial, FDA review and analysis of those results, and the 2016 AC Meeting input have resulted in our decision to make labeling changes for Chantix, including removing the boxed warning and description of observational studies and meta-analyses, and adding the results of the recent postmarket safety outcome trial. A complete listing of the neuropsychiatric adverse events will remain in the WARNINGS AND PRECAUTIONS section of the Chantix labeling. As always, FDA will continue to monitor the safety data, including adverse event reports, for Chantix and all other drugs regulated by FDA.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research