Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
September 14, 2016

Location: FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, Maryland.

Topic: The committees discussed a completed postmarketing-requirement randomized, placebo controlled trial of the neuropsychiatric effects of CHANTIX (varenicline), ZYBAN (bupropion), and nicotine replacement therapy, along with relevant published observational studies to determine whether the findings support changes to product labeling.

These summary minutes for the September 14, 2016 joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration were approved on October 3, 2016.

I certify that I attended the September 14, 2016 meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Kalyani Bhatt, BS, MS
Designated Federal Officer
Psychopharmacologic Drugs Advisory Committee (PDAC)

/s/
Ruth Parker, MD
Acting Committee Chairperson, PDAC

Summary Minutes of the Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
September 14, 2016

The following is the final report of the joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on September 14, 2016. A verbatim transcript will be available in approximately six weeks, sent to the Division of Anesthesia, Analgesia, and Addiction Products and the Office of Surveillance and Epidemiology and posted on the Food and Drug Administration (FDA) website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm475314.htm and
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm486856.htm
All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee met jointly on September 14, 2016, at the FDA White Oak Campus, 10903 New Hampshire Ave., Building 31 Conference Center, , the Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided briefing materials from FDA and Pfizer, Inc. The meeting was called to order by Ruth Parker, MD (Acting Chairperson); the conflict of interest statement was read into the record by Kalyani Bhatt, BS, MS, (Designated Federal Officer). There were approximately 150 people in attendance. There were fifteen (15) Open Public Hearing speakers.

Issue: The committees discussed a completed postmarketing-requirement randomized, placebo controlled trial of the neuropsychiatric effects of CHANTIX (varenicline), ZYBAN (bupropion), and nicotine replacement therapy, along with relevant published observational studies to determine whether the findings support changes to product labeling.

Attendance:

Psychopharmacologic Drugs Advisory Committee Members Present (Voting): Jess G. Fiedorowicz, MD, PhD; Rajesh Narendran, MD; David Pickar, MD

Psychopharmacologic Drugs Advisory Committee Members Not Present (Voting): Thomas A. Grieger, MD; Dawn F. Ionescu, MD; Satish Iyengar, PhD; Jessica J. Jeffrey, MD, MPH, MBA; Erik H. Turner, MD; Kim O. Wictzak

Psychopharmacologic Drugs Advisory Committee Members (Non-Voting): Robert R. Conley, MD (Industry Representative)

Drug Safety and Risk Management Advisory Committee Members (Voting): Kelly Besco, PharmD, FISMP, CPPS (via telephone); Tobias Gerhard, PhD, RPh; Almut Winterstein, RPh, PhD, FISPE

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Niteesh K. Choudhry, MD, PhD; Christopher H. Schmid, PhD; Andy S. Stergachis, PhD, RPh Til Stürmer, MD, MPH, PhD; RPh; Linda Tyler, PharmD, FASHP

Drugs Safety and Risk Management Advisory Committee Members Not Present (Non- Voting): Linda Scarazini, MD, RPh (Industry Representative)

Temporary Members (Voting): Daniel Budnitz, MD, MPH; Scott S. Emerson, MD, PhD; Terry Gillespie (Patient Representative); Sean Hennessy, PharmD, PhD; Sonia Hernandez-Diaz, MD, DrPH; Jennifer Higgins, PhD (Acting Consumer Representative); Stephen R. Marder, MD; Glen Morgan, PhD; Elaine H. Morrato, DrPH, MPH, CPH; Ruth M. Parker, MD (Acting Chairperson); Kenneth Perkins, PhD; Rajiv Rimal, PhD; Christianne L. Roumie, MD, MPH

FDA Participants (Non-Voting):
Mary Thanh Hai, MD; Sharon Hertz, MD; Judith A. Racoosin, MD; Celia Winchell, MD; MPH; Eugenio Andraca-Carrera, PhD, CAPT David Moeny, RPh, MPH

Designated Federal Officer (Non-Voting): Kalyani Bhatt, BS, MS

Open Public Hearing Speakers: Raymond Niaura, PhD (The Society for Research on Nicotine and Tobacco); Diana Zuckerman, PhD (National Center for Health Research); Matthew P. Bars, MS, CTTS (Association for the Treatment of Tobacco Use and Dependence); Stephanie Fox-Rawlings, PhD (National Center for Research); Thomas J. Moore (Drug Safety and Policy Institute for Safe Medication Practices); Sammy Almashat, MD, MPH (Public Citizen); Carol Southard, RN, MSN(Osher Center for Integrative Medicine) ; Thomas J. Berger, PhD (The Veterans Health Council, Vietnam Veterans of America); Nathaniel Counts, J.D. (Mental Health America); David P.L. Sachs, MD (Palo Alto Center for Pulmonary Disease Prevention); Gary J. Kerkvliet, MD; Shelina Foderingham, MSW, MPH (National Council for Behavioral Health); Matthew L. Myers (Campaign for Tobacco-Free Kids); Andrew Sterling, MD (National Alliance on Mental Illness); Kim Witczak; (Woodymatters)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Ruth Parker, MD** Acting Chairperson, PDAC
Conflict of Interest Statement	**Kalyani Bhatt, BS, MS** Designated Federal Officer, PDAC
FDA Introductory Remarks / Regulatory History	**Judith A. Racoosin, MD, MPH** Deputy Director for Safety Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) Office of Drug Evaluation II (ODE II) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Pfizer, Inc.**

Introduction	**James Rusnak, MD, PhD** Chief Development Officer, Cardiovascular and Metabolic Diseases Pfizer
Evidence from Observational Studies	**Judith Prochaska, PhD, MPH** Associate Professor, Department of Medicine Stanford University
EAGLES Study Design, Investigator's Perspective on Study Conduct and on Treating Patients for Smoking Cessation	**Robert M. Anthenelli, MD** Professor and Executive Vice Chair, Department of Psychiatry University of California, San Diego, School of Medicine
EAGLES Study Execution	**James Rusnak, MD, PhD** Chief Development Officer, Cardiovascular and Metabolic Diseases Pfizer
EAGLES Study Results I	**Cristina Russ, MD, PhD** Director, Medical Affairs Pfizer
Clinical Perspective on EAGLES Study Results	**A. Eden Evins, MD, MPH** Director, Center for Addiction Medicine Massachusetts General Hospital and Cox Family Associate Professor of Psychiatry Harvard Medical School
Conclusions and Labeling Proposal	**James Rusnak, MD, PhD** Chief Development Officer, Cardiovascular and Metabolic Diseases Pfizer
Clarifying Questions to Applicant	

BREAK

FDA PRESENTATIONS

Clinical Review of the PMR Safety Outcome Trial	**Celia Winchell, MD** Clinical Team Leader, Addiction Products Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) Office of Drug Evaluation II (ODE II) Office of New Drugs (OND), CDER, FDA

Statistical Review of the PMR Safety Outcome Trial	**Eugenio Andraca-Carrera, PhD** Reviewer, Division of Biometrics VII Office of Translational Sciences (OTS) CDER, FDA
Review of Observational Studies	**Chih-Ying (Natasha) Pratt, PhD** Reviewer, Division of Epidemiology Office of Surveillance and Epidemiology (OSE) CDER, FDA
Clarifying Questions to FDA	

OPEN PUBLIC HEARING

Charge to the Committee	**Judith A. Racoosin, MD, MPH**

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the strengths and weaknesses of the completed randomized controlled trial (RCT) with regard to the study design including the novel primary endpoint.

   Committee Discussion: *Overall, panel members agreed that the trial design was good and applauded the completion of an RCT to add to prior studies. There were concerns regarding the number of sites and difficulty with data monitoring and control across so many countries, languages, cultures, and investigators. The committee members also expressed concerns with the lack of power to address suicidal events. Some panel members noted the need for having design that holds to rigorous standards for safety related outcomes, and stated power calculations a priori for this deserved closer attention. Some of the committee members expressed concerns for 15-20% of study subjects having had prior exposure to drugs under evaluation—potential for underestimating adverse events related this feature of study design, which may have enriched the population for individuals able to tolerate the drugs. Please see the transcript for details of the committee's discussion.*

2. **DISCUSSION:** Discuss the potential impact of the variability in data collection, adverse event coding, and case definition on the primary endpoint. Because of this variability, discuss which analysis and results most appropriately describe the effect of the smoking cessation therapies on neuropsychiatric events.

Committee Discussion: *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 and for using the alternate statistical approach employed by the FDA team. It was suggested that an additional analysis of patients without prior experience with the study drugs would be useful. There was a lot of mention of the potential impact of the variability of data collection practices and coding of adverse events on the final study results, with discussion that the potential impact of this variability may be large. Some committee members noted that they did not expect that the variability would affect the adverse event (AE) data differentially across treatment arms. There were comments highlighting the heterogeneity in the rate of NPS events across sites, the numerous languages/cultures of instruments and potential there for quality control and the validity of measures. In addition, there was some discussion related to whether there could be systematic under-reporting of AE's, as well as concern about face validity because the AE incidence in the placebo group was low. Committee members expressed disappointment in the nature of the narratives, which were intended to be completed per study design, and wondered if the study had captured the type of events that were seen in post-marketing. Please see the transcript for details of the committee's discussion.*

3. **DISCUSSION:** Discuss how you weigh the evidence contributed by the observational studies when evaluating the risk of serious neuropsychiatric adverse events in patients taking smoking cessation products.

   Committee Discussion: *In general, the committee did not think emphasis should be placed on the observational studies and concluded that they did not contribute additional insight beyond the findings of the RCT. Some panel members noted that observational studies have large numbers, and that both observational studies and clinical trials can have utility. Others expressed concerns related to biases, specifically related to channeling: sicker patients seemed to be treated more often with nicotine replacement therapy and healthier patients with Chantix and Zyban. The majority of the panel members agreed on the low utility of observational studies in this setting, and their biggest concern was that psychiatric outcomes were not well captured in claims data used in observational studies. Please see the transcript for details of the committee's discussion.*

4. **DISCUSSION:** Based on the results of the clinical trial and observational studies, discuss the impact of psychiatric history on the occurrence of neuropsychiatric adverse events during smoking cessation therapy.

   Committee Discussion: *The majority of the panel members noted the increased risk for neuropsychiatric events in the population with a psychiatric history. Several committee members who noted this difference recommended that this information needs to be added in the product labeling. Please see the transcript for details of the committee's discussion.*

Please note: Questions #5 and #6 were discussed together.

5. **VOTE:** Based on the data presented on the risk of serious neuropsychiatric adverse events with smoking cessation products, what would you recommend?

   A. Remove the boxed warning statements regarding risk of serious neuropsychiatric adverse events

   B. Modify the language in the boxed warning

   C. Keep the current boxed warning

   Vote Result: *A: 10* *B: 4* *C: 5* *Abstain: 0*

6. **DISCUSSION:** Explain the rationale for your answer to #5, and discuss any additional labeling actions you think the Agency should take regarding the risk of serious neuropsychiatric adverse events with smoking cessation products.

   Committee Discussion: *The majority of the committee voted to remove the boxed warning statements regarding the risk of serious neuropsychiatric adverse events. The majority of the committee, who voted to remove the black box warning, noted how difficult this decision was for them, citing their concerns with the limitations from the study results presented. Some panel members who also voted "A", agreed that the study results showed there was lack of evidence of increased risk overall. Some also noted the public health importance of effective smoking cessation therapies being available for patients who need smoking cessation aids, especially those with psychiatric illness.*

   Those members who voted to keep the boxed warning and to have its language modified recommended that the boxed warning should remain to ensure that patients and healthcare providers are aware of the risk of neuropsychiatric side effects with Chantix and Zyban. There was also concern about the potential precedent-setting nature of the removal of the boxed warning, in that the boxed warning removal may signal to the public that the drugs do not have neuropsychiatric safety concerns. In addition the panel members who voted "B" expressed concern with trial conduct/data collection and that coding left too much 'unknown' to remove the safety warning. Some members of the committee voted to keep the box warning, citing that due to concerns about the study endpoint, study conduct, and the inadequate statistical power to detect more rare events (like suicide), the recent study does not adequately address whether there is safety concern with the drug. Please see the transcript for details of the committee's discussion.

The meeting was adjourned at approximately 5:00 p.m.