Dear Dr. Curtis:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between August 15, 2016, and September 14, 2016. Ms. Corrine Carter, Ms. Myra Casey, and Ms. Melanie Daniels, representing FDA, reviewed your conduct of a clinical investigation (Protocol A3051123, “A Phase 4, Randomized, Double-Blind, Active and Placebo-Controlled, Multicenter Study Evaluating the Neuropsychiatric Safety and Efficacy of 12 Weeks Varenicline Tartrate 1 mg BID and Bupropion Hydrochloride 150 mg BID for Smoking Cessation in Subjects with and Without a History of Psychiatric Disorders”) of the investigational drug Varenicline Tartrate (Chantix®), performed for Pfizer, Inc.

This inspection is a part of FDA’s Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure
that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Ms. Carter, Ms. Casey, and Ms. Daniels presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your October 4, 2016, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We wish to emphasize the following:

1. **You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].**

As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocol A3051123 requires you to exclude subjects who meet the exclusion criteria and who do not meet the inclusion criteria. In addition, Protocol A3051123 prohibits the use of certain medications. You failed to adhere to these requirements. Specifically:

a. Protocol A3051123 specified that for subjects to be enrolled, they must have smoked an average of at least 10 cigarettes per day during the past year, as well as during the month before the screening visit; and they must have exhaled >10 parts per million (ppm) of carbon monoxide (CO) at screening. However, you enrolled three subjects who did not meet these criteria. Specifically:

   i. Subject 1001 was enrolled into Protocol A3051123 with an average number of six cigarettes smoked daily over the past month, which is less than the protocol-required ten cigarettes per day.

   ii. Subject 1013 was enrolled into Protocol A3051123 with an average number of five cigarettes smoked daily over the past month, which is less than the protocol-required ten cigarettes per day.

   iii. Subject 1018 was enrolled into Protocol A3051123 with a CO reading of 8 ppm, which is less than the protocol-required 10 ppm.

b. Protocol A3051123 requires that you exclude subjects with severe chronic obstructive pulmonary disease (COPD), defined as any subject who fulfills any of the following criteria:

   i. Having a history of repeated exacerbations of COPD (defined as three or more exacerbations within the previous 3 years)

   ii. Requiring systemic corticosteroid maintenance (for example, oral prednisolone) for management of chronic symptoms
iii. Being maintained on oxygen therapy for management of chronic symptoms

You enrolled Subject 1021 into Protocol A3051123 on June 13, 2012, even though Subject 1021 had chronic COPD symptoms that required corticosteroid maintenance, including oral prednisolone and Medrol (methylprednisolone), before study enrollment.

In your October 4, 2016, written response to the violations listed above, you acknowledged that the observed issues convey a need for adequate oversight of study staff, training of study staff, and protocol adherence. Your response indicated that corrective actions have been or will be implemented to ensure that “principal investigators are aware of their obligations; that PIs and staff understand the importance of following the protocol SOPs.” Your response also indicated that the Protocol-Specific Training and Source Document Completion Standard Operating Procedures (SOPs) have been updated, and that “all site PIs and staff will be trained” by October 14, 2016.

We are unable to undertake an informed evaluation of your written response because you did not include any corrective actions that you, as a clinical investigator, have taken to prevent similar violations in the future. We are concerned that the majority of corrective actions appear to represent actions taken by American Health Network (AHN) and do not reflect corrective actions that you personally have taken. Although you indicated that on October 3, 2016, you notified AHN that you no longer “intend to serve as principal investigator for any future research studies at AHN” and that you “will continue to serve as principal investigator for my only current open study, which is a registry study,” you did not provide details on how you personally plan to prevent similar violations in any future studies you may conduct at sites other than AHN.

Enrollment of subjects who do not meet eligibility criteria and failure to ensure discontinuation of prohibited medications, as required by the protocol, jeopardize subject safety and welfare, and raise concerns about the validity and integrity of the data collected at your site.

2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

As a clinical investigator, you are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include records for the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) Axis I and II Disorders (SCID I and II). Subjects were to be classified into one of two cohorts: (1) those with an established and stable diagnosis of a psychiatric disorder, confirmed by these SCID I and II interviews conducted at screening, and (2) those without a diagnosis of a psychiatric disorder. You have failed
to maintain adequate and accurate case histories for the SCID I and II records. Specifically, source records indicate that the SCID I or II forms were not completed for the following subjects at Screening Visits:

a. Subject 1002’s SCID I diagnosis summary score sheet was not completed. However, despite the blank SCID I form, the electronic case report form (eCRF) for Subject 1002’s screening visit indicates that you made a determination of no psychiatric diagnosis identified using an SCID I form.

b. Subject 1018’s SCID II diagnosis summary score sheet was not completed. However, despite the blank SCID II form, the eCRF for Subject 1018’s screening visit indicates that you made a determination of no psychiatric diagnosis identified using an SCID II form.

c. Subject 1039’s SCID II diagnosis summary score sheet was not completed. However, despite the blank SCID II form, the eCRF for Subject 1039’s screening visit indicates that you made a determination of no psychiatric diagnosis identified using a SCID II form.

In your October 4, 2016, written response to the violations noted above, you noted that the observed issues convey a need for adequate oversight of study staff, training of study staff and protocol adherence. Your response indicated that corrective actions have or will be implemented to ensure that “principal investigators are aware of their obligations; that PIs and staff understand the importance of following the protocol and SOPs.” Your response also indicated that the Protocol Specific Training and Source Document Completion SOPs have been updated and that “all site PIs and staff will be trained” by October 14, 2016.

We are unable to undertake an informed evaluation of your written response because you did not include any corrective actions that you, as a clinical investigator, have taken to prevent similar violations in the future. We are concerned that the majority of corrective actions appear to represent actions taken by AHN and do not reflect corrective actions that you personally have taken. Although you indicated that on October 3, 2016, you notified AHN that you no longer “intend to serve as principal investigator for any future research studies at AHN” and that you “will continue to serve as principal investigator for my only current open study, which is a registry study,” you did not provide details on how you personally plan to prevent similar violations in any future studies you may conduct at sites other than AHN.

Your failure to maintain adequate and accurate case histories, including the failure to adequately document the SCID I and II summary diagnosis records, compromises the validity and integrity of data captured at your site. Study cohort placement (that is, subjects having a diagnosed psychiatric disorder versus those having no diagnosed psychiatric disorder) was confirmed by these Screening SCID I and II interviews.

3. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].
As a clinical investigator, you are required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. For Protocol A3051123, drug disposition records include study drug accountability records and records documenting drug return, such as the Order for Return of Clinical Trial Material (ORCTM) form. You did not maintain adequate records with respect to these documents. Examples of this failure include, but are not limited to, the following:

The following discrepancies were observed between the amount of drug given to subjects at study visits, the amount of drug taken, and the amount of drug returned, as recorded on the source records and eCRFs for the following subjects:

a. Subject 1001 was provided study drug at Visit Week 8 (March 28, 2012) for drug administration during Weeks 9-10; however, the amount of drug dispensed at the Week 8 Visit does not match the amount of drug taken, according to the eCRFs. In addition, the amount of drug returned to the site does not match the amount of drug that should have been returned, based on the reported drug dosing records and the ORCTM record.

<table>
<thead>
<tr>
<th>Visit 8/ Weeks 9-10</th>
<th>Drug Dispensed</th>
<th>Drug Taken</th>
<th>Calculated return per reported dosing</th>
<th>Returned to Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline</td>
<td>40</td>
<td>44</td>
<td>-4</td>
<td>10</td>
</tr>
<tr>
<td>Bupropion</td>
<td>40</td>
<td>44</td>
<td>-4</td>
<td>10</td>
</tr>
<tr>
<td>Patches</td>
<td>20</td>
<td>22</td>
<td>-2</td>
<td>5</td>
</tr>
</tbody>
</table>

b. Subject 1005 was provided study drug at Visit Week 10 (May 25, 2012) for drug administration during Weeks 11-12 (time frame: 14 days); however, the amount of drug returned to the site does not match the amount of drug that should have been returned, based on the reported drug dosing records and the ORCTM record.

<table>
<thead>
<tr>
<th>Visit 10/ Weeks 11-12</th>
<th>Drug Dispensed</th>
<th>Drug Taken</th>
<th>Calculated return per reported dosing</th>
<th>Returned to Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline</td>
<td>40</td>
<td>28</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Bupropion</td>
<td>40</td>
<td>28</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Patches</td>
<td>20</td>
<td>14</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

In your October 4, 2016, written response to the violations noted above, you indicated that AHN updated its Test Article Accountability SOP to address issues related to investigational drug return. In addition, your response noted that AHN’s “Dispensing of Investigational Product” SOP requires that each administration/dispensation of an investigational drug be doubled-checked by another person. The Data Management SOP requires that “investigators and study staff take care to ensure that all source data is documented accurately, completely, and consistently.” Your response stated that training on these SOPs will be conducted for site investigators and staff by October 14, 2016.
We are unable to undertake an informed evaluation of your written response because you did not include any corrective actions that you, as a clinical investigator, have taken to prevent similar violations in the future. We are concerned that the majority of corrective actions appear to represent actions taken by AHN and do not reflect corrective actions that you personally have taken. Although you indicated that on October 3, 2016, you notified AHN that you no longer “intend to serve as principal investigator for any future research studies at AHN” and that you “will continue to serve as principal investigator for my only current open study, which is a registry study,” you did not provide details on how you personally plan to prevent similar violations in any future studies you may conduct at sites other than AHN.

Your failure to maintain adequate and accurate drug accountability records, including documents recording drug return, raises significant concerns about the adequacy of your oversight and control of investigational drug, which could impact the validity and integrity of the data at your site.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to address the violations noted above adequately and promptly may result in regulatory action without further notice. If you believe that your written response to the Form FDA 483 dated October 4, 2016, fully explains the actions you have taken to prevent similar violations in the future, please communicate that to us in writing within fifteen (15) business days. You may refer to the written response dated October 4, 2016, in your response to this letter.

If you have any questions, please contact Adam Donat, at 301-796-5316; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

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Division of Enforcement and Postmarketing Safety
Office of Scientific Investigations
Office of Compliance
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Building 51, Room 5352
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Silver Spring, MD 20993

Sincerely yours,
(See appended electronic signature page)
David Burrow, Pharm.D., J.D.
Acting Director
Office of Scientific Investigations
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Food and Drug Administration

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID C BURROW
01/27/2017

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