Pfizer Inc., 4/9/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 10-HFD-45-04-01

Mr. Martin Mackay, Ph.D.
Senior Vice President
Global Research and Development
Pfizer, Inc.
50 Pequot Avenue
New London, CT 06320

Dear Dr. Mackay:

Between May 4, 2009 and June 3, 2009, Ms. Michelle M. Noe and Dr. Cynthia Kleppinger, representing the Food and Drug Administration (FDA), conducted an investigation and met with John Oidtman, Vice President of Worldwide Regulatory Operations, to review your firm's practices as the sponsor of the clinical investigation Protocol **(b)(4)**, entitled "**(b)(4)**" of the investigational drug, **(b)(4)** performed for Pfizer, Inc.

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected. This inspection was performed due to significant violations found during inspections of several clinical investigators conducting Protocol **(b)(4)**.

We are aware that at the conclusion of the inspection, Ms. Noe and Dr. Kleppinger presented and discussed with John Oidtman Form FDA 483, Inspectional Observations. From our review of the

establishment inspection report, the documents submitted with that report, and your firm's July 2, 2009 letter written in response to the Form FDA 483, 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 proper monitoring of the investigation [21 CFR 312.50].

This is a repeat violation of findings communicated to you in an untitled letter generated after an April 25, 2005 to June 6, 2005 inspection of Pfizer's monitoring of clinical investigations for **(b)(4)**

FDA regulations require that sponsors ensure proper monitoring of clinical investigations. Our investigation found that Pfizer failed to properly ensure monitoring of the study referenced above. As a result of inadequate monitoring, widespread overdosing of study subjects at multiple study sites was neither detected nor corrected in a timely manner.

a. Study monitors failed to ensure that the investigation was conducted in accordance with the investigational plan. Overdosing at Dr.**(b)(4)** 's site (site **(b)(4)**) was neither recognized nor reported by study monitors in a timely manner.

The protocol specified that a dose of 160 mg/day was not to be achieved before Day 8 of treatment and that total daily dose of study medication was not to exceed 160 mg for subjects with a body weight $\geq$ 45 kg, or 80 mg for subject with a body weight < 45 kg.

Based on the inspection conducted at your firm, at Dr. **(b)(4)**'s site (site **(b)(4)**), dosing errors occurred and overdosing extended over several days for all seven pediatric subjects; in one case for as long as 22 days. The following are some examples of pediatric subject overdosing at Dr. **(b)(4)**'s site (site **(b)(4)**) noted during the site inspection:

i. Subject 1001 with a documented weight of 46.8 kg, was overdosed on study medication for 20 consecutive days. On Treatment Days 8 and 9, this subject received 180 mg/day; on Treatment Days 10 and 11, this subject received 240 mg/day; on Treatment Days 12 and 13, this subject received 320 mg/day; on Treatment Day 14, this subject received 400 mg/day; and on Treatment Days 15 through 27, this subject received 180 mg/day.

ii. Subject 1003, with a documented weight of 65 kg, was overdosed on study medication for 21 consecutive days. On Treatment Day 7, this subject received 180 mg/day; on Treatment Days 8 and 9, this subject received 240 mg/day; on Treatment Days 10 through 26, this subject received 400 mg/day; and on Treatment Day 27, this subject received 280 mg/day.

iii. Subject 1004 was overdosed on study medication for 3 consecutive days. On Treatment Day 9, this subject received 320 mg/day; and on Treatment Days 10 and 11, this subject received 240 mg/day.

iv. Subject 1005 was overdosed on study medication for 16 consecutive days. On Treatment Days 8 and 9, this subject received 180 mg/day; on Treatment Days 10 through 14, this subject received 240 mg/day; and on Treatment Days 15 through 20 and Days 22 through 23, this subject received 400 mg/day. On Treatment Day 21 this subject received 200mg/day.

v. Subject 1006, with a documented weight less than 45 kg, was overdosed on study medication for 7 consecutive days. On Treatment Days 16 through 22, this subject received 400 mg/day.

vi. Subject 1007, with a documented weight of 39.5 kg, was overdosed on study medication for 13 consecutive days. On Treatment Days 16 through 28, this subject received 120 mg/day.

Study monitors visited the site on a total of nine days: March 13 and 15, April 25, May 15-16, June 6-7 and July 5-6, 2006. However, the overdosing was not discovered until July 25, 2006, and not by a study monitor but rather by a Pfizer data management unit. In addition, our investigation found an internal Pfizer report dated November 7, 2006 entitled "Report of Dosing Errors Due to Misunderstanding of Medication Cards in Pfizer Studies **(b)(4)** " that states that "on July 25, 2006, the Pfizer study team became aware of possible dosing errors." We note that all three studies involved the study medication **(b)(4)** with the same packaging.

The report indicated that the Pfizer study team examined the dosing records for all subjects enrolled as of November 7, 2006 in the three referenced studies, identified two sites at which dosing errors occurred, and took various steps to remedy the problem such as suspending enrollment at certain sites pending re-training of the sites, and reassessment of the sites' ability to conduct the studies according to the protocol. It is noteworthy that the report states that the study team "determined that the dosing procedures were clearly described in the protocols, protocol appendix, and medication card, and that no revisions of these documents were required. The study team re-trained all sites and all study monitors on correct dosing procedures. Monitoring of drug accountability was increased to 100% for all sites. The directive that data be entered into the electronic CRF within 48 hours of study visits was reinforced with all sites."

b. We observe that a Pfizer internal document dated October 3, 2007 and entitled "Safety Information on Affected Subjects" refers to the overdosing of an additional six pediatric subjects in study **(b)(4)** at two different sites (subject #1170-1001, 1170-1002, 1170-1003, 1136-1001, 1136-1002, 1136-1003). These overdoses occurred in June, July and August of 2007, several months after Pfizer retrained study monitors on correct dosing procedures.

vii. Subject 1136-1001 experienced 30 days of overdosing with subsequent moderate somnolence, high prolactin level, buccal facial dyskinesia, skin petechiae, low bicarbonate, low phosphate, and one ECG with prolonged QTcF

viii. Subject 1136-1002 experienced 22 days of overdosing

ix. Subject 1136-1003 experienced 17 days of overdosing with moderate akathisia, mild dyskinesia and mild extrapyramidal symptoms

x. Subject 1070-1001 experienced 12 days of overdosing with moderate akathisia and severe tremor

xi. Subject 1070-1002 experienced 11 days of overdosing with mild akathisia an mild tremor

xii. Subject 1070-1003 experienced 7 days of overdosing

2. You failed to ensure that the investigations were conducted in accordance with the general investigational plan and protocols contained in the IND [21 CFR 312.50].

a. Subjects at multiple sites conducting Protocol **(b)(4)** were not given the correct doses.

i. The final Clinical Study Report submitted to the FDA lists 40 total subjects reported to have had a protocol deviation related to dosing error, including 20 subjects who exceeded the maximum protocol dose.

ii. Your programmatic review of the dosing records identified 26 subjects whose total daily dose exceeded the maximum allowed by the protocol for their weight range on any occasion.

iii. Based on the inspection conducted at your firm, at Dr. **(b)(4)**'s site (site **(b)(4)**), there were significant dosing errors for all subjects. The overdosing extended over several days for all subjects (up to 22 days in one subject).

iv. Based on the inspection conducted at your firm, at Dr. **(b)(4)**'s (site **(b)(4)**), Subject 1026 experienced two days of overdosing with extrapyramidal symptoms.

v. Based on the inspection conducted at your firm, at Dr. **(b)(4)**'s (site **(b)(4)**), Subject 1005 experienced six days of overdosing.

vi. Based on the inspection conducted at your firm, at Dr.**(b)(4)**'s (site **(b)(4)**), Subject 1010 experienced six days of overdosing.

vii. Based on the inspection conducted at your firm, at Dr.**(b)(4)**'s site (site **(b)(4)**), Subject 1001 experienced 12 days of overdosing with mild somnolence, and mild agitation and Subject 1002 experienced 14 days of overdosing.

b. Protocol **(b)(4)** specified that, at baseline, the investigator was to develop a titration plan to increase the subject's total daily dose of study medication from a 20 mg starting dose (at the baseline visit) to a target dose achieved over two weeks, in general. The protocol specified that this plan would consider the subject's **(b)(4)** history, current **(b)(4)** status, and weight, and could be modified at any time based on clinical response and toleration.

i. Based on the inspection conducted at your firm, at Dr. **(b)(4)**'s site (site **(b)(4)**), there was no dosing titration plan developed for enrolled subjects, and subjects were not dosed according to the protocol.

ii. Based on the inspection conducted at your firm, at Dr. **(b)(4)**' site (site **(b)(4)**), there was no dosing titration plan developed for enrolled subjects, and subjects were not dosed according to the protocol.

c. Protocol **(b)(4)** specified that all electrocardiograms (ECGs) were to be reviewed for safety at the site by a physician qualified to read and interpret the results (i.e., a pediatric cardiologist or pediatric intensive care specialist or a clinician who was experienced in interpreting pediatric ECGs).

i. There was insufficient documentation to show that all sites had a pediatric cardiologist or pediatric intensive care specialist reading the ECGs on the day performed.

ii. Dr. **(b)(4)** (site **(b)(4)**), a board certified child **(b)(4)**, was granted permission, through a Study Issue Form, to read the ECGs based on his training in medical school and residency. There was no documentation to show additional training and/or qualifications to justify this grant of permission.

d. Protocol **(b)(4)** specified that the **(b)(4)** must be administered by the principal investigator or a sub-investigator, who is a child and adolescent **(b)(4)** or Ph.D.-level clinical **(b)(4)**, and who has participated in the Pfizer rater qualification program.

i. There was no documentation to show that the principal investigator and/or sub investigators at all sites participated in a Pfizer rater qualification program for the **(b)(4)**. Moreover, in your written response, you stated that a Pfizer rater qualification program does not exist and you have not proposed institution of a rater qualification program for the **(b)(4)**, as required by the protocol.

ii. At Dr. **(b)(4)**'s site (site**(b)(4)**), the **(b)(4)** was not administered by the principal investigator or a subinvestigator, who was a child and adolescent **(b)(4)** or Ph.D.-level clinical **(b)(4)**. Moreover, for Subjects 1008, 1010, 1011, 1012 and 1013, **(b)(4)**) was used as the diagnostic instrument in place of the **(b)(4)**.

iii. At Dr. **(b)(4)**'s site (site **(b)(4)**), the **(b)(4)** for Subjects 1001 and 1002 was not administered by the principal investigator or a subinvestigator,who was a child and adolescent **(b)(4)** or Ph.D.-level clinical **(b)(4)**.

e. Protocol **(b)(4)** specified that diagnostic eligibility for the study was to be determined by a board certified or board eligible child/adolescent **(b)(4)**.

There was insufficient documentation to show that all sites had a board-certified or board-eligible child/adolescent **(b)(4)** determining diagnostic eligibility.

f. Protocol **(b)(4)** specified that the person obtaining the informed consent must be sufficiently trained on medical issues so that questions can be adequately addressed and that this person must be an M.D., Ph.D., or R.N., and that persons without one of these degrees must be approved by Pfizer.

Our investigation found that informed consent was not obtained by a M.D., Ph.D., or R.N., and/or there was insufficient documentation to support that persons not otherwise qualified by holding one of the required degrees were approved by Pfizer prior to consenting subjects at the following sites:

i. Dr. **(b)(4)** (site **(b)(4)**)

ii. Dr. **(b)(4)** (site **(b)(4)**)

iii. Dr. **(b)(4)** (site **(b)(4)**)

g. Protocol **(b)(4)** specified that the informed consent form must be agreed to by Pfizer and the IRB/IEC (Institutional Review Board/Independent Ethics Committee) and must be in compliance with ICH GCP (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice), local regulatory requirements, and legal requirements. The protocol specified that the informed consent form used in this trial, and any changes made during the course of the trial, must be prospectively approved by both the IRB/IEC and Pfizer before use.

At Dr. **(b)(4)**' site (site **(b)(4)**), Subject 1010 was consented with a consent form with hand-written information/language added to the form, which denied payment to subjects for inpatient visits. This additional information/language was not approved by the IRB/IEC and Pfizer.

3. You failed to keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use [21 CFR 312.55(b)].

There is no documentation to show that all sites conducting Protocol **(b)(4)** received safety reports which describe the dosing errors discovered. Your written response does not address the issue of keeping investigators informed of new observations (i.e., dosing errors).

In your firm's July 2, 2009, letter written in response to the Form FDA 483, Inspectional Observations, your firm acknowledged that the clinical investigations were not conducted in accordance with the protocols contained in the IND. Your firm's response stated that procedures will be put into place to ensure compliance with the FDA regulations in the future. We acknowledge your firm's assurance that corrective actions will be taken. However, we note that the response did not contain a detailed outline of procedures or processes that would be implemented to prevent the future occurrence of these observations.

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 on-going 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 (including corrective action plans and standard operating procedures) to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Cullity (formerly Lewin), M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Cullity (formerly Lewin), M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Bldg 51, Room 5354
Silver Spring, MD 20993

Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research

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

/s/

LESLIE K BALL
04/09/2010