



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Daniel M. Paulson, M.D.
3565 Freeland Avenue
Philadelphia, PA 19128

09-HFD-45-03-01

Dear Dr. Paulson:

Between April 21, 2008 and May 29, 2008 and on December 4, 2008, Ms. Dianne Milazzo and Mr. Emmanuel Dimanno Jr., representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (Protocol (b) (4) entitled "A Randomized, Double Blind, Placebo-Controlled, Parallel Group Trial Assessing the Proportion of Patients Experiencing an Exacerbation and Proportion of Patients Hospitalized for an Exacerbation Over 6 months During Treatment with Tiotropium 18 mcg Capsule Once Daily in Patients with COPD in a (b) (4) Setting") of the investigational drug SPIRIVA® Handihaler (tiotropium bromide), performed for Boehringer Ingelheim Pharmaceuticals.

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.

From our review of the establishment inspection report (EIR) 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 and the protection of human subjects. We are aware that at the conclusion of the inspection, our investigators presented and discussed with your previous sub-investigator, Dr. (b) (6), a Form FDA 483, Inspectional Observations. We note that you were present via telephone during the discussion of the Form FDA 483. In addition, we note that a copy

of the Form FDA 483 was sent to you in a letter dated May 29, 2008. In reference to the findings noted during the inspection, we wish to emphasize the following:

1. You failed to conduct the studies or ensure they were conducted according to the investigational plan [21 CFR 312.60].

- A. The protocol specified that at the screening visit, all subjects were to have an Electrocardiogram (ECG) performed, and this ECG was to be interpreted by the investigator or medically qualified designee prior to randomization. In addition, the protocol specifically stated that “[t]he purpose of the baseline ECG is to obtain information about the patient’s baseline condition that may determine eligibility for participation in this trial.” The protocol further specified that subjects were to be excluded from the study if they had any unstable medical condition (e.g. neurologic, cardiac, etc.,) which the investigator feels would preclude effective participation in the study, or which would be expected to reduce life expectancy to less than six months.

In FDA’s audit of 58 subjects’ screening ECGs, there was a significant delay in the documentation of your review of 38 screening ECGs such that the subjects had either (1) already been randomized into the study and received investigational drug by the time of your review and/or (2) subjects had already completed the study. The FDA is unable to assess how you could have adequately made the determination that the subjects met the protocol required condition for eligibility into the study given that the ECGs were not documented as having been reviewed prior to the randomization visit. Examples include but were not limited to the following:

Subject Number	Date ECG Performed	Date Subject Received Investigational Drug	Date Subject Completed Study	Date Documented on ECG as Reviewed	Abnormal result(s) noted on ECG
(b) (6)	5/6/2002	5/29/02	12/4/02	9/13/2002	Nonspecific T wave abnormality; Abnormal ECG
(b) (6)	10/15/2001	10/22/01	4/8/02	5/9/2002	Sinus bradycardia; Indeterminate axis; Inferior infarct, age undetermined; Abnormal ECG
(b) (6)	9/24/2001	10/17/01	4/15/02	6/17/2002	Sinus rhythm with 1 st degree AV block; Septal infarct, age undetermined; Abnormal ECG
(b) (6)	1/15/2002	1/23/02	2/24/02 Subject Died - (b) (6)	8/15/2002	Left bundle branch block; Abnormal ECG

Your delayed review of ECGs prior to enrollment of the subjects into the study leads to significant concerns regarding your oversight over subjects' safety during the course of the study.

- B. The protocol specified inclusionary and exclusionary criteria for enrollment in this study. You failed to identify multiple subjects who should have been excluded based on these criteria. This included:
1. Subjects with a clinical diagnosis of asthma were to be excluded from the study. Source documents for Subjects (b) (6) indicated that these subjects had been diagnosed with asthma.
 2. Subjects who had been hospitalized for cardiac failure during the past year were to be excluded from the study. Subject (b) (6) was enrolled into the study on December 10, 2001. Source documents identified that this subject was hospitalized twice in the previous year (i.e. (b) (6) and (b) (6)) for congestive heart failure.
 3. The protocol specified that inclusion in the study required that subjects have a diagnosis of Chronic Obstructive Pulmonary Disease and have moderate to severe airway obstruction with an $FEV_1 \leq 60\%$ of predicted normal and an $FEV_1 \leq 70\%$ of FVC. The protocol further specified that pulmonary function testing was to be performed at Visits 2, 3 and 4, approximately 1 hr prior to the time the subjects usually took their morning dose of respiratory medication, with the best of 3 efforts being defined as the highest FEV_1 and the highest FVC each obtained on any of the three blows (maximum 5 attempts was allowed per the protocol). Source records showed that Subject (b) (6) did not meet the inclusion criteria of having an $FEV_1 \leq 60\%$ of predicted normal. Specifically, at Visit #2 (October 3, 2001), Subject (b) (6) spirometry showed that the highest FEV_1 value for 5 tests was 1.16 L. However, the Visit 2 spirometry worksheet and other source documents inaccurately reported the highest value of 1.12 L. FDA notes that had the FEV_1 value of 1.16 L been accurately transcribed, this subject would have been ineligible for the study.
- C. The protocol specified that any serious adverse event (SAE), whether or not considered related to the investigational product, and whether or not the investigational product has been administered, must be reported immediately by telephone/fax to the sponsor. The protocol also stated that in the event of an SAE, the investigator must complete the SAE form (part of the case report form) and send it immediately by fax to the study chairman and to the sponsor.

Per the EIR, FDA investigators could not find a fax date to indicate that the SAE form was submitted to the sponsor for 11 of 58 subjects' records (i.e. Subject (b) (6) and

(b) (6) reviewed. We note that the time period between your site becoming aware of an SAE and you signing the sponsor’s SAE report varied between 11 days to greater than 51 weeks. Examples include but were not limited to the following:

Subject Number	SAE	Date of Onset	Date Your Site Became Aware of SAE	Date SAE report signed by your site.
(b) (6)	Strokes	12/25/2001 & 1/2002	4/15/2002	4/11/2003
(b) (6)	Motor vehicle accident	10/25/2001	11/7/2001	11/18/2001
(b) (6)	CHF Exacerbation	1/8/2002	1/18/2002	1/30/2002
(b) (6)	Recurrent Malignant lymphoma	4/1/2002	4/1/2002	4/11/2003

D. The protocol specified that certain medications were not allowed during the treatment period including (a) inhaled anticholinergic medications formulated alone or in combination with other medications (e.g. Atrovent, Oxitropim, Combivent, Berodual, Duovent) and (b) Intranasal anticholinergic formulations such as Atrovent Nasal spray. FDA’s inspection documented that subjects received prohibited concomitant medications. Specifically,

- i. Subject (b) (6) experienced a COPD exacerbation between the dates of November 28, 2001 and December 2, 2001 and was given Combivent. While this SAE occurred prior to Visit 3 on January 9, 2002, the Visit 3 CRF inaccurately noted that the subject did not receive Combivent.
- ii. Subject (b) (6) experienced unstable angina on March 8, 2002 and was admitted to the hospital on (b) (6). Records indicate that you were aware of this SAE per the signed SAE report which you dated on March 20, 2002. Source records indicate that the subject received Combivent while hospitalized. Your site, however, failed to update the SAE report to notify the sponsor that Combivent was taken as a concomitant therapy during the hospitalization.

2. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].

Per the protocol, the subjects were to be provided a handihaler and a supply of 110 blinded capsules (11 packages of 10 capsules) at randomization (i.e. Visit 2), and a new supply of 110 capsules (11 packages of 10 capsules) was to be dispensed at Visit 3. The protocol further stated that at the beginning of Visits 3 and 4, all study medication capsules (used and unused) were to be collected. For 13 of 58 subject records reviewed, however (i.e. Subject (b) (6)), there was no documentation of reconciliation between quantities of study drug dispensed and quantities of study drug returned by subject. Examples include but were not limited to the following:

Subject Number	Visit #	Amount of drug capsules dispensed	Visit #	Total amount (used and unused) drug returned	Unreconciled number of drug capsules
(b) (6)	3	110	4	91	19
(b) (6)	3	110	4	12	88
(b) (6)	3	110	4	116	16
(b) (6)	2	110	3	99	11
(b) (6)	2	110	3	105	5

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 or will be taking 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 Tejashri Purohit-Sheth, M.D., at 301-796-3402; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg 51, Room 5358
10903 New Hampshire Avenue
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

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this page is the manifestation of the electronic signature.**

/s/

Leslie Ball
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