

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Taber, Louise A., MD 10/9/14



Department of Health and Human Services

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

OCT 9, 2014

WARNING LETTER

CERTIFIED MAIL RETURN RECEIPT REQUESTED

Louise A. Taber, M.D.
45-10-01
2525 W. Greenway Road, Suite 114
Phoenix, AZ 85023-4226

Ref.: 14-HFD-

Dear Dr. Taber:

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 July 7 and July 18, 2014. Ms. Sonia R. Peterson, representing FDA, reviewed your conduct of the following clinical investigations of the investigational drug hydrocodone bitartrate, performed for Purdue Pharma L.P.:

- Protocol HYD3002, "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Run-in to Assess the Efficacy and Safety of Hydrocodone Bitartrate (HYD) Tablets 20 to 120 mg Once Daily in Subjects with Moderate to Severe Chronic Low Back Pain"; and
- **(b)(4)**

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. Peterson presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your August

1, 2014, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your written response dated August 1, 2014, 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 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 for Protocol (b)(4) included pure-tone air-conduction audiometry reports. You failed to maintain adequate and accurate case histories with respect to these reports.

Specifically, for 4 of the 19 subjects whose records were reviewed during the inspection, pure-tone air-conduction audiometry reports that were represented as reports for these subjects were originally reports for other subjects. The original subject identification numbers and visit dates on audiometry reports were obscured with black marks, and handwritten subject identification numbers and visit dates that do not correspond with the original subject identification numbers were subsequently added to these reports.

- a. For Subject 3045003, audiometry reports that were represented as reports for this subject at Visit 2 (August 31, 2011) and Visit 3 (September 22, 2011) are obscured audiometry reports that were originally for other subjects.
 - i. The audiometry report for Visit 2 (August 31, 2011) was originally a report for Subject 3045026. Also of note, the audiometry results entered into Subject 3045003's electronic case report form (eCRF) for Visit 2 are identical to the results in Subject 3045026's eCRF for Visit 2.
 - ii. The audiometry report for Visit 3 (September 22, 2011) was originally a report for Subject 3045040. Also of note, the audiometry results entered into Subject 3045003's eCRF for Visit 3 are identical to the results in Subject 3045040's eCRF for Visit 2.
- b. For Subject 3045005, audiometry reports that were represented as reports for this subject at Visit 2 (September 6, 2011) and Visit 3 (September 21, 2011) are obscured audiometry reports that were originally for other subjects.
 - i. The audiometry report for Visit 2 (September 6, 2011) was originally a report for Subject 3045012. Also of note, the audiometry results entered into Subject 3045005's eCRF for Visit 2 are identical to the results in Subject

3045012's eCRF for Visit 3.

ii. The audiometry report for Visit 3 (September 21, 2011) was originally a report for Subject 3045016. Also of note, the audiometry results entered into Subject 3045005's eCRF for Visit 3 are identical to the results in Subject 3045016's eCRF for Visit 2.

c. For Subject 3045011, audiometry reports that were represented as reports for this subject at Visit 2 (September 20, 2011) and Visit 3 (October 13, 2011) are obscured audiometry reports that were originally for other subjects.

i. The audiometry report for Visit 2 (September 20, 2011) was originally a report for Subject 3045012. Also of note, the audiometry results entered into Subject 3045011's eCRF for Visit 2 are identical to the results in Subject 3045012's eCRF for Visit 3, except that Subject 3045011's eCRF contains a transcription error.

ii. The audiometry report for Visit 3 (October 13, 2011) was originally a report for Subject 3045015. Also of note, the audiometry results entered into Subject 3045011's eCRF for Visit 3 are identical to the audiometry report results for Subject 3045015 for Visit 2.

d. For Subject 3045013, audiometry reports that were represented as reports for this subject at Visit 2 (September 21, 2011) and Visit 3 (October 7, 2011) are obscured audiometry reports that were originally for other subjects.

i. The audiometry report for Visit 2 (September 21, 2011) was originally a report for Subject 3045026. Also of note, the audiometry results entered into Subject 3045013's eCRF for Visit 2 are identical to the results in Subject 3045026's eCRF for Visit 2.

ii. The audiometry report for Visit 3 (October 7, 2011) was originally a report for Subject 3045026. Also of note, the audiometry results entered into Subject 3045013's eCRF for Visit 3 are identical to the results in Subject 3045026's eCRF for Visit 2.

In your August 1, 2014, written response to the Form FDA 483, you indicated that **(b)(4)**, the clinical research organization (CRO) site monitor, instructed your study coordinator to obscure identifying subject information. In addition, you acknowledged that your study coordinator made errors in transcribing the subject information. You indicated that the errors in transcribing the subject information were not intentional and involved only 5% of all audiograms that your site generated for Protocol **(b)(4)**.

You further indicated that, where applicable, you have instituted additional measures and procedures to address the inspection findings.

Your response is inadequate, because you did not provide sufficient information to enable us to evaluate the adequacy of your corrective action plans for use in any

future clinical research that you may conduct. You did not provide any details of a corrective action plan to prevent similar violations from occurring in the future, nor have you provided sufficient details regarding your plan to implement additional measures and procedures to address the inspection findings. Without these details, we are unable to determine whether your corrective action plan appears sufficient to prevent similar violations in the future.

Your failure to maintain adequate and accurate case histories with respect to audiology reports raises concerns about the validity and integrity of the data captured at your site.

2. 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 HYD3002 required that pure-tone air-conduction audiometry testing be performed within the 5 days before Visit 3 (randomization visit) for subjects who were eligible for randomization in the double-blind phase of the study. Of note, audiometry testing was an important safety assessment in this study.

You failed to adhere to these requirements. Specifically, you did not perform pure-tone air-conduction audiometry tests before randomization of the following subjects:

- a. Subject 2033030 was randomized on September 6, 2012; however, audiometry testing was not performed until October 4, 2012, approximately 28 days after randomization.
- b. Subject 2033034 was randomized on September 18, 2012; however, audiometry testing was not performed until October 11, 2012, approximately 23 days after randomization.
- c. Subject 2033037 was randomized on August 29, 2012; however, no audiometry testing was performed.
- d. Subject 2033038 was randomized on August 31, 2012; however, audiometry testing was not performed until October 2, 2012, approximately 32 days after randomization.
- e. Subject 2033043 was randomized on September 12, 2012; however, audiometry testing was not performed until October 2, 2012, approximately 20 days after randomization.
- f. Subject 2033044 was randomized on September 24, 2012; however, audiometry testing was not performed until November 5, 2012, approximately 42 days after randomization.
- g. Subject 2033053 was randomized on August 28, 2012; however,

audiometry testing was not performed until October 4, 2012, approximately 37 days after randomization.

In your August 1, 2014, written response to the Form FDA 483, you acknowledged that some subjects did not have audiometry testing at Visit 3, as required by the protocol. You noted that this protocol procedure was omitted as an entry on revisions to source documents. You also acknowledged that you overlooked this protocol requirement, and that error resulted in missed audiograms for 6% of all audiograms that your site generated for Protocol HYD3002. You indicated that, where applicable, you have instituted additional measures and procedures to address the inspection findings. You further indicated that for the last several years, you have personally reviewed “drafts of source documents for inclusion of all protocol procedures,” and you have also designated an in-house quality assurance coordinator to review source documents against the protocol.

Your response is inadequate because your corrective action plan is insufficiently detailed. For example, it is unclear why you would have source documents in draft form, and whether these drafts are instead draft templates for capturing study information. As a result, we are unable to determine whether your corrective action appears sufficient to prevent similar violations in the future.

You failed to conduct audiometry tests before subject randomization, and this failure jeopardized subject safety and welfare. Of particular concern is the fact that, for Protocol HYD3002, audiometry tests that were used to assess the safety of subjects were not performed before randomization for 7 of the 16 enrolled subjects whose study records were reviewed.

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 you have complied with FDA regulations, include your reasoning and any supporting information for our consideration.

If you have any questions, please contact Constance Cullity, 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, M.D., M.P.H.
Branch Chief
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance

Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Building 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

{See appended electronic signature page}

Sean Y. Kassim, Ph.D.

Director

Office of Scientific Investigations

Office of Compliance

Center for Drug Evaluation and Research

U.S. 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/

SEAN Y KASSIM

10/09/2014

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