Inspections, Compliance, Enforcement, and Criminal Investigations

Teneo IRB, 11/10/09

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Center for Biologics
Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448

November 10, 2009

By Facsimile Transmission and Overnight Delivery

CBER-10-01

Warning Letter

Craig N. Lamb, Ph.D., President
Teneo Institutional Review Board
2706 South 109th East Avenue
Tulsa, Oklahoma 74129-7634

Dear Dr. Lamb:

This letter describes the results of a Food and Drug Administration (FDA) inspection of the Teneo Institutional Review Board (hereafter referred to as "the IRB") that was conducted from March 12 to 18, 2009. An FDA investigator met with you to conduct an inspection of the IRB to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 56. The inspection was part of FDA's Bioresearch Monitoring Program, which includes inspections designed to review IRB operations for clinical studies using investigational products and for the protection of human subjects.

The FDA investigator issued and discussed the Form FDA 483, Inspectional Observations, with you at the end of the inspection. In addition, FDA reviewed Teneo IRB documents provided in response to FDA inquiries during a **(b)(4)**.

We have determined that the IRB significantly violated applicable federal regulations

governing the operation and responsibilities of IRBs as published under 21 CFR Part 56 (available at http://www.fda.gov/ScienceResearch/SpeciaITopics/RunningClinicaITrials/default.htm).

The applicable provisions of the CFR are cited for the violation.

The Teneo IRB failed to prepare and maintain adequate documentation of IRB activities. [21 CFR § 56.115(a)(1) and (2)].

During the Teneo IRB inspection the FDA investigator asked for a complete set of the IRB's meeting minutes, and you provided the FDA investigator with the minutes we refer to in this letter as the "Teneo Minutes from Teneo." During the inspection, provided FDA with copies of documents had received from the Teneo IRB. One set of documents, entitled "IND Matters", is the same as the Teneo Minutes from Teneo.

A second set of documents is entitled "Medical Practice and Treatment Matters" which we refer to in this letter as the "Teneo Minutes from **(b)(4)**. Although we refer to this second set of documents as the Teneo Minutes from **(b)(4)** to reflect the origin of the minutes collected by our investigator, these minutes (letterhead, signatures, etc.) document activities of the Teneo IRB.

FDA's review of the Teneo Minutes from **(b)(4)** show that the Teneo IRB reviewed and approved **(b)(4)** studies that are not included in the Teneo Minutes from Teneo. The Teneo Minutes from Teneo report activities related only to the study entitled **(b)(4)** (hereafter referred to as the "**(b)(4)** study"). However, the Teneo Minutes from **(b)(4)** document that the Teneo IRB conducted a full range of IRB activities that are not described in the Teneo Minutes from Teneo: the Teneo IRB approved **(b)(4)** protocols and consent forms; conducted continuing review; discussed the enrollment, treatment, and consent of pediatric subjects; granted emergency approvals; evaluated adverse event reports; and revised the Teneo IRB Standard Operating Procedures (SOP) without documenting these activities in the Teneo Minutes from Teneo. Compared to the Teneo Minutes from **(b)(4)**, the Teneo Minutes from Teneo are inaccurate and incomplete, as shown in the following examples.

1. There are discrepancies between the the Teneo Minutes from Teneo and the Teneo Minutes from **(b)(4)** for IRB meetings held on the following dates: October 23, 2008, September 16, 2008, July 8, 2008, March 4, 2008, February 5, 2008, May 2, 2007, April 3, 2007, March 6, 2007, January 9, 2007, December 5, 2006, and October 12, 2006. Also, there are no Teneo Minutes from Teneo for the January 8, 2008, July 10, 2007 or February 6, 2007 IRB meetings.

A. In some cases, the Teneo Minutes from Teneo do not include the individual vote of Teneo IRB members. For example, on October 23, 2008 the Teneo IRB voted to make a change in the informed consent for the **(b)(4)** procedure. The individual member vote was recorded in the Teneo Minutes from , but does not appear in the Teneo Minutes from Teneo.

Also, the Teneo Minutes from **(b)(4)** document an individual vote for adjournment that shows the absence of one member, for a meeting held on February 5, 2008. The Teneo Minutes from Teneo for the same meeting, do not show the absence of a member.

Furthermore, for a meeting conducted on January 8, 2008 the Teneo Minutes from **(b)(4)** show an individual roll call vote for the postponement of review of minutes from the previous meeting. There are no Teneo Minutes from Teneo for this meeting.

B.The Teneo Minutes from Teneo omit serious adverse events reported to the Teneo IRB and investigation of these events. The Teneo Minutes from **(b)(4)** show that adverse events were discussed at meetings held on September 16,2008, July 10, 2008, March 4,2008, February 5,2008 and January 8, 2008.

C. The Teneo Minutes from Teneo did not include the following Teneo IRB business items:

i. The Teneo Minutes from **(b)(4)** show that the Teneo IRB approved the following: all SOPs that were current as of the July 10, 2007 meeting; SOP 8 on January 8, 2008; and SOPs 5, 7, 8, and 47 on March 4, 2008. The Teneo Minutes from Teneo for March 4, 2008 do not include the approval of SOPs 5, 7,8, and 47.

ii The Teneo Minutes from Teneo do not show the addition of a new Teneo IRB member at the March 4, 2008 meeting.

D. The Teneo Minutes from Teneo do not show that on September 16, 2008 the Teneo IRB voted to amend the minutes of the meeting held on July 8, 2008. The Teneo Minutes from **(b)(4)** include a copy of the amended minutes; however, the Teneo Minutes from Teneo do not contain any record of such amendment.

2. The Teneo Minutes from Teneo do not include any records for Teneo IRB meetings held on January 8, 2008, July 10, 2007, and February 6, 2007. Minutes for these three meetings exist in the Teneo Minutes from **(b)(4)** and show discussion of items pertinent to Teneo IRB operations.

For example, the Teneo Minutes from **(b)(4)** for the January 8, 2008 meeting show the Teneo IRB voted to postpone review of IRB meeting minutes from the previous meeting and discussed changes to SOP 8. The Teneo Minutes from Teneo have no record of this meeting.

The Teneo Minutes from **(b)(4)** for the meeting held July 10, 2007 show that the IRB discussed communication between the IRB and investigator, compensation for research subjects, and providing subjects with copies of informed consents. The Teneo Minutes **(b)(4)** from Teneo have no record of the July 10, 2007 meeting.

The February 6, 2007 Teneo Minutes from **(b)(4)** show that the Teneo IRB discussed the following: review of informed consent forms, the availability of classes providing Human Subject Training for Teneo IRB members, Teneo IRB membership, the Teneo IRB's website, the format of Teneo IRB's meeting minutes, and new protocols to be discussed at the next meeting. The Teneo Minutes from Teneo have no record of this meeting.

3. The Teneo Minutes from **(b)(4)** include electronic correspondence showing an agenda for meetings on August 7, 2007, September 5, 2007, and November 6, 2007 and the statement "Please acknowledge receipt of this email and your attendance at

the Teneo IRB Board of Directors meeting today". The Teneo Minutes from Teneo do not include any reference to meetings on these dates.

4. The Teneo Minutes from Teneo omit that the Teneo IRB reviewed and approved several **(b)(4)** studies, **(b)(4).**

5. The Teneo IRB did not maintain copies of approval letters that it issued. These approval letters were submitted to FDA on August 17, 2009 by **(b)(4)**. These approvals are not in the Teneo records.

A. Two approval letters were issued to **(b)(4)** by the Teneo IRB on November 1, 2008 for the protocols and informed consents of studies entitled , **(b)(4)** which permits the enrollment of pediatric subjects, and **(b)(4).** The letters state the approval date for both studies is October 23, 2008 and the due date for continuing review is October 23, 2009.

B. The Teneo IRB issued an approval letter to **(b)(4)** on November 1, 2007 for the protocol and consent form for the study **(b)(4).**

6. The Teneo IRB did not maintain documentation of requests for "emergency approvals" or the IRB action taken on these requests. An electronic communication from you to the members of the Teneo Board of Directors on October 25, 2007 in the Teneo Minutes from **(b)(4)** shows you voted for the "emergency approval" of the "**(b)(4)**" and the proposed "**(b)(4)'**.

7. The Teneo Minutes from Teneo for the Teneo IRB meeting held on July 8, 2008 fail to show that the Teneo IRB discussed pediatric consent forms and the hiring of pediatric specialists. The Teneo Minutes from **(b)(4)** for the July 8, 2008 meeting document that the IRB considered the addition of a pediatric oncologist, pediatric cardiologist, or a neuropediatric oncologist to the Teneo Board because **(b)(4)** is currently working with several pediatric cancer cases and expects more in the future."

8. Sections of the protocol and informed consent are inconsistent with regard to the participation of children in the study **(b)(4).** The Teneo IRB approved the research without resolving the following inconsistencies during the review and approval process:

A. The "Patient Criteria of Treatment" section of the protocol specifies "Patients must be 18 years or older to be eligible for this treatment protocol. Patients under age 18 must have the consent of their legal guardian."

B. The Inclusion Criteria makes no provision for subjects under 18 as it clearly states "Patients 18 and older presenting with **(b)(4)**."

C. The Exclusion Criteria excludes subjects "age less than 18 years (unless consent is given by legal guardian)".

D. Consent Forms entitled "Adolescent (12-17) Agreement to Receive **(b)(4)** "Treatment" and "General Adolescent (12-17) Agreement to Receive **(b)(4)** Treatment" are available for ages 12 to 17.

During the inspection you told the FDA investigator that the IRB did not review any studies other than the **(b)(4)** study, that the IRB received no adverse event reports, that no studies were reviewed by Teneo IRB involving children, and that the minutes provided to the FDA investigator were complete. Please explain.

The following corrective actions were initiated by you at the close of the inspection: an updated membership roster was provided to the FDA investigator that identified members as scientific or non-scientific and SOP #5 was revised to change the requirement for monthly IRB meetings to one meeting in October of each year with additional meetings scheduled by the Chair as needed. You also revised the approval letter dated February 11, 2009 for the study An *Open Label, Single Site, Safety and Efficacy Study of the Effects* of **(b)(4).** The approval letter initially showed an expiration of three years, you revised the letter to show expiration of approval to occur at one year.

In addition, we remind you of a regulation that was not in effect at the time of the Teneo IRB inspection. 21 CFR § 56.106 requires "Each IRB in the United States that reviews clinical investigations regulated by FDA under sections 505(i) or 520(g) of the act and each IRB in the United States that reviews clinical investigations that are intended to support applications for research or marketing permits for FDA-regulated products must register at a site maintained by the Department of Health and Human Services (HHS)." Each IRB may register electronically through http://ohrp.cit.nih.gov/file or in writing at:

Good Clinical Practice Program (HF-34)
Office of Science and Health Coordination
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

This letter is not an all-inclusive list of violations. It is incumbent upon you and the IRB to correct the violations cited in this letter, and to conduct a thorough review of the IRB's SOPs and practices to ensure full compliance with the regulations.

As a result of the IRB's noncompliance with FDA regulations, described above, in accordance with 21 CFR §§ 56.120(b)(1) and (2), and effective immediately,

● FDA will withhold approval of all new studies reviewed by this IRB; and

● No new subjects are to be enrolled in any ongoing studies subject to 21 CFR Part 56.

These restrictions will remain until such time that you have received written notification from this office that adequate corrections have been made. These restrictions do not relieve the IRB of its responsibility for receiving and reacting to reports of unexpected and serious reactions and routine progress reports from ongoing studies.

You are to notify this office of the specific actions you have taken or plan to take to bring the IRB into full compliance with FDA regulations. Your response should address each item listed above, and should include any documentation necessary to show that

full and adequate correction has been achieved. Include the projected completion dates for each action to be accomplished.

Include with your response a copy of the IRB's written communication to each of the affected sponsors and clinical investigators, notifying them of the current FDA imposed restrictions. Please provide an updated list of all studies currently being reviewed by Teneo IRB, identify those that are subject to 21 CFR Part 56, and list all studies that are affected by the "Withhold approval of' and "No new subjects" restrictions.

On the basis of your written response, FDA may schedule a reinspection to confirm the adequacy of your corrective actions.

Christine Drabick
Division of Inspections and Surveillance (HFM-664)
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Should you have any questions or comments about the contents of this letter or any aspects of the operations and responsibilities of an Institutional Review Board, you may contact Christine Drabick at (301) 827-6323.

We request that you also send a copy of your response to the FDA District Office listed below.

Sincerely,

/s/

Mary Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc: Reynaldo Rodriguez, District Director
Food and Drug Administration
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(b)(4)