DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Food and Drug Administration
Rockville, Maryland 20857

WARNING LETTER

CERTIFIED MAIL
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Ref: 09-HFD-46-04-01

Mr. Daniel Dueber
Chief Executive Officer
Coast IRB, LLC
5475 Mark Dabling Blvd., Suite 351
Colorado Springs, CO 80918

April 14, 2009

Dear Mr. Dueber:

On March 26, 2009, the U.S. House of Representatives' Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce held a hearing entitled, "Institutional Review Boards that Oversee Experimental Human Testing for Profit" (the Hearing). During the Hearing, Mr. Gregory Kutz, Managing Director, Forensic Audits and Special Investigations Unit of the U.S. Government Accountability Office (GAO), presented the testimony "Undercover Tests Show the Institutional Review Board System is Vulnerable to Unethical Manipulation."[1]

This testimony related to an investigation the GAO conducted between January 2008 and March 2009 to test, in part, whether institutional review boards (IRBs) are adequately evaluating studies submitted for approval. In this test, the GAO created "a bogus medical device company" and "a research protocol for a fictitious medical device with no proven test history and bogus specifications." The protocol was designed "so that it would contain vague information about certain aspects of our proposed study." The "fictitious device was a post-surgical healing device for women that matched multiple examples of 'significant risk' devices provided in publicly available FDA guidance."

The GAO selected three independent IRBs from on an online search and submitted a fictitious protocol to each IRB for their review. The GAO testified that Coast IRB, LLC, was the only IRB selected that reviewed and approved the research protocol and did so with only minor edits to the submitted materials. Mr. Kutz testified that Coast IRB failed to verify the falseassertion contained in the protocol submission that the Food and Drug Administration (FDA) had already cleared the device for marketing, which could have been accomplished through a search of FDA's online database. In addition, the GAO testified that Coast IRB meeting minutes showed that the board members thought the protocol was "probably very safe" and voted unanimously to approve it even though the materials submitted to the IRB for review contained insufficient safety information to make such a determination.

[1] Accessed on April 9, 2009 at http://www.gao.gov/new.items/d09448t.pdf

In a telephone conversation on April 14, 2009, between Mr. Daniel Dueber, Chief Executive Officer of Coast IRB and Dr. Leslie Ball and Dr. Michael Marcarelli of the FDA, we discussed the GAO's written testimony and other information made publicly available at the Hearing, including the device clinical study protocol provided to Coast IRB and the informed consent form approved by Coast IRB.[2] During this discussion, FDA identified the following serious violations of Title 21, Code of Federal Regulations (21 CFR) Part 56 – Institutional Review Boards, Part 812 – Investigational Device Exemptions (IDE), and Part 50 – Protection of Human Subjects.[3] Under 21 CFR § 56.111(a), in order to approve research covered by these regulations, the IRB shall determine, among other things, that risks to subjects are minimized and that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. FDA does not believe Coast IRB had sufficient information needed in order to make the determinations required for approval of an investigation under 21 CFR § 56.111. Below we have cited applicable provisions of the CFR relevant to this violation. We have also described several other serious violations of FDA regulations at 21 CFR parts 50, 56, and 812.

1. **The IRB failed to determine that risks to subjects are minimized. [21 CFR § 56.111(a)(1)].**

   Based on the GAO's written testimony and our review of the publicly available information, Coast IRB did not have sufficient information to identify potential risks to subjects and to determine that risks to subjects are minimized, as required under 21 CFR § 56.111(a)(1). The information submitted to Coast IRB by the GAO did not include a complete device description or results from preclinical testing. For example, the protocol provided to Coast IRB mentioned use of the ADHESIABLOC® Gel in "preclinical animal models" (p. 3) without providing any further information. Without a complete device description or results from preclinical testing, a determination that risks to subjects are minimized could not be made.

2. **The IRB failed to determine that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. [21 CFR § 56.111(a)(2)].**

   As noted above, Coast IRB did not have sufficient information to identify risks to subjects; nor was sufficient information available to assess anticipated benefits. For example, while the background information in the protocol states, "In clinical evaluations conducted by Device Med-Systems, Propylene Glycol [an apparent component of the device] is found to be safe and marginally effective" (p. 2), the results of these evaluations were not provided. Similarly, the protocol states that the ADHESIABLOC® Gel "has shown to prevent or reduce adhesion formation by hydro floatation [and] is as effective as the starting solution in preclinical animal models" (p. 3), without identifying the "starting solution" or providing results of this preclinical testing. Based on this limited information, Coast IRB could not

[2] Available at http://energycommerce.house.gov/index.php?option=com_content&task=view&id=1552
[3] Available at http://www.gpoaccess.gov/crf/index.html

determine that the risks to subjects were reasonable in relation to the anticipated benefits, as required under 21 CFR § 56.111(a)(2).

3. The IRB failed to determine the applicability of 21 CFR Part 812 and failed to make a risk determination for the investigational device study. [21 CFR §§ 812.2(c)(2), 812.66, 812.20(a)].

Coast IRB did not take appropriate steps to determine the applicability of 21 CFR Part 812 to the investigation. The information submitted indicated the device had a cleared premarket notification (510(k)). In order for the device investigation to proceed without an FDA-approved IDE, Coast IRB needed to determine that the investigation was exempt under 21 CFR § 812.2(c). Specifically, in light of the information submitted, Coast IRB needed to determine whether the device was being investigated in accordance with the indications for which the device was apparently cleared (i.e., the indications in the labeling that FDA had apparently reviewed under 21 CFR part 807). 21 CFR § 812.2(c)(2). Coast IRB failed to make this determination. Based on the GAO's written testimony and other information made publicly available at the Hearing, we have determined that the investigation would not have been exempt under 21 CFR § 812.2(c).

For device investigations that are not exempt from the submission requirements of 21 CFR Part 812, IRBs are required to make the significant/non-significant risk determination under 21 CFR § 812.66. [4] Coast IRB failed to make such a determination. Based on the GAO's written testimony and our review of the publicly available information, we have determined that a study involving the ADHESIABLOC® Gel device would be considered a significant risk device investigation,[5] requiring submission to FDA and FDA approval of an IDE before the investigation could be initiated. 21 CFR § 812.20(a).

4. The IRB failed to ensure that basic elements of informed consent are included in the IRB-approved consent form. [21 CFR §§ 50.25(a)(2), 56.109(b)].

Under 21 CFR § 56.109(b), the IRB shall require that information given to subjects as part of informed consent is in accordance with 21 CFR § 50.25. One of the basic elements of informed consent, required under 21 CFR § 50.25(a)(2), is a description of any reasonably foreseeable risks or discomforts to the subject. As discussed above, Coast IRB did not have sufficient information to identify any reasonably foreseeable risks to subjects. Coast IRB did not have a complete device description or results from the preclinical and clinical testing referenced in the background section of the protocol (pp. 2-3). Under the heading "What are

[4] For more information on this determination, see "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies," available at http://www.fda.gov/oc/ohrt/irbs/devrisk.pdf.

[5] Significant risk device means an investigational device that: (1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; (3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. [21 CFR § 812.3(m)].

the possible risks or discomforts involved with being in the study?" the consent form approved by Coast IRB states, "There are no known side effects or discomforts associated with ADHESIABLOC® Gel, but there may be uncommon or previously unknown risks" (p. 3). Because Coast IRB approved this consent form without having sufficient information to identify foreseeable risks to subjects, it did not meet its obligation under 21 CFR § 56.109(b) to require that the information provided to subjects as part of informed consent include a description of any foreseeable risks or discomforts.

5. **The IRB failed to demonstrate its ability to ascertain the acceptability of the proposed research in terms of regulations, applicable law, and standards of professional conduct and practice. [21 CFR § 56.107(a)].**

   Under 21 CFR § 56.107(a), an IRB must be able to ascertain the acceptability of the proposed research in terms of regulations, applicable law, and standards of professional conduct and practices. Coast IRB failed to demonstrate this ability. As discussed above, Coast IRB approved a device investigation without adequate information on the risks posed to subjects, without a qualified clinical investigator, without assuring that the investigation met the exemption criteria under 21 CFR § 812.2(c)(2), and without assuring that the information provided to subjects as part of informed consent is in accordance with 21 CFR § 50.25(a)(2). FDA believes the above findings indicate a lack of understanding of the applicable regulations, law, and standards of professional conduct and practice.

Given the seriousness of these violations and the risk to the rights and welfare of human research subjects, on April 14, 2009 Coast IRB, LLC voluntarily agreed to the following restrictions:

1. No new studies subject to the requirements of 21 CFR Part 56 will be approved; and

2. No new subjects will be added to on-going studies subject to 21 CFR Part 56.

These restrictions will remain in effect until such time that you receive written notification from FDA that adequate corrections have been made. These restrictions do not relieve Coast IRB of its responsibility for receiving and responding to reports of unexpected and serious reactions and routine progress reports from ongoing studies.

Within fifteen (15) working days of receiving this letter, you are to notify the Agency of the specific actions you have taken or plan to take to bring Coast IRB into full compliance with FDA regulations. Your response should include any documentation necessary to show that full and adequate correction has been achieved and include the projected completion dates for each action to be accomplished.

It is your responsibility to notify all affected sponsors and clinical investigators of the restrictions described above. Include with your response to the FDA a representative sample copy of the IRB's written communication(s) to affected sponsors and clinical investigators, notifying them of the current restrictions. Please also provide a complete list of all sponsors and investigators notified as a result of this action and the date on which they were notified.

Please provide a list of all studies currently being conducted that are affected by the above restrictions and include the titles of the studies (with IDE or IND numbers, if applicable), the names of the test articles, the names of the clinical investigators, dates of initial reviews and approvals, and dates of continuing reviews. IND and IDE numbers can be obtained through the sponsor of the protocols affected by these restrictions.

Failure to respond to this letter and take appropriate corrective action could result in FDA taking regulatory actions, as authorized by 21 CFR §§ 56.120, 56.124, and 56.121. These actions include, but are not limited to, continuation of the restrictions described above, the termination of on-going studies subject to 21 CFR Part 56 and approved by your IRB, and the initiation of regulatory proceedings for disqualification of your IRB.

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 Dr. Leslie Ball at (301) 796-3150.

Please send your written response to:

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg 51, Room 5342
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely,

/s/
Deborah M. Autor, Esq.
Director
Office of Compliance
Center for Drug Evaluation and Research

/s/
Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and Radiological Health