Inspections, Compliance, Enforcement, and Criminal Investigations

Essex Institutional Review Board, Inc 7/26/11

Department of Health and Human Services

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

WARNING LETTER

July 26, 2011

UPS Ref: 11-HFD-45-07-03

Ms. Nancy Waggoner
Chief Executive Officer
Essex Institutional Review Board, Inc.
121 Main Street
Lebanon, NJ 08833

Dear Ms. Waggoner:

Between March 14, 2011 and March 21, 2011, Ms. Dawn Wydner, Dr. Denise Visco, and Ms. Janet Donnelly, representing the Food and Drug Administration (FDA), inspected Essex Institutional Review Board (IRB), Inc. The purpose of this inspection was to determine whether the IRB procedures for the protection of human subjects complied with Title 21 of the Code of Federal Regulations (CFR), parts 50 and 56. These regulations apply to clinical investigations of products regulated by FDA. We are aware that at the conclusion of the inspection, our investigators presented and discussed with Ms. Loretta Szczepanski, R.N., IRB Vice Chairperson, and your staff, a Form FDA 483, Inspectional Observations.

As discussed during the inspection with Dr. Glenn Lambert, IRB Chairman, in January 2011, FDA received information regarding the submission of fictitious applications for research to several IRBs. FDA's investigation determined that a fictitious sponsor submitted protocol **(b)(4)** entitled, "**(b)(4)**" to several IRBs for review. FDA determined that the **(b)(4)** protocol is an actual protocol that was previously conducted and completed by a different sponsor. The fictitious sponsor also submitted information regarding a fictitious clinical investigator. On January 27, 2011, FDA posted an alert notice on the FDA web page to notify IRBs and other stakeholders of these submissions. On February 8, 2011, Dr. Lambert notified FDA that Essex IRB had reviewed and approved this fictitious clinical investigator to conduct the **(b)(4)** protocol.

From our review of the establishment inspection report, the documents submitted with that report, and Dr. Lambert's written response dated April 11, 2011, we conclude that the IRB did not adhere to the applicable statutory requirements and FDA regulations governing the protection of human subjects. We wish to emphasize the following:

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

Under 21 CFR 56.111(a), one of the criteria for IRB approval of research is that the IRB must determine that risks to subjects are minimized. In its review of proposed research, Essex IRB failed to ensure risks to subjects were minimized. Specifically:

A. The **(b)(4)** protocol and the Investigator's Brochure submitted to Essex IRB by the fictitious sponsor clearly indicate that the test article is a **(b)(4)**. With this drug class, there is a well established association with the potential for increased risk of

serious cardiovascular events. However, there is no evidence in the IRB meeting minutes for the initial review of this protocol (October 25, 2010) to indicate that the IRB considered this risk in determining whether risks to subject were minimized. The potential for associated cardiovascular risks was also not included in the IRB-approved informed consent form.

The IRB's written response indicates that the IRB determined, in hindsight, that the information provided to the IRB by the fictitious sponsor was inadequate in describing risk information, including cardiovascular risk. Your proposed corrective action is that for future submissions, the IRB will require sponsors and investigators to attest to the completeness and accuracy of study submissions. This response is inadequate because it fails to address what actions the IRB will take to ensure a comprehensive review of information associated with proposed research.

While Essex IRB requires that specific study documents be submitted for IRB review, and relies on the information submitted by the sponsor and investigator, it is incumbent upon the IRB to conduct a thorough, independent, systematic, non-arbitrary analysis of risks and benefits. The regulations at 21 CFR 56.107 require the IRB to use its experience, expertise, and professional competence to ascertain the acceptability of the proposed research. IRB members should consider the information submitted to the IRB, as well as information accessible to the IRB members through other resources.

We note that the IRB's written response indicates that the IRB will undertake additional measures to assess the completeness of the study information submitted to the IRB by referring to authoritative sources, such as PubMed, for a review of the available published literature related to or concerning the study agent. Your written response also provides that the IRB administrators will be trained on conducting such PubMed reviews. While the IRB administrators may assist the IRB, the overall responsibility for assessment of the adequacy of the proposed research requires the expertise of the IRB members.

An IRB review of proposed research that fails to adequately minimize risk may result in the approval of unethical research and may jeopardize the rights and welfare of human subjects. A thorough IRB review should ensure that human subjects are adequately protected, are not exposed to unnecessary risks, and are provided with enough information about a study so that they can give effective informed consent.

Please provide a written response that details the procedure Essex IRB intends to follow to ensure that the IRB members conduct a comprehensive review of proposed research, in accordance with the regulatory requirements for ensuring that risks to the subjects are minimized. Please submit a copy of any revised or new Standard Operating Procedures (SOPs) or written procedures developed to address this finding. Also, we note that your written response refers to the Essex IRB administrators, and we assume you are referring to the Essex IRB support staff. However, during the inspection, the FDA Investigators reviewed the job descriptions for the IRB support staff and found that none of the Essex IRB staff hold a title of IRB administrator. Please explain who you are referring to as the IRB administrators and clarify their role.

B. Our inspection revealed that Essex IRB failed to appropriately apply the FDA's regulatory definition of minimal risk. The regulations at 21 CFR 56.102(i) define minimal risk as, "*the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.*" Based on our review of the available documentation, the IRB's practice of applying this definition and assessing risk in review of proposed research fails to adequately consider the risks associated with an investigational test article. Essex IRB incorrectly determined that the following two studies, which involve the use of investigational test articles, posed no more than minimal risk to subjects:

- **(b)(4)** (fictitious sponsor, **(b)(4)**)
- **(b)(4)** (**(b)(4)**, protocol **(b)(4)**)

The IRB's written response indicates that the IRB agrees that it incorrectly identified these studies as presenting no more than minimal risk to subjects, and outlines proposed corrective actions that include revision of an SOP to include the regulatory definition of minimal risk, and training on the new SOP for IRB members and administrators. The IRB also indicates that all determinations about the degree of risk presented by a study will be made in accordance with the regulatory definition of minimal risk. This response is incomplete because it does not describe the criteria the IRB intends to establish and follow to ensure adequate interpretation and application of this regulatory definition in the future (i.e., the procedure describing how the IRB will determine whether a study involves no more than minimal risk).

The IRB's failure to adequately assess minimal risk may lead the IRB to underestimate risk to subjects. Although, as noted in the IRB's written response the full IRB reviewed both studies listed above, any future misapplication of minimal risk may lead the IRB to review greater than minimal risk studies using an inappropriate review procedure, in violation of the IRB regulations, including the expedited review regulations found at 21 CFR 56.110. In addition, misapplication of the definition of minimal risk may lead the IRB to inadequately review research involving children, in violation of the additional safeguards for children in clinical investigations found at 21 CFR 50, subpart D.

Please provide a written response that outlines the criteria and the method the IRB will use to review proposed research in the future to ensure that the IRB appropriately assesses minimal risk. Please submit a copy of the revised SOP mentioned in your written response and any new SOPs or written procedures developed to address this finding.

2. The IRB failed to demonstrate its ability to ascertain the acceptability of the proposed research in terms of institutional commitments, 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 institutional commitments, regulations, applicable law, and standards of professional conduct and practices. Our inspection revealed that the IRB failed to adequately assess the professional qualifications of the clinical investigator purported to be associated with protocol **(b)(4)** submitted by the fictitious sponsor. While we acknowledge the IRB's written response that it is the sponsor's responsibility to select qualified investigators, the IRB did not corroborate that the clinical investigator was a qualified clinical investigator. The IRB could have checked, among other things, that the medical license submitted to the IRB was valid in the State of Virginia where the research study was purported to be conducted. Failure to adequately consider the qualifications of the clinical investigator may expose subjects to unnecessary risks.

The IRB's written response indicates that, going forward, Essex IRB has implemented new procedures to verify the medical license documents submitted for all principal investigators as part of its review process, and that IRB administrators and IRB members will be trained on the revised SOP. This response is acceptable. Please submit a copy of the revised SOP mentioned in your written response.

3. The IRB failed to determine at the time of initial review that studies involving children are in compliance with 21 CFR Part 50, Subpart D, Additional Safeguards for Children in Clinical Investigations [21 CFR 56.109(h)].

Under 21 CFR 56.109(h), when some or all of the subjects in a study are children, the IRB must determine that the research study is in compliance with 21 CFR part 50, subpart D (Additional Safeguards for Children in Clinical Investigations) at the time of initial review. Under 21 CFR 50.50, an IRB may approve only those clinical investigations that satisfy the criteria described in 50.51 (clinical investigations not involving greater than minimal risk), 50.52 (clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects), or 50.53 (clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition).

Under 21 CFR 50.51, 50.52, and 50.53, the IRB must make and document certain findings. Our inspection revealed that in its review and approval of research involving pediatric subjects, Essex IRB failed to adequately find and document that the research satisfied the criteria of 50.51, 50.52, or 50.53. Specifically, the following pediatric study was reviewed and approved by the IRB, but the IRB records do not specify whether the study was approved under 50.51, 50.52, or 50.53:

- **(b)(4)** (**(b)(4)** protocol **(b)(4)**)

Failure to determine that the additional safeguards for children in research are met may expose this vulnerable population to unnecessary risks, and result in the child's parent(s) or guardian(s) not being fully informed about the proposed research.

In addition, we note that IRB records for this protocol (**(b)(4)**) and a second pediatric study (Pediatric Constipation Study **(b)(4)**) reviewed during the inspection include multiple inaccurate regulatory references with regard to 21 CFR part 50, subpart D. These records include, but are not limited to the following documents:

- The sample pediatric protocol checklist attached to SOP SX-SOP-10-13
- The pediatric protocol checklist used for each study
- The letter to the sponsor from the IRB for the constipation study
- The IRB meeting minutes for the constipation study

The IRB's written response states that Essex IRB has an SOP governing the assessment of the degree of pediatric risk in accordance with 21 CFR part 50, subpart D, but the IRB failed to document that determination. The written response also states that the IRB administrators and IRB members will be retrained on the need to document in the meeting minutes the risk determination, along with other required documentation depending on the identified risk determination. This response is incomplete because it does not describe the actual process the IRB will use to ascertain that the research satisfies the

criteria of 50.51, 50.52, or 50.53 for research involving children. We remain concerned that the IRB may not fully understand the additional safeguards for children that must be met in the review of research involving pediatric subjects. Please provide a written response that details the process the IRB will use to adequately evaluate and document that the research satisfies the criteria of 50.51, 50.52, or 50.53 in its review of future research involving pediatric subjects. Please submit a copy of any revised or new SOPs or written procedures developed to address this finding.

Lastly, the IRB's written response says that Essex IRB will also audit all ongoing pediatric studies to assure that the risk determination has been appropriately completed and documented. Please submit the results to FDA as soon as the audit is completed.

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

Under 21 CFR 56.109(b), the IRB must require that information given to subjects as part of the informed consent is in accordance with 21 CFR 50.25 (elements of informed consent). Our inspection revealed that Essex IRB failed to ensure that the IRB-approved informed consent forms for the following two studies contained adequate information about reasonably foreseeable risks or discomforts as required by 21 CFR 50.25(a)(2):

- **(b)(4)** (fictitious sponsor, protocol **(b)(4)**)
- **(b)(4)** (**(b)(4)**, protocol number **(b)(4)**)

As described in item #1A above, because it appears that the IRB failed to discuss the potential for increased risk of serious cardiovascular events for the **(b)(4)** study, the IRB failed to ensure that the potential for associated cardiovascular risks was included in the IRB-approved informed consent form.

The protocol provided to Essex IRB by the sponsor for the **(b)(4)** study lists graft rejection as a common adverse reaction in adult patients taking **(b)(4)**. The IRB meeting minutes for September 7, 2010, indicate that the IRB requested that the sponsor reformat the informed consent form to move the risk of graft rejection to a different paragraph in the informed consent document. Our inspection revealed that the IRB failed to ensure that graft rejection was included in the final IRB-approved informed consent form, as this risk was not included at all.

Failure to ensure that all of the FDA required elements of informed consent are met may result in human subjects not being provided with enough information about a study so that they can give effective informed consent.

The IRB's written response does not specifically address Form FDA 483 Observation 3. However, in response to Form FDA 483 Observation 1C, the IRB indicated that for the **(b)(4)** study, the IRB recognizes that the adverse event of graft rejection was inadvertently removed instead of being moved to a new location in the informed consent document. The IRB also indicates that the informed consent checklist will be revised to prompt IRB reviewers and staff to ensure that risk information in the informed consent document is consistent with risk information identified in the protocol, investigator brochure, or other relevant document (e.g. package insert) and will also prompt the IRB to request information from the sponsor or investigator where inconsistencies are identified. This response is acceptable. Please submit a copy of the revised informed consent checklist, and any revised or new SOPs or written procedures developed to accompany the revised form.

This letter is not intended to be an all-inclusive list of deficiencies for the protocols reviewed and approved by the IRB. It is your responsibility to ensure that Essex IRB's practices and procedures comply fully with all applicable statutes and regulations.

Within fifteen (15) business 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. Your written response should include any documentation necessary to show that full and adequate correction will be achieved. Please include the projected completion dates for each action to be accomplished. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

We recommend that you visit the following FDA web page for information on human subject protections that may assist you in your efforts to bring the IRB into compliance with FDA regulations:

http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm

We appreciate the cooperation shown to FDA Investigators Wydner, Visco and Donnelly during the inspection. If you have any questions, please contact Kevin Prohaska, D.O., M.P.H., at 301-796-3707; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

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Sincerely,
/S/

Leslie K. Ball, M.D.
Acting Director
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Office of Compliance
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cc: Glenn Lambert, M.D., IRB Chairman
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