DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10 Waterview Blvd., 3rd Floor Parsippany, NJ 07054 (973) 331-4900 Fax:(973) 331-4969 Industry Information: www.fda.gov/oc/industry	03/14/2011 - 03/21/2011
	FEI NUMBER 2246448

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Loretta P. Szczepanski, RN, Essex IRB Vice Chairperson

FIRM NAME	STREET ADDRESS
Essex Institutional Review Board, Inc	121 Main St
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Lebanon, NJ 08833-2162	Institutional Review Board

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

The IRB is not composed of at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.

Specifically, Essex IRB failed to demonstrate the ability to ascertain acceptability of the proposed research in terms of regulations, applicable law and standards of professional conduct and practice. For example:

A. Essex IRB approved a proposed clinical investigation (Protocol [(b) (4)] for a fictitious sponsor [(b) (4)] to be conducted by a fictitious clinical investigator [(b) (4)]. In the initial review, the IRB failed to:

1. Verify that this Clinical Investigator [(b) (4)] held a valid medical license in the state of [(b) (4)]
2. Recognize that the Clinical Investigator ([(b) (4)] had the same name, street address, city and state as the fictitous investigator [(b) (4)] conducted in 2009.
3. Identify that the proposed protocol was studying an investigational drug [(b) (4)] that was a previously approved product that had been withdrawn from the market in 2004 because of an increased risk of heart attacks and strokes with long term use.
4. Assess the potential for cardiovascular risk with the use of the drug when this class of drug [(b) (4)] is known to exhibit increased risk of cardiovascular events.
5. Identify this exact study protocol (Protoco[(b) (4)] had been previously completed by another company
6. Identify that IND [(b) (4)] submitted by the sponsor [(b) (4)] belonged to another company who had withdrawn the IND in 2008.

	EMPLOYEE(S) SIGNATURE	DATE ISSUED
SEE REVERSE OF THIS PAGE	Dawn L. Wydner, Investigator Janet Donnelly, Investigator Denise M. Visco, Investigator	03/21/2011

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B. Essex IRB reviewed a Phase I (first in man) investigational vaccine study [redacted (b) (4)] Protocol [redacted (b) (4)]), and incorrectly determined that the research was no more than minimal risk to subjects.

C. Essex IRB reviewed [redacted (b) (4)] Protocol #[redacted (b) (4)] for an anti-viral, and failed to include known side effects (acute renal failure in elderly patients) provided in the Package insert into the IRB approved consent form. In addition, the IRB removed a known adverse event (graft rejection) from the original sponsor provided ICF with no documented rationale.

OBSERVATION 2

The IRB approved the conduct of research, but did not determine that risks to subjects were minimized by using procedures which were consistent with sound research design and which did not unnecessarily expose subjects to risk.

Specifically, one of the criteria for IRB approval is that the IRB determine that risks to subjects are minimized. Essex IRB's process for assessment of risk in proposed research is inadequate.

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.*" Essex IRB's application of this definition to proposed research routinely fails to consider the type of test article, the investigational nature of the test article, and its use in the proposed research.

For example,

The IRB incorrectly determined that the two (2) following studies, which involve the use of an investigational drug or vaccine respectively, were no more than minimal risk:

1. [redacted (b) (4)]

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Dawn L. Wydner, Investigator Janet Donnelly, Investigator Denise M. Visco, Investigator	DATE ISSUED 03/21/2011

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2. [redacted]

OBSERVATION 3

The IRB does not require that information given to subjects as part of informed consent contain all necessary elements of informed consent.

Specifically, ICF review does not ensure safety of all subjects in that it does not have all information necessary to ensure subjects are fully educated on the reasonably foreseeable risks or discomforts. For example:

A. For clinical investigation (Protocol [redacted] for a fictitious sponsor [redacted] the potential for cardiovascular risk with the use of the investigational drug when this class of drug [redacted]) is known to exhibit increased risk of cardiovascular events was not included.

B. Essex IRB reviewed [redacted] Protocol [redacted] for an [redacted] and failed to include known side effects (acute renal failure in elderly patients) provided in the Package insert into the IRB approved consent form. In addition, the IRB removed a known adverse event (graft rejection) from the original sponsor provided ICF.

OBSERVATION 4

The IRB did not determine at the time of initial review that a study was in compliance with 21 CFR Part 50 Subpart D, "Additional Safeguards for Children in Clinical Investigations."

Specifically, for 2 out of 2 Pediatric studies reviewed, Essex IRB failed to document and provide communication of the pediatric risk category assigned to the research as determined by the IRB.

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	Dawn L. Wydner, Investigator Janet Donnelly, Investigator Denise M. Visco, Investigator	03/21/2011

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OBSERVATION 5 (b)(4)

Minutes of IRB meetings have not been prepared in sufficient detail to show actions taken by the IRB and a written summary of the discussion of controverted issues and their resolution.

Specifically, minutes of IRB meetings have not been prepared in sufficient detail to show pediatric risk determinations, non-significant vs. significant device determinations, and controverted issues and their resolution.

OBSERVATION 6

The IRB did not follow written procedures for ensuring prompt reporting to appropriate institutional officials and the FDA of any suspension or termination of IRB approval .

Specifically, SOP SX-SOP-20-6-1/3, "Suspension or Termination of Apprval of Research" requires the IRB to suspend or terminate its approval of a research study if there is evidence of ethical or scientific misconduct. Essex IRB became aware on February 7, 2011, that the [redacted (b)(4)] study to be conducted by [redacted (b)(4)] was fictitious, however to date, the IRB failed to terminate its approval in accordance with their SOP.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Dawn L. Wydner, Investigator Janet Donnelly, Investigator Denise M. Visco, Investigator	03/21/2011

Essex Institutional Review Board, Inc.
121 Main Street • Lebanon, New Jersey 08833
Telephone (908) 236-7735 • Fax (908) 236-2027
www.essexirb.com

April 11, 2011

Douglas I. Ellsworth
District Director HFR-CE300
New Jersey District (NWJ-DO)
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Dear Mr. Ellsworth:

Reference is made to the inspection by the Food and Drug Administration inspectors, LCDR. Dawn Wydner, USPHS, Janet C. Donnelly, RAC, and Denise Visco, PhD, at our facility located at 121 Main Street, Lebanon, NJ 08833, on March 14 -21, 2011. This correspondence addresses the six observations delineated in the resulting Form FDA 483 presented after the inspection. Each observation (in bold) is listed below followed by our response and corrective actions.

Essex Institutional Review Board, Inc. ("Essex IRB") is committed to ensuring the protection of human subjects involved in clinical research and as such takes all FDA observations very seriously. In light of the unusual events associated with this inspection, Essex IRB has undertaken a complete review of its standard operating practices and procedures to ensure compliance with all applicable FDA laws and regulations. To that end, Essex IRB is in the process of engaging a consultant that can assist the firm with the evaluation of its IRB review process. Because Essex IRB recognizes the seriousness of the issues raised by the FDA, the firm has begun the review of the operating practices and procedures and retraining of Board members and staff.

Observation 1:
The IRB is not composed of at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. Specifically, Essex IRB failed to demonstrate the ability to ascertain acceptability of the proposed research in terms of regulations, applicable law and standards of professional conduct and practice. For example:

Before addressing each item identified in this Observation, Essex IRB believes it is important to address the larger question concerning the composition of its Board. Essex IRB believe that its IRB is duly constituted with the necessary scientific and non-scientific expertise to provide adequate and complete review of the studies it commonly reviews. However, the firm recognized that procedural changes and additional training of its Board members and staff must be implemented in order to provide the Board with the information necessary to conduct its review function. The procedural changes and training that Essex IRB has adopted, or will be adopting are described below.

A. Essex IRB approved a proposed clinical investigation (Protocol [redacted] for a fictitious sponsor [redacted] to be conducted by a fictitious clinical investigator [redacted]). In the initial review, the IRB failed to:

1. **Verify that this Clinical Investigator [redacted] held a valid medical license in the state of Virginia (VA [redacted]**
2. **Recognize that the Clinical Investigator [redacted] had the same name, street address, city and state as the fictitious investigator [redacted] conducted in 2009.**
3. **Identify that the proposed protocol was studying an investigational drug [redacted] that was a previously approved product that had been withdrawn from the market in 2004 because of an increased risk of [redacted] with long term use.**
4. **Assess the potential for cardiovascular risk with the use of the drug when this class of drug [redacted] is known to exhibit increased risk of cardiovascular events.**
5. **Indentify this exact study protocol (Protocol [redacted] had been previously completed by another company.**
6. **Indentify the IND [redacted] submitted by the sponsor [redacted] belonged to another company who had withdrawn the IND in 2008.**

Under Observation 1.A, the FDA points to six items that Essex did not identify during its initial review of the fictitiou[redacted] study. Essex IRB's procedures were set up to review clinical research, not to detect fabricated submissions such as those submitted by the bogus [redacted] company. However, Essex IRB recognizes that this fabricated submission raises questions about the robustness of its review process as it relates to legitimate study submissions, and thus, the firm is taking steps to revise its study intake procedures to address this concern.

Items 1 and 2 concern a failure to verify the qualifications of the clinical investigator. According to FDA's regulations, it is the sponsor's responsibility to select "qualified investigators" pursuant to 21 CFR § 312.50 and 21 CFR § 812.40. Thus, consistent with the regulations and Essex IRB's procedures, the firm relied on the medical licensure information provided by the fictitious sponsor, along with additional information about the non-existent principal investigator provided in the Essex IRB Site Application Letter (SAL), to confirm the clinical investigator's qualifications. However, going forward, Essex IRB has implemented procedures to verify the medical license documents submitted for all principal investigators as part of its review process. The medical license verification process will require Essex to check the submitted license against authoritative sources such as the specific board of medical examiners identified as issuing the license to the principal investigator.[1] This step will eliminate attempts to submit a study that includes a fictitious clinical investigator, but it will also benefit the review process by adding an additional check on the information submitted by real sponsors and investigators. The IRB administrators and Board members will be trained on the revised SOP.

Items 3 and 4 involve a failure to identify risks associated with the study agent. As part of the study submission to Essex IRB, the firm requires sponsors and investigators to submit the study protocol and investigator brochure or investigational plan, if applicable, to the IRB for review. Where an Investigational New Drug ("IND") or Investigational Device Exemption ("IDE") is required these documents must contain, under 21 CFR § 312.23 or 21 CFR § 812.25, among other things, a summary of all safety and efficacy information concerning the study agent, including bibliographies of all published literature. In hindsight, it is now clear that the documents submitted by the fictitious sponsor were intentionally inadequate in describing risk information, including cardiovascular risks. While the study in this case was fictitious, Essex IRB recognizes the need to impose additional requirements on sponsors and investigators to assure that such documents are complete.

[1] As part of its site review process, Essex IRB also checks the principal investigator's name against FDA Warning Letters, Form FDA 483s, and the disqualification and debarment lists maintained of www.fda.gov. In addition, Essex IRB maintains a list of clinical investigators that have reported receipt of Form FDA 483s and/or FDA Warning Letters while under the firm's oversight.

Therefore, going forward, sponsors and investigators will be required to attest to the completeness and accuracy of study submissions consistent with regulatory requirements.

Further, the Board will undertake additional measures to assess the completeness of the study information submitted by referring to authoritative sources, such as PubMed, for a review of the available published literature related to or concerning the study agent. Essex IRB is revising its SOP "Criteria for Approval of Research" to adopt this requirement, and IRB administrators will be trained on conducting such reviews.

Items 5 and 6 above cite Essex IRB for not recognizing the [redacted] protocol as one that had been previously completed by another company, and for failure to identify the IND number as belonging to another company who had withdrawn the IND in 2008. As the FDA knows, the FDA does not make public the IND number assigned to a particular drug study during the investigational stage of drug development due to sponsor confidentiality considerations. Further, despite the IRB's role in the review process of these studies, the FDA does not provide IRBs with access to the IND number so that the IRB can validate the number submitted by the sponsor or investigator. Thus, while Essex IRB recognizes that it was deceived by this fictitious sponsor in this particular case, and that in this rare case the IND number was publicly available; the firm does not believe that regular internet checks of IND numbers will serve a purpose useful to the IRB review process. Nevertheless, going forward, sponsors and investigators will be required to attest to the accuracy of the study information submitted to Essex IRB.

B. Essex IRB reviewed a Phase I (first in man) investigational [redacted] study [redacted] Protocol [redacted] and incorrectly determined that the research was no more than minimal risk to subjects.

This item addresses Essex IRB's process for undertaking risk determinations. Because this matter is also addressed in connection with Observation 2, Essex IRB addresses this item in its response to Observation 2.

C. Essex IRB reviewed [redacted] Study [redacted] for an [redacted] and failed to include known side effects [redacted] in elderly patients) provided in the Package insert into the IRB approved consent form. In addition, the IRB removed a known adverse event (graft rejection) from the original sponsor provided ICF with no documented rationale.

Essex IRB agrees that the known side effect provided in the package insert should have been included as part of the informed consent form. As a result, Essex will be reviewing and revising its "Informed Consent Checklist" to assess, among other things, 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 to request information from the sponsor or investigator where inconsistencies are identified. Essex IRB administrators and Board members will be trained on the revised procedures.

With regard to the known adverse event that was removed from the informed consent form, Essex IRB inadvertently failed to document the reason for the removal of the adverse event. After reviewing the information on this adverse event with the Board, Essex IRB determined that it should have been removed from one paragraph and moved to another paragraph. The information was inadvertently removed and not moved to the new paragraph. However, going forward, Essex IRB will assure that such information is documented in the IRB meeting. In its responses to Observation 4 below, Essex discusses new procedures and training as it relates to good meeting minutes practices.

Observation 2:

The IRB approved the conduct of research, but did not determine that the risks to subjects were minimized by using procedures which were consistent with sound research design and which did not unnecessarily expose subjects to risk. Specifically, one of the criteria for IRB approval is that the IRB determine that the risks to subjects are minimized. Essex IRB's process for assessment of risk in proposed research is inadequate.

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."* Essex IRB's application of this definition to proposed research routinely fails to consider the type of test article, the investigational nature of the test article, and its use in the proposed research.

For example,

The IRB incorrectly determined that the two (2) following studies, which involve the use of an investigational drug or vaccine respectively, were no more than minimal risk:

1. (b) (4)
2. [redacted]

Essex IRB agrees that it incorrectly identified the studies mentioned above as presenting no more than minimal risk to subjects. Despite the minimal risk decision the studies were still subject to full board review. As a result, Essex IRB is revising its SOPs to assist the Board when making risk determinations. As noted by FDA, 21 CFR 56.102(i) defines minimal risk to mean

> [t]he 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 test.

All determinations about the degree of risk presented by a study will be made in accordance with the regulatory definition of minimal risk. All Essex Board members and administrators will be provided training on the revised SOP, with an emphasis on the meaning of minimal risk.

This Observation raises the same issues with regard to the informed consent document presented under Observations 1.A.3 and 4, and 1C. A summary of the corrective actions that will be implemented by Essex IRB are described below, but please see the firm's response to Observation 1 for a complete discussion of the corrective actions that will be adopted by Essex IRB in response to the issues raised by the FDA.

In summary, in order to assure that Essex IRB has information sufficient to conduct its review function and assure completeness of the informed consent document, sponsors and investigators must attest to the completeness and accuracy of the study submission consistent with regulatory requirements. The Board will also undertake additional measures to assess the completeness of the study information submitted by referring to authoritative sources for a review of available published literature related to or concerning the study agent.

Further, Essex is revising its Informed Consent Checklist to require review of the risk information in the Informed Consent document to assure it is consistent with the risk information identified in the protocol,

investigator brochure, or other relevant document, and to request information from the sponsor or investigator where inconsistencies are identified.

IRB administrators and Board members training associated with these procedural changes is described in Essex IRB's response to Observation 1.

Observation 4:
The IRB did not determine at the time of initial review that a study was in compliance with 21 CFR Part 50 Subpart D, "Additional Safeguards for Children in Clinical Investigations." Specifically, for 2 out of 2 Pediatric studies reviewed, Essex IRB failed to document and provide communication of the pediatric risk category assigned to the research as determined by the IRB.

Essex IRB has in place an SOP governing the assessment of degree of pediatric risk in accordance with 21 CFR Part 50, Subpart D. Essex IRB failed to document its pediatric risk determination for these two studies. As a result of this Observation, Essex IRB will be retraining its IRB administrators and Board members on the need to document in the meeting minutes the risk determination, along with other required documentation depending on the identified risk determination.

In addition, Essex IRB is developing an SOP describing how to prepare good meeting minutes. Essex IRB employees will be trained on this SOP, which explains how to summarize the details gathered during the Board meeting, how to incorporate those details into the meeting minutes to ensure that comprehensive meeting minutes are prepared in a timely fashion, and the elements that must be included in the meeting minutes. The training will be conducted when the SOP review is complete.

Finally, Essex is in the process of auditing all ongoing pediatric studies subject to Essex IRB review to assure that the risk determination has been appropriately documented.

Observation 5:
Minutes of IRB meetings have not been prepared in sufficient detail to show actions taken by the IRB and a written summary of the discussion of controverted issues and their resolutions. Specifically, minutes of IRB meetings have not been prepared in sufficient detail to show pediatric risk determinations, non-significant vs. significant device determinations, and controverted issues and their resolution.

This Observation raised issues similar to those raised as Observations 4. As stated in our response to Observation 4, an SOP is being developed and staff will be trained on good meeting minutes and practices. Among other things, the SOP includes the requirement to document pediatric risk determinations, non-significant v. significant device determinations, and the discussion of controverted issues.

Observation 6:
The IRB did not follow written procedures for ensuring prompt reporting to appropriate institutional officials and the FDA of any suspension or termination of IRB approval. Specifically, SOP SX-SOP-20-6-1/3, "Suspension or Termination of Approval of Research" requires the IRB to suspend or terminate its approval of a research study if there is evidence of ethical or scientific misconduct. Essex IRB became aware on February 7, 2011, that the [redacted] (b) (4) study to be conducted by [redacted] (b) (4) was fictitious, however to date, the IRB failed to terminate its approval in accordance with their SOP.

As the FDA knows, Essex IRB notified the FDA about the fictitious study on February 8, 2011. While Essex IRB took the necessary measures to notify the FDA about the fraudulent study submission, it failed to recognize the need to internally terminate its approval of a fraudulent study. After being so informed during the FDA inspection of our facility, Essex IRB immediately terminated its approval of the fictitious

study. Because the mechanism for such action for a legitimate study is already established in our SOPs, Essex is confident that it would follow the appropriate procedures in the future.

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We appreciate the professional conduct and thoroughness of Lieutenant Commander Wydner, Ms. Donnelly and Dr. Visco during the inspection. Their observations, recommendations and information shared with us are taken very seriously and shall be adhered to as Essex resumes its function as an Independent IRB. As noted above, we have begun the process of revising our SOPs and retraining of the Board and staff. We will be updating FDA on our actions.

Respectfully,

Glenn P. Lambert, MD
Chairman

Cc.: Andrea Slavin, Consumer Safety Officer, CDER
Silver Spring, MD 20993