

Inspections, Compliance, Enforcement, and Criminal Investigations

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VIA EXPRESS COURIER

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Dr. Ball:

We received a thorough FDA audit by Ms. Stephanie Hubbard in April 2003 and wrote an explanation of the issues raised shortly thereafter. Here, we will detail further the actions taken by us since that audit and in response to the Warning Letter dated December 19, 2005.

Response to FDA Warning Letter using item numbered therein:

(1-A) The Principal Investigator (PI) protected the safety and rights of patients by ordering required labs and observing for signs and symptoms of risks such as myopathy. Clinical assessments as part of study visits during daily infusions were performed per protocol. Laboratory collections as required per the study were incomplete as noted by the auditor. Overall medical care was delivered to each subject while hospitalized by a multi-disciplinary team. The study team worked in tandem with hospital staff to insure the safety and well-being of the patient, for their overall medical condition as well as their participation in the research study.

With respect to safety laboratory assessments, we now only utilize specific research labs which have SOPs in place, notifying us of out-of-range values or failure of specimens to arrive intact. We have not since relied on non-study hospital staff or other third-parties to carry-out laboratory assessments per physician orders. Specimen collections are all now performed by our certified research staff.

In follow-up to the Form 483 previously issued and in an effort to identify where procedures needed to be changed in order to prevent similar laboratory protocol deviations in the future, the following table was developed. It has been included in this letter to provide additional detail and explanation as part of the overall response.

Labs Drawn & On Record	Labs Drawn 1 Day Late	Labs Not Drawn As Ordered	Reason given by institution in source documents
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(b)(6)		Day 3,5,7-10,13,14, EOT UA	Central port clogged. No venous access. EOT-pt couldn't urinate
(b)(6)	Day 3	Day 5 & 7	Day 3 drawn on Day 4. Did not collect Day 5 since Day 4 obtained & Day 7
(b)(6)	Day 3	Day 5,7-9,EOT	Day 3 drawn on Day 4. EOT-Patient was discharged before lab drew blood.
(b)(6)	Day 3	Day 5,7-11,EOT UA	No required 'Day 2' labs. Day 3 drawn on Day 4. EOT-unable to urinate for sample.
(b)(6)		Day 5	Ordered. Not done due to error.
(b)(6)	Day 1 & 3	Day 5	Day 1=Admission per order. Admission labs done. Day 3 labs done-see copy.
(b)(6)	Day 1	Day 3 & 7	Day 1=Admission per order. Admission labs done. Day 3 & 7 not drawn.
(b)(6)		Day 5 & 7	Ordered. Not done due to error.
(b)(6)	Day 3	Day 5,7-9,EOT Hem, UA	Day 3 drawn on Day 4. Others ordered but not done due to error
(b)(6)		Day 3,5,7	Ordered. Not done due to error.
(b)(6)	Day 3	Day 5,7,UA	Day 3 drawn on Day 4. Others ordered-not done due to error
(b)(6)	Day 3	Day 5,7,UA,EOT Hem.	Day 3 drawn on Day 4. Others ordered-not done due to error
(b)(6)		Day 5,7,8-20	Ordered. Not done due to error.
(b)(6)		Day 3,5,7,EOT UA & Hem	Day 5 drawn and submitted. Misplaced by lab-see apology letter from quest. Others ordered

* All labs ordered per doctor's standing study protocol orders.

* Daily CK performed through local laboratory while subjects in-house.

* Only 1 slightly elevated CK observed during entire study, which was within normal limits when redrawn on Day 5 & EOT. No patients with symptoms of myopathy during daily study doctor visits.

(1-B) The PI did not order, on study entry or discharge, a HMG Coenzyme A reductase inhibitor (statin) on subject **(b)(6)** as excluded by protocol. The study protocol did not exclude patients with prior use of a those medications. The PI should have obtained approval from the medical monitor to concurrently treat the subject with Lipitor. As stated, HMG Coenzyme A reductase inhibitors are associated with increases in CK and myopathy. If such an elevation were to occur, it would make causality difficult to differentiate between the concurrent medication (statin) and the study medication.

(2-A & H) Only subjects who met the extensive list of entry criteria and who had a clinical diagnosis of confirmed or presumed complicated skin and skin structure infections were considered for the study. The PI only enrolled subjects who met these criteria and who had appropriate infections with culturable material (drainage). Although **[(b)(4)]** (and subsequent cultures) were obtained on all subjects, a misinterpretation of the protocol requirements that these tests first confirm a **[(b)(4)]** pathogen as part of the entry criteria occurred. All patients entered into the trial did in fact have a clinical diagnosis of complicated skin and skin structure infections.

(2-B) As the auditor points out, there was an inadvertent break of the randomization blind on subject **(b)(6)**. A system is now in place that maintains the blind in the absence of a second full-time investigator. In the future, River Birch Research, LLC will document with the sponsor any solutions, or temporarily

withdraw from the study when personnel changes compromise the blinding requirement of a study.

(2-D & E) In all cases, switching the patients (#(b)(6)) to oral medication followed the requirements per the study protocol, except for obtaining approval by the sponsor's medical monitor beforehand. Each patient had appropriate study assessments completed per protocol at the time of the switch and during subsequent post-treatment follow-up visits.

(2-F) The PI did not order topical treatments not approved per the study protocol on the four study patients noted. These treatments were ordered and performed by non-study hospital staff. They were recorded as part of the study data since they were treatments the patients did receive as per source documents. When the PI became aware that these topical treatments were being given, he requested that the hospital staff cease them. In the future, additional training will be provided to non-study hospital/clinic staff regarding prohibited medications. Additionally, a research participant "cover sheet" might be applied to the front of each patient's medical record, informing the multi-disciplinary staff that the patient is in a research study, that certain treatments could impact the study, and to consult with the research staff if appropriate before ordering/delivering such treatments.

(2-G) Fourteen patients were enrolled in the study between 7/19/2000 and 6/29/2001 requiring 70 study visits per patient. Nine deviations from visit windows occurred, of which, eight were by patient choice and one because of PI's schedule. Notations were kept in appointment book and source documents why patients requested or required deviation from appointment schedules, and are reflected in the table below. This study, by design, included patients more ill with various co morbidities than usual clinic patients. This area has no taxi service or public transportation. River Birch, on special need basis, has and will continue to offer a hired driver to bring a patient to an appointment. Patients however maintain their free choice in these matters.

Subject	Visit	Due Date (window)	Actual Date	Explanation in Source Documents
(b)(6)	Post Therapy	10/10/00-10/15/00	10/18/2000	Conflict with pt's work schedule
(b)(6)	Post Therapy	11/20/00-11/27/00	11/14/2000	Transportation issue for pt's family to bring them in
(b)(6)	On Therapy	1/25/01-1/26/01	1/24/2001	Visit was made at admission. Pt wasn't given first dose until next day which changed dates. Staff unaware.
	EOT	1/29/2001	1/29/2001	EOT WAS on 1/29/01
	Post Therapy	2/4/01-2/9/01	2/19/2001	Conflict with pt's schedule
	Post Study	2/18/01-2/25/01	2/27/2001	Reason not noted
(b)(6)	Post Study	3/7/01-3/14/01	2/28/2001	(Coordinator) made an error while scheduling visit
(b)(6)	EOT	5/2/01-5/3/01	5/1/2001	Staff at Investigator Meeting 5/2 & 5/3
(b)(6)	EOT	7/6/01-7/8/01	7/9/2001	Was scheduled for Fri, 7/6.Pt. Rescheduled for following Mon., 7/9/01

The audit completely confirmed, for us, the risk of working with [(b)(4)], which despite training and

support from the River Branch research staff, had difficulty appreciating the requirements and demands of a research study layered over routine patient care. We have ceased (and turned down grants) which would have us do in-patient studies in that facility. We have since moved our in-patient care to another hospital. We will not, in the future, take on a clinical study which requires the compliance of a third-party (such as an in-patient facility) that is not willing to do so.

Study laboratory assessments, ordered by the PI, were not obtained by the in-patient institution, nor was there a fail-safe SOP in place to alert the PI that the specimens were not obtained. The third-party institution is responsible for not executing doctors' orders. The investigator becomes at fault when he continues to use a facility that does not follow orders. In this case, we have ceased all research activity at the inpatient institution.

We are able to learn from our mistakes. Our response is not to use the third-party hospital as a 'scape-goat'. On the contrary, we consider it our failure in not recognizing them as unable or unwilling to follow the rigors of clinical care in a research protocol. To date, we have yet to identify a capable institution in our rural area to perform in-patient studies. As such, we continue to decline any and all clinical study proposals requiring hospital admissions as part of the protocol. Additionally, we have moved our primary in-patient care to a new hospital in the region.

Finally, the safety of the study participants was paramount despite missing safety laboratory assessments. Care was delivered to the patients as part of their hospital stay by staff there, and frequent per-protocol assessments were performed by the PI or delegate. This included assessing local CK results and any reported or observed adverse events. We are happy to report that only one slightly elevated CK result was noted, which returned to normal limits when it was re-tested at the day 5 and EOT visit, and that no symptoms or complaints of myopathy were reported.

We trust that you will find our responses to the audit findings and the corrective actions we have put in place appropriate, and our ongoing commitment to conduct safe, ethical, and meaningful clinical research in the future. Please do not hesitate to contact me should you have any questions. Thank you for your time.

Sincerely,

Raymond E. Tidman, MD