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Inspections, Compliance, Enforcement, and Criminal Investigations

Chawla, Sant P., M.D. 3/17/10



Department of Health and Human Services

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

WARNING LETTER

CERTIFIED MAIL RETURN RECEIPT REQUESTED

Sant P. Chawla, M.D.
Sarcoma Oncology Center
2811 Wilshire Boulevard, Suite 414
Santa Monica, CA 90403

Ref: 10-HFD-45-03-02

Dear Dr. Chawla:

Between August 5 and 27, 2009, Ms. Diane Van Leeuwen, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations:

- Protocol **(b)(4)**, entitled "**(b)(4)**" of the investigational drug **(b)(4)**, performed for **(b)(4)**.; and
- Protocol **(b)(4)**, entitled "**(b)(4)**," of the investigational drug **(b)(4)**, performed for **(b)(4)**.

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your September 14, 2009 written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Van Leeuwen presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

Regarding Protocol **(b)(4)**:

1. You failed to conduct the studies or ensure they were conducted according to the investigational plans [21 CFR 312.60].

a. Protocol **(b)(4)**, Section 7.4.1 (Dose Escalation and Modification) specified study drug dosages to be administered based on assigned cohort. Subject 008 was assigned to Cohort 4, with a study drug dose specification of 150 mg/m². For Cycle 4, Day 1 on September 3, 2008, the subject's height and weight were recorded as 5'0" and 132 lbs., respectively. The subject's body surface area was documented as 1.59 m²,

and the dose was inaccurately calculated and recorded as 274.5 mg. The correct dosage should have been calculated as 238.5 mg [150 mg/m² x 1.59 m²]. The subject's chemotherapy flow sheet documents that the subject received 274.5 mg of study drug on September 3, 2008. The administration of this miscalculated dose unnecessarily exposed the subject to an overdose, with the potential for increased adverse events.

In your September 14, 2009, written response, you indicated that the subject's chart was reviewed with the study nurses and pharmacists, and the dosing error was confirmed. As corrective measures, you indicated that your site's nurses and pharmacists were retrained on study dosing requirements and chart documentation of calculation parameters (height/weight), with a reminder to ensure consistency of data and dosing changes. Additionally, you noted that your site has implemented a policy whereby a nurse or pharmacist double-checks dosages prior to all study-related infusions. We acknowledge your response and find your corrective measures to prevent future recurrence acceptable.

b. Protocol **(b)(4)** Section 10.1.1 (Pharmacokinetics) required samples to be drawn on Day 1 at pre-dose, and at 15 minutes, 30 minutes, 45 minutes, 1 hour, and 2 hours after study drug infusion was **initiated**. The following subjects' pharmacokinetic (PK) samples were drawn at the incorrect time intervals. Specifically, the samples were collected after the **completion** of the infusion rather than after the **initiation** of the infusion:

Protocol-specified PK sampling schedule (post infusion initiation)	PK sampling time according to protocol (2400 hours)	Actual time of PK sampling (2400 hours)
Subject 002 Day 1 Study Drug Infusion Time: 1330-1405	Subject 002 Day 1 Study Drug Infusion Time: 1330-1405	Subject 002 Day 1 Study Drug Infusion Time: 1330-1405
Just prior to dose	Just prior to dose	1325
15 minutes (post infusion initiation)	1345	1420
30 minutes (post infusion initiation)	1400	1435
45 minutes (post infusion initiation)	1415	1450
1 hour (post infusion initiation)	1430	1505
2 hours (post infusion initiation)	1530	1605

Protocol-specified PK sampling schedule (post infusion initiation)	PK sampling time according to protocol (2400 hours)	Actual time of PK sampling (2400 hours)
Subject 003 Day 1 Study Drug Infusion Time: 1420-1452	Subject 003 Day 1 Study Drug Infusion Time: 1420-1452	Subject 003 Day 1 Study Drug Infusion Time: 1420-1452
Just prior to dose	Just prior to dose	1330
15 minutes (post infusion initiation)	1435	1510
30 minutes (post infusion initiation)	1450	1525
45 minutes (post infusion initiation)	1505	1540
1 hour (post infusion initiation)	1520	1555
2 hours (post infusion initiation)	1620	1655

Protocol-specified PK sampling schedule (post infusion initiation)	PK sampling time according to protocol (2400 hours)	Actual time of PK sampling (2400 hours)
Subject 004 Day 1 Study Drug Infusion Time: 1440-1514	Subject 004 Day 1 Study Drug Infusion Time: 1440-1514	Subject 004 Day 1 Study Drug Infusion Time: 1440-1514
Just prior to dose	Just prior to dose	1330
15 minutes (post infusion initiation)	1455	1530
30 minutes (post infusion initiation)	1510	1545
45 minutes (post infusion initiation)	1525	1600
1 hour (post infusion initiation)	1540	1615
2 hours (post infusion initiation)	1640	1716

Protocol-specified PK sampling schedule (post infusion initiation)	PK sampling time according to protocol (2400 hours)	Actual time of PK sampling (2400 hours)
Subject 005 Day 1 Study Drug Infusion Time: 1245-1316	Subject 005 Day 1 Study Drug Infusion Time: 1245-1316	Subject 005 Day 1 Study Drug Infusion Time: 1245-1316
Just prior to dose	Just prior to dose	1220
15 minutes (post infusion initiation)	1300	1335
30 minutes (post infusion initiation)	1315	1347
45 minutes (post infusion initiation)	1330	1403
1 hour (post infusion initiation)	1345	1418
2 hours (post infusion initiation)	1445	1518

Protocol-specified PK sampling schedule (post infusion initiation)	PK sampling time according to protocol (2400 hours)	Actual time of PK sampling (2400 hours)
Subject 006 Day 1 Study Drug Infusion Time: 1222-1254	Subject 006 Day 1 Study Drug Infusion Time: 1222-1254	Subject 006 Day 1 Study Drug Infusion Time: 1222-1254
Just prior to dose	Just prior to dose	1140
15 minutes (post infusion initiation)	1237	1310
30 minutes (post infusion initiation)	1252	1325
45 minutes (post infusion initiation)	1307	1340
1 hour (post infusion initiation)	1322	1355

2 hours (post infusion initiation)	1422	1455
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Protocol-specified PK sampling schedule (post infusion initiation)	PK sampling time according to protocol (2400 hours)	Actual time of PK sampling (2400 hours)
Subject 010 Day 1 Study Drug Infusion Time: 1330-1402	Subject 010 Day 1 Study Drug Infusion Time: 1330-1402	Subject 010 Day 1 Study Drug Infusion Time: 1330-1402
Just prior to dose	Just prior to dose	1315
15 minutes (post infusion initiation)	1345	1417
30 minutes (post infusion initiation)	1400	1432
45 minutes (post infusion initiation)	1415	1447
1 hour (post infusion initiation)	1430	1502
2 hours (post infusion initiation)	1530	1602

Protocol-specified PK sampling schedule (post infusion initiation)	PK sampling time according to protocol (2400 hours)	Actual time of PK sampling (2400 hours)
Subject 012 Day 1 Study Drug Infusion Time: 1521-1555	Subject 012 Day 1 Study Drug Infusion Time: 1521-1555	Subject 012 Day 1 Study Drug Infusion Time: 1521-1555
Just prior to dose	Just prior to dose	1420
15 minutes (post infusion initiation)	1536	1611
30 minutes (post infusion initiation)	1551	1632
45 minutes (post infusion initiation)	1606	1648
1 hour (post infusion initiation)	1621	1700
2 hours (post infusion initiation)	1721	1758

In your September 14, 2009, written response, you indicated that your site misunderstood the timing of the PK samples. You noted that your site interpreted the protocol-required PK sampling to begin at the **end** of the drug infusion time rather than at the **start** of the drug infusion time. You stated that your site will pay particular attention to the protocol requirement for PK sampling in the future. We acknowledge your response. However, we are concerned that the response is not adequate to prevent future recurrence of the violation noted above. In particular, we are concerned that you did not properly understand the protocol specified PK sampling schedule from the start of the study, and that you did not ensure that the PK samples were collected according to the protocol throughout the study. Your failure to collect PK samples as specified in the protocol significantly undermines the reliability and integrity of the data captured at your site.

Regarding Protocols **(b)(4)** and **(b)(4)**

2. You failed to maintain adequate and accurate case histories that record all observations and

other data pertinent to the investigation [21 CFR 312.62(b)].

The inspection revealed that there were numerous adverse events recorded in progress notes of subjects' records that had not been reported on the case report forms (CRFs), and there was no explanation regarding this discrepancy. The following are examples of adverse events that had not been reported on the electronic CRFs at the time of the inspection. Note that since the inspection occurred in August 2009, the examples below represent delays in transcribing adverse events from progress notes to electronic CRFs that range from at least 8 months to 15 months.

- a. Subject **(b)(4)** 071 003: Progress notes documented weakness of upper and lower extremities on May 7, 2008.
- b. Subject **(b)(4)** 071 005: Progress notes documented nausea and vomiting on July 2, 2008.
- c. Subject **(b)(4)** 071 008: Progress notes documented alopecia on August 14, 2008, as well as dark nails on October 28, 2008.
- d. Subject **(b)(4)** 071 012: Progress notes documented difficulty swallowing food on November 3, 2008, as well as nausea and vomiting on December 31, 2008.
- e. Subject **(b)(4)** 071 001: Progress notes documented decreased breath sounds with wheezing on September 10, 2008, as well as nausea and vomiting on December 8, 2008.
- f. Subject **(b)(4)** 071 004: Progress notes documented difficulty reading on January 5, 2009.
- g. Subject **(b)(4)** 071 005: Physical examination notes documented a small lump on the left posterior scalp on January 12, 2009; progress notes documented alopecia on January 28, 2009.
- h. Subject **(b)(4)** 071 006: Progress notes documented difficulty sleeping on December 10, 2008, due to left thigh pain.

In your September 14, 2009 written response, you stated that your site staff enters all adverse events and concomitant medications in subjects' charts at the time of each visit. You indicated that at the start of the study, your site staff members were entering data (adverse events and concomitant medications) in CRFs prior to the sponsor's monitoring visits. However, you indicated that your site staff stopped entering data in CRFs in advance of the monitoring visits so that they could enter data with the monitors present, to avoid additional system queries. As a corrective measure, you noted that your site staff members have implemented a policy requiring that all CRFs be completed in a timely manner, defined as 30 days following a study visit, regardless of scheduled monitoring visits.

We acknowledge your response. However, the lack of timely adverse event information in the electronic CRFs may have jeopardized subject safety as well as the reliability and integrity of the data captured on the CRFs at your site. We find your corrective measures to prevent future recurrence to be acceptable, if implemented as proposed.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) working 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. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Cullity (formerly Lewin), M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Cullity (formerly Lewin), M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
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Building 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,
{See appended electronic signature page}
Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
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Food and Drug Administration

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/s/

LESLIE K BALL
03/17/2010

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