Bioresearch Monitoring Final Review Memo – ARTISS

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research
DATE January 31, 2008
FROM
Robert L. Wesley, Bioresearch Monitoring, HFM-664
Division of Inspections and Surveillance
Office of Compliance and Biologics Quality
THROUGH Patricia A. Holobaugh, Bioresearch Monitoring Branch Chief, HFM-664
TO
Pratibha Rana, HFM-380, RPM
Kimberly Lindsey, HFM-392, Chair
SUBJECT
Bioresearch Monitoring Final Review memo
STN: BLA 125266/0
Sponsor: Baxter Healthcare Corp.
Product: Fibrin Sealant

SUMMARY STATEMENT
The bioresearch monitoring inspections of three clinical investigators did not reveal significant problems that impact the data submitted to the BLA, with one exception. Dr. Gibran's site had significant recordkeeping deviations, including assignment of study subject numbers, and date and amount of product dispensed. The noted discrepancies made it difficult to determine the overall accuracy of the data at this site.
BACKGROUND
Inspections and data audits of the following three clinical investigators were conducted in support of the BLA.

Clinical Investigator	Site	Location	No. of Subjects	FDA-483	Classification
David Mozingo, MD	#13	Gainesville , FL	22	Yes	NAI
Kevin Foster, MD	#04	Phoenix , AZ	18	No	VAI
Nicole Gibran, MD	#05	Seattle , WA	13	No	VAI

INSPECTIONAL FINDINGS

Major focus of the inspections was to compare data points from the BLA with source documents and subject's case report forms at each site. Data points included Inclusion/Exclusion criteria, SAEs/AEs, and Part A - 28-day post-op follow-up.
The inspections of the three clinical investigators revealed the following deviations from the applicable federal regulations.

1. **Failure to ensure that the investigation is conducted according to the signed investigator statement and the investigational plan. [21 CFR § 312.60].**
   Site #05 Dr. Nicole Gibran
   a. An adverse event experienced by a subject was incorrectly categorized as not severe. The subject received the test article during surgery, was discharged and later readmitted to the hospital due to an infection related to the grafted test site. The IRB and sponsor were not notified within 24 hours of this serious adverse event as stipulated by the protocol.
   b. The protocol required timeframes, for the 3, 6 and 12-month follow-up visits, were not met for 6 of the 17 study subjects enrolled at this site. Three subjects had follow-up visits that ranged from 13-32 days late for the 3 and 6-month visits, and three subjects had follow-up visits that ranged from 17-29 days early for the 12-month visit.
   c. There were four subjects who were missing at least one of the protocol required photographs.

   Site #04 Dr. Kevin Foster
   Three subjects were missing photos that were to be used by the blinded independent review committee to asses the primary efficacy endpoint of the study.
   Site #04 Dr. David Mozingo
   The Screening Physical Examination for one subject was not properly filled out, and a clinical research coordinator signed off on several physicals that were performed by one of the co-investigators.
2. **Failure to maintain adequate records of the disposition of the investigational drug; including dates, quantity, and use by subjects, and failure to maintain adequate and accurate case histories. [21 CFR § 312.62].**
   Site #05 Dr. Nicole Gibran
   a. The investigational drug-dispensing and accountability records contained numerous illegible entries, cross-outs and changes, and lacked an explanation for many of the changes, making it difficult to determine the accuracy of the information. The study subject numbers, initials, and dates the test article was dispensed were not consistently recorded on the Investigational Product Receipt and Dispensing Record (DR), Dispensing Log (DL) and the Investigational Agent Accountability Record (AR), for example:
      i. "Subject 0001" was initially assigned to Subject -- after randomization. Subject was subsequently treated off-protocol with a different product. "Subject #0001" was then reassigned to another person with the initials --. The disposition of the product dispensed for Subject -- is unclear.
      ii. The DL and AR forms contain contradictory information for Subject 0001/--. The first page of the DR indicates this subject received two units of the investigational product on 9/14/05; this entry was later voided. The AR indicates this subject received two units on 1/10/05.

iii. Subject -- was recorded as Subject 5 on the DL form, and 0004 on the DR, both indicating the subject received two units of the investigational product on 3/11/05. The entry for that date on the AR identifies the recipient as Subject --.
iv. Subject -- was recorded as 2456465 on the DL, and as 0005 on the DR.
v. For Subject 0006/--, the DL documents 4/29/05 as the date the investigational product was dispensed. However, the Technician and Pharmacist initialed the DL on 4/28/05. Both the AR and DR document the date the product was dispensed as 4/28/05. The "Day 0 Intraoperative" CRF form lists the surgery date as 4/29/05.
vi. The DL and DR forms both document that Subject 0008/-- received two units of the investigational product on 8/22/05, but the AR documents the date as 5/22/05.
vii. For Subject 0009/--, the DR and DL both document the investigational product was dispensed on 9/19/05, but the AR states 9/12/05.
viii. Subject -- was initially assigned study number 0015 it was then changed to 0012. A note dated 12/10/05 on the DL states subject number should be 0015, but it was never changed. The DR lists Subject 0015/-- as receiving product on 12/9/05. The Subject Humanistic Outcome measures form identifies Subject -- as 0013.
ix. Subject -- was initially assigned study number 0011, then it was changed to 0013 or 0015 on the DL; the entry is illegible. The DR documents that Subject 0011/-- received the study drug on 10/10/05.

b. The Subject Screening Log (SL) indicates Screening Number 0066/--- was randomized, assigned Subject number 0009, and consented on 9/16/05. The SL also documents the subject declined to be in study. The DR, DL, and Day 0 Intraoperative form document the subject received one unit of the investigational product on 9/19/05.
c. Other recordkeeping discrepancies noted included: undated, un-initialed cross-outs, and the use of correction fluid.

Site #04 Dr. Kevin Foster

The entire medical file, which included study progress notes and nurse's notes, was either missing or otherwise un-retrievable for one subject.

SPONSOR FINDINGS

There were no sponsor issues noted during the inspections.

BIMO ADMINISTRATIVE FOLLOW-UP

Letters describing the inspectional findings were issued to each of the clinical investigators. Should you have any questions or comments about this memorandum or any aspect of Bioresearch Monitoring, please contact me at (301) 827-6348.

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Robert L. Wesley
Consumer Safety Officer

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