U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

AB Science 6/16/15

Department of Health and Human Services

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

WARNING LETTER
Jun 16, 2015

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 15-HFD-45-06-01

Alain Moussy
Chief Executive Officer
AB Science
3 Avenue George V
Paris, France

Dear Mr. Moussy:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at AB Science between September 22 and September 26, 2014. Ms. Barbara Wright, Ni A. Khin, M.D., and Michelle Safarik, MSPAS, PA-C, RAC, representing the FDA, reviewed AB Science's conduct as the sponsor of the following clinical investigations for investigational drug **(b)(4)**:

- Protocol **(b)(4)**, "**(b)(4)**";

- Protocol **(b)(4)**, "**(b)(4)**"; and
- Protocol **(b)(4)**, "**(b)(4)**."

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

At the conclusion of the inspection, Ms. Wright presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your October 10, 2014 written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your October 10, 2014 written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

Failure to ensure proper monitoring of the investigations and failure to ensure that the investigations are conducted in accordance with the general investigational plan and protocols contained in the IND [21 CFR 312.50 and 312.56(a)].

1. FDA regulations require that sponsors ensure proper monitoring of clinical investigations and ensure that their clinical investigators conduct the investigations in accordance with the protocols contained in the Investigational New Drug (IND) application. Our investigation found that you failed to ensure proper monitoring of Protocols **(b)(4)**, **(b)(4)**, and **(b)(4)**, and failed to ensure that clinical investigators conducted investigations in accordance with those three protocols. As a result of your inadequate monitoring, you did not identify, and did not correct in a timely manner, the clinical investigators' failure to report serious adverse events (SAEs) according to protocol-specified timeframes and failure to perform protocol-required laboratory tests. Examples include but are not limited to the following:

a. Your monitoring failed to identify and correct clinical investigators' failure to report SAEs within protocol-specified timeframes.

Protocols **(b)(4)** and **(b)(4)** require that SAEs, whether or not considered related to study drug, be reported on an SAE form and faxed to the sponsor within 24 hours of occurrence or the investigator's knowledge of the event. Reporting is required even if the event does not appear to be treatment-related. Both protocols define an SAE as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, or is another important medical condition that may jeopardize the subject's health or may require intervention to prevent one of the preceding outcomes. Protocol **(b)(4)** also includes emergence of cancer in the definition of an SAE.

The following SAEs were not reported within 24 hours of the occurrence or the investigator's knowledge of the event in accordance with the protocol, and were not identified by the monitor in monitoring visit reports:

i. Subject 03102 in Protocol **(b)(4)** experienced thrombocytopenia on May 4, 2009, but the site did not report the thrombocytopenia to the sponsor on an SAE form until April 30, 2013.

ii. Subject 03111 in Protocol **(b)(4)** experienced leukopenia and neutropenia on June 8, 2010, but the site did not report the leukopenia and neutropenia to the sponsor on an SAE form until May 2, 2013.

iii. Subject 03303 in Protocol **(b)(4)** was hospitalized for worsening abdominal pain (superior mesenteric vein thrombosis) **(b)(6)**, but the site failed to report the hospitalization on an SAE form.

iv. Subject 1302 in Protocol **(b)(4)** was hospitalized and received blood transfusions for grade 3 anemia on **(b)(6)**. A sub-investigator noted the subject's hospitalization in a progress note dated January 13, 2010. However, the site did not report the hospitalization to the sponsor on an SAE form until August 26, 2010.

v. Subject 1311 in Protocol **(b)(4)** had surgery **(b)(6)**, for knee arthritis complicated by an episode of phlebitis. The investigator noted the subject's surgery in a progress note dated March 15, 2013. However, the site did not report the hospitalization to the sponsor on an SAE form until April 10, 2013.

In the October 10, 2014 written response to the Form FDA 483, you acknowledged these observations and stated that investigators did not respect the SAE reporting requirements. You also indicated that sponsor monitoring activities were inadequate to detect non-compliance by investigators as described above. You proposed a corrective action plan for implementation in the fourth quarter of 2014 which included training on risk-based monitoring with a focus on **(b)(4)** SAEs and key adverse events. You noted that you would also train monitors and site staff on safety reporting before the end of 2014. Your written response is inadequate because your proposed corrective actions make no provisions for assessing the effectiveness of and ensuring sustained compliance with your monitoring practices.

b. Your monitoring failed to identify and correct a clinical investigator's failure to perform protocol-required laboratory tests.

i. Protocol **(b)(4)** requires that subjects in France undergo hematologic laboratory tests at Screening; Baseline; Weeks 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12; and then every four weeks thereafter, up to and including the End of Study/Final Visit. The hematologic laboratory tests include hematocrit and hemoglobin; red blood cell count; total and differential white blood cell counts, including neutrophils, lymphocytes, monocytes, eosinophils, and basophils; platelet count; prothrombin time; partial thromboplastin time; and international normalized ratio. These hematologic laboratory tests are safety assessments in the study because they are used to monitor for **(b)(4)**-related adverse events such as neutropenia, for which subjects will have their dose interrupted or discontinued, depending on its severity. Failure to diagnose neutropenia in a timely manner places subjects at increased risk of developing serious infections and sepsis. Therefore, missed hematologic laboratory tests compromise subject safety.

The following protocol-required hematologic laboratory tests were not performed and were not identified by the monitor during monitoring visits:

1) Week 1 for Subjects 033-008-01 and 033-008-02
2) Week 5 for Subject 033-008-05
3) Week 6 for Subject 033-008-05
4) Week 7 for Subject 033-008-05

ii. Protocol **(b)(4)** requires that urine dipstick be performed at Screening; Baseline; Weeks 4, 8, 12, 16, and 24; and then every 12 weeks thereafter, up to and including the End of Study/Final Visit. The urine dipstick test includes measurement of blood, leukocytes, and protein. A 24-hour urine collection to measure protein is performed if protein ≥30 mg/dL is detected on the dipstick. The urine dipstick test is a safety assessment that is used to monitor for **(b)(4)**-related renal disorders, and the study protocol requires that a subject's **(b)(4)** dose be interrupted, reduced, or discontinued based on the number of times a subject experiences protein ≥30 mg/dL on the dipstick and confirmed by 24-hour urinary protein >1.5 g/24 hours. Therefore, missed protocol-required urine dipstick tests compromise subject safety, because subjects can develop **(b)(4)**-related renal disorders.

Subject 033-008-02's urine dipstick measured protein to be 30 mg/dL at Week 36. The subject did not complete the protocol-required 24-hour urine collection based on the 30 mg/dL measurement. This protocol deviation was not noted in monitoring reports.

In the October 10, 2014 written response to the Form FDA 483, you acknowledged the observations described in Item1.b. You proposed a corrective action plan which includes instituting a risk-based monitoring strategy starting in October 2014 with new quality documents and training of AB Science personnel and investigators. You indicated that starting in the fourth quarter of 2014, local laboratory values will be captured and queried immediately at the test site in the CRF.

Your written response is inadequate because the proposed corrective actions make no provisions for assessing the effectiveness of your monitoring practices and ensuring that your monitoring practices will detect whether laboratory tests related to safety assessments such as hematology and urinalysis were performed at protocol-specified time points.

You failed to ensure proper monitoring of these clinical investigations because you did not identify and correct clinical investigators' failure to report SAEs and failure to perform protocol-required laboratory tests within timeframes specified in the protocols. As a result, you have failed to ensure that the clinical investigations were conducted in accordance with the investigational plan.

2. You failed to ensure proper monitoring of the investigations contained in your INDs because you did not follow the monitoring guidelines you developed.

a. Your monitoring guidelines for Protocols **(b)(4)** and **(b)(4)** require that monitoring reports be written by the Clinical Research Associate (CRA) and approved by the Clinical Project Manager (CPM) within specific timeframes. However, some monitoring reports were not completed and approved within the timeframes specified in the monitoring guidelines, and in some instances, were not completed at all. Examples include but are not limited to the following:

i. According to your monitoring guidelines for Protocol **(b)(4)**, interim/periodic monitoring reports should have been prepared within five business days after the corresponding monitoring visit and approved by the CPM within 10 business days after receipt of the report.

1) At Site 31:
   - The monitoring report for the January 22, 2009 site initiation visit should have been completed within five business days after the visit, but it was not completed until March 4, 2009. The report had not been approved by the CPM as of September 2014 when FDA conducted its inspection;
   - The monitoring report for the July 8, 2010 visit was not completed until November 2, 2012, and the report had not been approved by the CPM as of September 2014 when FDA conducted its inspection;
   - The monitoring report for the June 19, 2012 closeout visit was not completed until November 2, 2012; and
   - No corresponding monitoring reports were written for the following dates listed on the Site Visit Log: August 10, 2009, June 7, 2010, and November 16, 2010.

2) At Site 33:
   - The monitoring report dated March 4, 2009, had not been approved by the CPM as of September 2014 when FDA conducted its inspection;
   - The monitoring report for the August 30, 2010 periodic visit was not completed until November 1, 2012, and the report had not been approved by the CPM as of September 2014 when FDA conducted its inspection;
   - The monitoring report for the May 31, 2012 closeout visit was not completed until November 2, 2012, and had not been approved by the CPM as of September 2014 when FDA conducted its inspection; and No corresponding monitoring reports were written for the following dates listed on the Site Visit Log: April 2, 2010 and June 29-30, 2011.

3) At Site 34:
   - The monitoring report for the June 28, 2012 closeout visit was not completed until October 20, 2012, and the report had not been approved by the CPM as of September 2014 when FDA conducted its inspection; and
   - No corresponding monitoring reports were written for the following dates listed on the Site Visit Log: November 11, 2009, and April 29, 2010.

ii. According to your monitoring guidelines for Protocol **(b)(4)**, monitoring reports should have been prepared within five business days after the corresponding monitoring visit and approved by the CPM within five business days after receipt of the report.

1) At Site 004:
   - No corresponding monitoring reports were written for the following dates listed on the Site Visit Log: October 19, 2012 and November 20, 2012;
   - The following monitoring reports were not completed within five business days of the monitoring visit:

Date of Monitoring Visit	Date CRA Signed Monitoring Report
April 11, 2013	July 1, 2013
May 14, 2013	July 1, 2013
June 11-12, 2014	July 16, 2014
July 29-30, 2014	September 16, 2014

· The following monitoring reports were not approved by the CPM within five business days in accordance with your monitoring guidelines:

Date of Monitoring Visit	Date CRA Signed Monitoring Report	Date CPM Signed Monitoring Report
September 18, 2012	October 4, 2012	December 13, 2012
December 19, 2012	January 13, 2013	August 26, 2013

2) At Site 008:

· The following monitoring reports were not completed within five business days of the monitoring visit:

Date of Monitoring Visit	Date CRA Signed Monitoring Report
November 26, 2012	January 30, 2013
April 9, 2013	July 1, 2013
June 10, 2013	September 16, 2013
July 27, 2013	September 16, 2013
July 24-25, 2014	September 16, 2014

· The following monitoring reports were not approved by the CPM within five business days in accordance with your monitoring guidelines:

Date of Monitoring Visit	Date CRA Signed Monitoring Report	Date CPM Signed Monitoring Report
September 21, 2012	October 4, 2012	January 21, 2013
October 2, 2012	October 4, 2012	October 21, 2013
November 21, 2012	November 22, 2012	January 21, 2013
July 27, 2013	September 16, 2013	Not Signed

In the October 10, 2014 written response to the Form FDA 483, you acknowledged this observation. You stated that prior to January 2013, there was no electronic system to track reporting timelines. You indicated that an electronic tracking system was implemented in January 2013 to track monitoring visits and monitoring report reviews. You noted that CRAs receive automatic e-mail reminders and reconciliation is done once per month by the CPM and AB Science management team.

Your written response is inadequate because there are still multiple instances of delayed written reports by the CRAs and delayed approval by the CPM after January 2013.

b. AB Science monitoring guidelines for Protocol **(b)(4)** require that monitors retrieve lab results from sites and submit them to the Data Management team. However, you failed to follow your own monitoring guidelines by not collecting and submitting numerous lab results to the Data Management team. Examples include but are not limited to the following:

i. For Subject 033-004-02, no lab results were submitted to the Data Management team for Weeks 1, 5, 6, 8, 10, and 20.

ii. For Subject 033-004-03, no lab results were submitted to the Data Management team for Weeks 2, 3, 4, 5, 6, 7, and 10.

iii. For Subject 033-004-04, no labs were submitted to the Data Management team for Baseline and Weeks 1, 2, 3, 5, 6, 7, 8, 10, 16, 20, and 24.

iv. For Subject 033-004-05, no lab results were submitted to the Data Management team for Weeks 5, 20, and 24.

v. For Subject 033-004-06, no lab results were submitted to the Data Management team for Weeks 1, 4, 24, and 36.

vi. For Subject 033-008-04, no lab results were submitted to the Data Management team for Baseline and Weeks 1, 2, 3, 4, and 8.

vii. For Subject 033-008-07, no lab results were submitted to the Data Management team for Baseline and Weeks 1, 5, 6, 7, 8, 10, 12, and 16.

In the October 10, 2014 written response to the Form FDA 483, you acknowledged this observation. You proposed a corrective action plan for implementation in the fourth quarter of 2014 where local labs will be captured and queried immediately at the site in the eCRF, and you will continue to use the central lab in phase III trials in addition to local labs for managing safety information.

Your written response is inadequate because your proposed corrective actions make no provisions for assessing the effectiveness of and ensuring sustained compliance with your monitoring practices.

We acknowledge that the findings noted in Items 2.b.iv (Subject 033-004-05) and 2.b.v (Subject 033-004-06) were not included on the Form FDA 483 that you received, and therefore, the written response does not address these findings.

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 address the violations noted above adequately and promptly may result in regulatory action without further notice. If you believe that you have complied with FDA regulations, include your reasoning and any supporting information for our consideration.

If you have any questions, please contact Khin M. U, M.D., at 301-796-1156; Fax 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Khin M. U, M.D.
Acting Branch Chief
Compliance Enforcement Branch

Division of Enforcement and Postmarketing Safety
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Sincerely yours,
{See appended electronic signature page}
Sean Y. Kassim, Ph.D.
Office Director
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/s/

SEAN Y KASSIM
06/16/2015