

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Biologics Evaluation and Research

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DATE November 16, 2016

FROM Bhanu Kannan, Bioresearch Monitoring Branch  
Division of Inspections and Surveillance  
Office of Compliance and Biologics Quality

THROUGH Patricia Holobaugh, Chief, Bioresearch Monitoring Branch

THROUGH Carrie Mampilly, Director, Division of Inspections and Surveillance

THROUGH Mary Malarkey, Director, Office of Compliance and Biologics Quality

TO Marian Major, Ph.D., Chair, BLA Licensing Committee  
Richard Daemer, Ph.D., RPM  
Katherine Berkhausen, RPM

SUBJECT Bioresearch Monitoring Final Discipline Review Memo  
APPLICANT: Dynavax Technologies Corporation  
Biologics Licensing Application (BLA): STN 125428/0  
PRODUCT: HEPLISAV™ (HBsAg-1018)

**Summary Statement:**

The Bioresearch Monitoring inspections of five clinical investigators revealed substantive problems that resulted in two items for the Complete Response (CR) letter issued on November 10, 2016. These issues include an incomplete accounting of the number of subjects who were Lost To Follow-Up, and the sponsor's instructions for the sites to keep track of protocol deviations using Excel spreadsheets, a basis for defining the study population, without the ability to track changes to the data.

**Background**

Five clinical investigator (CIs) inspections were conducted in support of the BLA in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The inspection assignment included specific questions about the clinical study DV2-HBV-23 entitled *A Phase 3, Observer-Blinded, Randomized, Active-Controlled (Engerix-B®), Multicenter Trial of the Safety and Immunogenicity of HEPLISAV™ in Adults 18 to 70 years of Age*.

The inspections conducted at five clinical sites for data verification represent about 17% of the total subjects enrolled in the study, and were based on the data submitted by the sponsor in the BLA. The data audit portion of the inspections focused on the verification of the study data on safety and immunogenicity endpoints submitted by the sponsor in the BLA.

The following table identifies the results of the FDA inspections regarding this BLA:

**Inspection of the clinical sites and outcome**

Site number	Study site	Location	Issue of Form FDA 483	Final classification*
122 and 222	Radiant Research, Inc.	Chicago, Illinois	Yes	VAI
119	Clinical Research Advantage, Inc.	Birmingham, Alabama	No	NAI
124	Clinical Research Advantage, Inc.	Las Vegas, Nevada	No	NAI
132	Radiant Research, Inc.	Columbus, Ohio	No	NAI
138	Radiant Research, Inc.	Atlanta, Georgia	No	NAI

\* VAI-Voluntary Action Indicated      NAI-No Action Indicated

Financial disclosure

The Clinical Investigator Compliance Program directs the FDA investigator to ask the CI if and when he/she disclosed information about his/her financial interests to the sponsor and/or interests of any sub-investigators, spouse(s) and dependent children, and if and when the information was updated. The information submitted to the BLA was verified at the inspected sites, for the investigator and sub-investigators with no deviations.

Inspectional findings

The inspections of five clinical investigators verified the data submitted in the BLA including, but not limited to, the medical history, protocol deviations, subject exclusions and discontinuations, adverse events, study drug exposure, and laboratory data reported in data listings and datasets submitted by the sponsor. The protocol deviations that were verified included, but were not limited to, the enrollment of subjects who did not meet study eligibility criteria, administration of incorrect vaccine kit, improper storage of study vaccines, unblinding of the treatment assignment and site personnel, and subjects' out of window visits. No significant deviations were noted at three of the clinical investigator inspections. Some of the noteworthy deviations noted at two CI inspections are described below:

Clinical investigator issues:

Site 124:

1. Our inspection verified the accidental unblinding of the CI that was reported in the BLA. The CI was unblinded to subject level data on at least two occasions. For example, the CI signed a follow-up letter dated 8/5/14 for an unblinded monitoring visit on 7/18/14 that contained subject numbers and the vial numbers. Study records indicated that the site created a note to file on 1/28/15 acknowledging the accidental unblinding of the CI for vial numbers/vaccine assignment for at least 35 subjects on 8/5/14.

Sites #122 and #222:

2. The CI did not accurately capture the lost to follow-up (LTFU) subjects and those who were subsequently re-engaged in study DV2-HBV-23. For example, two subjects, #122666 and #122676 whose records were reviewed during the inspection, were LTFU and re-engaged but neither was identified on a site list of LTFU and re-engaged subjects, which included a total of 15 subjects. It is not clear how the site determined the number of LTFU subjects and subsequently re-engaged in the study. This resulted in item #41 in the CR letter issued on November 10, 2016.
3. The clinical sites were provided several versions of protocol deviation (PD) guidance documents and were asked to document the deviations categorized as “Major” or “Minor” based on the guidance documents. For example, the PD guidance document version 7.0 dated April 7, 2015 states the following as a “Major” protocol deviation:

“Visit Schedule/out of Window...The following visits occurring out of window (OOW) are considered major protocol deviations: Visit Week 4, Visit Week 28. Each OOW deviation should be documented on each site’s cumulative protocol deviation log, categorized as major, and should follow process for reporting deviations to the Institutional Review Board (IRB) for the cumulative PD log.”

Three of twelve randomly-selected subjects had OOW Week 28 visits with blood samples for anti-HBs that occurred on or after Week 40 following the initial Week 0 injection; these were not reported by the site as “Major” protocol deviations as instructed by version 7.0 of the PD guidance document and the deviations were not captured in the PD log for the site.

Furthermore, the PD guidance documents instructed the sites to maintain a PD log as an Excel spreadsheet, which could potentially be changed at any time by any individual and which did not track changes. This resulted in item #42 in the CR letter issued on November 10, 2016.

4. The CI did not maintain adequate records of the internet questionnaire for Week 8, Week 40, and Week 52 visits for three subjects. The protocol required that study visits, Week 8, Week 40, and Week 52 be conducted over the internet and specified that the CI review and document the subject responses contemporaneously. The CI did not maintain copies of the internet questionnaires contemporaneously and instead prepared a final report of all subject responses to the internet questionnaire at the end of the study.

Sponsor issue:

5. The Clinical Study Report submitted in the BLA defined the per-protocol (PP) population *as all randomized subjects who received all study injections, had no major protocol deviations, and had anti-HBs levels obtained within the protocol-defined study visit window at Week 28*. Hence, classification of a protocol deviation as “Major” or “Minor” plays a significant role in study data analyses. Further, the PP population was the primary analysis population for all immunogenicity analyses. Protocol deviation data are discrepant between the source data at sites #122 and #222, and the sponsor’s BLA data listing for three subjects as described in item 3 above. The protocol deviations of “OOW Week 28 visit” for three subjects are not reported in the BLA. Two of the subjects (#122794 and #222030) are classified as belonging to PP population and were not excluded from the PP population (BLA data Listing 16.8.1, Subjects Excluded from Per-Protocol Population). We note that one subject (#122676) was identified as not in PP population and was

included in the subject exclusion data listing 16.8.1 (Subject Exclusion from Per-Protocol Population). However, the subject exclusion was based on an eligibility criterion not met and not because of the above “OOW Week 28 visit”.

BIMO recommendations for sponsor response:

Based on our review of the BIMO clinical investigator inspections of study DV2-HBV-23 the following two items were included in the Complete Response letter:

41. Please provide a complete list of all subjects in study DV2-HBV-23 who were lost to follow-up (LTFU) and who were subsequently re-engaged. This request is based on the incomplete information obtained during the BIMO inspections. The inspections noted that sites did not accurately capture the LTFU subjects and those who were subsequently re-engaged. For example, two subjects whose records were reviewed during the inspection were LTFU and re-engaged but neither was identified on a site list of LTFU and re-engaged subjects. With an incomplete list of potentially affected subjects we are unable to determine the full scope of number of LTFU subjects and re-engaged in study DV2-HBV-23.

42. A BIMO inspection of study DV2-HBV-23 identified a Protocol Deviation guidance document instructing sites to maintain a protocol deviations log as an Excel spreadsheet. These documents could potentially be changed at any time by any individual without the ability to track who made changes and when they were made. Because the study populations were based upon protocol deviations, please explain how you verified that the information in the logs was complete and accurate.

BIMO follow-up

We plan to send informational letters to the inspected clinical investigators.

Should you have any questions or comments about the contents of this memo or any aspect of Bioresearch Monitoring, please contact me at 240-402-8979.

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