

Review Memo of the 483 Responses for the 2010 PLI at Dendreon's Manufacturing Facility for Sipuleucel-T at Morris Plains, New Jersey - Provenge

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

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File BLA STN 125197/0
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Subject: Review Memo of the 483 Responses for the 2010 PLI at Dendreon's manufacturing facility for sipuleucel-T at Morris Plains, New Jersey

REVIEW COMMENT

Based on the information submitted by Dendreon (BLA STN 125197/0/037), the responses to the three 483 observations made during the 2010 PLI appear to be adequate. The timeframe committed for completing the corrective actions appear to be acceptable.

INSPECTIONAL FOLLOW-UP

I recommend that the next inspection team -----(b)(5)-----
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REVIEW SUMMARY

The Center for Biologics Evaluation and Research (CBER) conducted a Pre-license Inspection (PLI) at Dendreon Corporation (US License # 1749) manufacturing facility located at Morris Plains, New Jersey, on January 25 – 29, 2010. The CBER inspection team consisted of Drs. Gang Wang, Randa Melhem, Thomas Finn and Steven Oh from CBER, and Inspector Barbara Wilimczyk from ORA. The scope of the inspection was to perform a Pre-license Inspection on Dendreon's manufacturing facility for sipuleucel-T (APC8015, PROVENGE®) under the BLA STN 125197/0.

Sipuleucel-T is an autologous active cellular immunotherapy product designed to stimulate immune responses for the treatment of men with asymptomatic or minimally

symptomatic metastatic castrate resistant (hormone refractory) prostate cancer. Each dose of sipuleucel-T contains a minimum of 50×10^6 autologous CD54+ cells activated with PAP-GM-CSF suspended in 250 mL of Lactated Ringer's Injection, USP in a sealed, patient-specific infusion bag. Upon approval, sipuleucel-T will be the first product manufactured at this facility for commercial distribution.

Dendreon's manufacturing facility in Morris Plains, NJ, was previously inspected by FDA in February 12 – 16, 2007. A Form FDA 483 with nine observations was issued to the firm at the conclusion of the PLI on February 16, 2010. Due to the significant deficiencies concerning the clinical, CMC and inspectional issues, CBER issued a Complete Response (CR) letter to the firm on May 8, 2007. Dendreon has since submitted multiple amendments to BLA to address the 483 observations. Their responses were subsequently reviewed and deemed to acceptable. All the inspectional issues have since been resolved.

On October 30, 2009, Dendreon submitted a Class 2 Response (BLA STN 125197/0/34) to address the deficiencies identified in the CR letter. Because the last PLI was conducted in almost three years ago in February 2007 and the facility has not been re-inspected since then, CBER decided to conduct a reinspection at Dendreon's NJ facility on January 25 – 29, 2010. Details of this inspection are documented in the EIR. The current PLI, conducted on January 25 – 29, 2010, focused on the systems that are used to manufacture and provide quality controls for the product. The inspection team reviewed the documents related to quality system, facility and equipment system, material management system, production system, packaging and labeling system, and QC laboratory control system. During the PLI, the inspection team also observed the entire production process of (b)(4) lots of sipuleucel-T from normal donors. At the conclusion of the PLI on January 29, 2010, the inspection team issued a Form FDA 483 with three observations to the firm.

On February 9, 2010, Dendreon submitted their official written responses to the 483 observations (BLA STN 125197/0/037), which I subsequently reviewed. The 483 observations (in *italics*), Dendreon's responses (in plain text) and comments (in Bold) are summarized below.

1. *The SOP-11020: Workstation Clearance and Change Over is deficient in that it does not require QA involvement for verifying and releasing the workstation after completion of the previous lot and prior to initiation.*

Dendreon Response:

Dendreon commits to revise *SOP 11020, Workstation Clearance and Change Over*, requiring QA review and approval that workstation (WS) clearance and change over of the previous lot have been completed prior to initiation of the next lot. SOP 11020 will be revised and implemented by March 8, 2010.

The SOP 11020 revisions will include a checklist to document post-manufacturing WS clearance and change over, as well as to document the state of readiness of the WS prior to manufacturing subsequent lots. Clearance and change over activities will be completed and documented by Manufacturing, and an additional Manufacturing Verifier will confirm the activities have been completed and documented on the checklist. Once the post-manufacturing checklist has been reviewed and approved by Quality Assurance, the WS will be released for use. SOP 11020 describes the steps required to clear all operating materials from each

WS, and to clean and prepare the WS for another processing lot. WS clearance and change over is performed at the -----(b)(4)----- manufacturing as described in SOP 11020. These steps have been documented in the Batch Record by Manufacturing staff, confirmed by a Manufacturing Verifier, and reviewed by QA.

CBER Comment:

The responses appear to be acceptable. I recommend that next inspection team verify -----(b)(5)-----

2. *Environmental monitoring for -----(b)(4)----- conducted during the manufacturing processes is inadequate in that the --b(4)----- inside the Class (b)(4) biological safety cabinets (BSC) within the Class (b)(4) cleanroom are not monitored throughout the entire manufacturing process.*

Dendreon Response:

Dendreon commits to expand the current dynamic monitoring program and implement the continuous monitoring of -----(b)(4)----- the Class (b)(4) BSC throughout the entire manufacturing process by April 16, 2010. This change will be in addition to Dendreon's current practice of monitoring -----(b)(4)----- in the BSC -----(b)(4)----- and during all Aseptic Process Validations and Operator Qualifications.

CBER Comment:

The responses appear to be acceptable. I recommend that next inspection team follow -----(b)(5)-----

3. *The current cleaning procedures used in the cleanroom have not been qualified.*

Dendreon Response:

Dendreon commits to qualify the cleaning procedures used in the cleanroom BSC by April 23, 2010. The cleaning qualification will augment existing disinfectant effectiveness studies reviewed during the inspection and will demonstrate the removal of residual process material from representative surfaces following cleaning.

CBER Comment:

The responses appear to be acceptable. I recommend that next inspection team -----(b)(4)-----

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