

DEPARTMENT OF HEALTH & HUMAN SERVICES



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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To: Thomas Finn, Ph.D., Microbiologist, OCTGT/DCGT/CTB, HFM-720  
File STN 125197/0/034 and STN 125197/0/045

From: Gang Wang, Ph.D., Biologist, OCBQ/DMPQ/MRB II, HFM-676

cc: Lori Tull, CSO, OCTGT/RMS, HFM-705

Through: Chiang Syin, Ph.D., Branch Chief, OCBQ/DMPQ/MRB II, HFM-676

Subject: Review Memo of the Class 2 Response to CR Letter Submitted by Dendreon to Seek Licensure of Sipuleucel-T for the Treatment of Men with Asymptomatic, Metastatic Androgen Independent Prostate Cancer

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**RECOMMENDATION**

Based on the information submitted in this Class 2 Response to CR letter (STN 125197/0/034), Amendment (STN 125197/0/045) and the sponsor's satisfactory responses to my review and inspectional questions, I recommend an approval to this BLA.

**ADDITIONAL COMMENTS**

During the Pre-licensing Inspection (PLI) conducted by CBER at Dendreon's manufacturing facility at Morris Plains, NJ on January 25 – 29, 2010, the inspectors discovered that since the submission of the current amendment (STN 125197/0/034), the sponsor has installed and implemented a -----(b)(4)----- software system and a -----(b)(4)----- system, which were not included in the current amendment. In addition, the ---(b)(4)--- for the HVAC system, which have been in service since 2007, were neglected to be included in the BLA.

The ----(b)(4)----- system is a comprehensive and sophisticated software that was specifically designed for scheduling, manufacturing and distribution of Dendreon's commercial product. Since the implementation of the ----(b)(4)----- system, the sponsor has been heavily relying on the system for their daily operations.

----(b)(4)----- was added to the manufacturing facility air system in 2007 prior to the 2007 PLI. However, due to an oversight, the change was not included in subsequent amendments to the BLA. -----(b)(4)----- were added to ----(b)(4)----- (serving cleanroom Modules --

(b)(4)-----) and ----(b)(4)----- (serving the product and non-product corridors). The units were commissioned and validated in 2007.

Subsequent to the submission of BLA Amendment 034, Dendreon has re-modified the ---(b)(4)----- system for the cleanroom and QC lab incubators by replacing the existing -----(b)(4)----- is part of the design for the phased expansion of the NJ facility currently under ---(b)(4)----- construction.

During the 2010 PLI, I have verified the documentations associated with the installation and qualification/validation of the new ----(b)(4)----- system, -----(b)(4)----- system, and requested the sponsor submit the relevant information as a BLA amendment to CBER. On March 3, 2010, CBER sent an Information Request to the sponsor requesting submission of the -----(b)(4)-----, among some other CMC information requests, as an amendment to the BLA.

The information for the ----(b)(4)----- system has since been submitted in a BLA amendment (STN 125197/0/043) and has been evaluated by the software expert in the product office. The initial review indicates that the system is acceptable. During the 2010 PLI, I verified the documents related to the qualification/validation of the ----(b)(4)----- system. From a regulatory perspective, the system was adequately validated, implemented and documented. No major deficiencies were noted. More detailed information can be found in my EIR and software review memo.

The documentations related to the ----(b)(4)----- were initially reviewed during the 2007 PLI and verified during the 2010 PLI and were deemed acceptable. Dendreon has submitted a BLA amendment (STN 125197/0/045) on March 26, 2010 to include the ----(b)(4)----- to their NJ facility.

On March 26, 2010, Dendreon submitted an Amendment 045 describing the -----(b)(4)-----





2 Pages determined to be not releasable: (b)(4)

Changes in the NJ facility have required modifications to the (b)(4) of the product and non-product -----(b)(4)-----  
These changes were related to the -----(b)(4)-----  
areas or to the phased construction of expansion spaces.

All clinical manufacturing of sipuleucel-T was halted while structural modifications were made to the ISO -----(b)(4)----- were installed prior to initiation of construction activities. Upon completion of the modifications, air flows were re-balanced, the --(b)(4)-- were properly cleaned, and EM was performed. All required criteria were met prior to restarting clinical manufacturing. I verified the information on cleaning and qualification during the 2010 PLI and found them to be acceptable.

During the 2010 PLI, it was discovered that Dendreon has installed a new -----  
----- (b)(4) -----  
----- facility, but the relevant information was not submitted in the BLA amendment. They have done the IQ/OQ of the system and qualified the (b)(4) and I have reviewed the documents. No major concerns were noted. I requested that the relevant information be submitted as an amendment (STN 125197/0/045) to the BLA.

### **New QC Lab Equipment**

As requested at the June 5, 2009 Type C meeting, Dendreon has provided information on the new QC lab equipment that has been added to the NJ facility since the 2007 PLI.

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The new QC equipment was qualified and/or calibrated as required. During the 2010 PLI, the inspection team verified the qualification of the newly added QC lab equipment. No major deficiencies were noted.

### **Master Batch Record Revisions**

An unexecuted copy of the sipuleucel-T master batch record, BR 45025, was provided in BLA 125197, Original Submission. The batch record has been modified to clarify some steps and to provide better process control at some points. The manufacturing procedures remain the same. The revisions to the batch record do not alter the basic steps used to produce sipuleucel-T, i.e., cell manipulations, buoyant density separations, ex vivo culture, harvest, and formulation. Table 3 (not included in this review memo) presents an overview of the revisions made to the sipuleucel-T batch record since the 2007 PLI. Items requiring additional explanation are further addressed following the table. Unique modifications have been categorized as key changes. Some changes were related to multiple steps throughout the batch record, and these have been categorized as general changes. A number of formatting changes have also been made for

clarification purposes. I would defer the evaluation of the revisions made the master batch record to product reviewers.

**Automated Calculations**

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**In-process --(b)(4)-- Results**

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