

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

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

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)

• (b)(4)

• (b)(4)

Reports are produced quarterly and annually, to summarize and analyze the routine and in-process EM results obtained at the NJ manufacturing facility. The annual reports for 2007 (TR 30616) and 2008 (TR 30645) are provided. These reports include summary tables, trend charts, and characterization of local isolates. Two quarterly reports are provided to address the on-going environmental monitoring for 2009: January 1st – March 31st 2009 and April 1st – June 30th 2009. The quarterly reports contain data similar to the annual reports but with limited analysis of those data. I have reviewed the EM summary reports and found them to be acceptable. The EM summary reports and trending analyses were further verified during the 2010 PLI. No major issues were noted.

Since CBER's 2007 PLI at the NJ facility, several changes have been made to the manufacturing support areas. These changes are summarized in the following table. Most facility changes have had little or no impact on --b(4)------. One set of changes included activities that impacted the outer corridors of ---b(4)----- area. These changes are discussed in more detail in Section of Facility Changes in Manufacturing Corridors. A complete set of updated facility drawings is provided and reviewed. No major concerns were noted.

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

-(b)(4)-

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

-b(4)-