

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

Date: April 13, 2007

To: Lori Tull, CSO, RPM, OCTGT/RMS, HFM-705
File STN 125197/0

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

cc: Keith Wonnacott, Ph.D., Chief, Committee Chair, OCTGT/DCGT/CTB, HFM-715
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Through: Chiang Syin, Ph.D., Chief, OCBQ/DMPQ/MRB II, HFM-676

Subject: Review of the Chemistry, Manufacturing, and Controls part of the Biological License Application (BLA) submitted by Dendreon Corporation to seek licensure of sipuleucel-T for the treatment of men with asymptomatic, metastatic androgen independent prostate cancer.

REVIEW RECOMMENDATION

I have completed my review of all the information related to CMC (pertaining to DMPQ's review responsibility) and facility issues in BLA STN 125197/0. Based on my review of the content submitted, the submission package appears to be complete, the validation studies appear to be properly designed and executed (with an exception in which the process validation for Module ■ has not been performed), and the information and data appear to be adequately reported. My review questions, other than the issues identified during the pre-license inspection, to Dendreon have been adequately addressed. The inspectional issues were discussed in more details in the Establishment Inspectional Report (EIR).

A pre-license inspection (PLI) of Dendreon's manufacturing facility in Morris Plains, New Jersey took place from February 12, 2007 to February 16, 2007. Form 483 observations were issued on February 16, 2007.

In summary, although the DMPQ-related review issues in this BLA have been addressed, the outstanding inspectional issues have yet to be resolved. Therefore, I would recommend a complete response (CR) letter be sent to Dendreon at this time.

REVIEW QUESTIONS AND COMMENTS

The following major issues resulting from my review of this BLA need to be addressed fully by the applicant:

1. The issues relating to [REDACTED] of commercial (sipuleucel-T) and clinical IND products within the same module needs to be further addressed. The information on the following issues need to be submitted and discussed:
 - 1) Typically, how many lots of products of clinical IND products per month and per year will be manufactured in the Modules [REDACTED]
 - 2) How many different products will be manufactured [REDACTED] at each time within a single module? How will the different products be handled? Are they manufactured in the same or separate workstations (WS) in the same module or separate modules? Are they incubated in the same incubators? How are the products segregated?
 - 3) What are the procedures to prevent products mixed up?
 - 4) Are operators and verifiers product-specific, i.e., do the operators and verifiers work on commercial products as well as on other IND products during the same time?
 - 5) Provide SOPs for product segregation, line clearance, product changeover, equipment and cleanroom cleaning, and procedural controls for processing multiple products.
2. Process validation (PV) was performed only [REDACTED] for Module [REDACTED] in which [REDACTED] lots were processed on the first day, followed by [REDACTED] lots in the next day. No PV has been performed for Module [REDACTED]. In fact, no product has ever been processed in Module [REDACTED] yet. Only aseptic process validation (APV), which was not included in this BLA but was later reviewed during the pre-licensure inspection (PLI) has been performed in Module [REDACTED]
3. There is no data to support that the multiple products and multiple lots [REDACTED] can be [REDACTED] Module [REDACTED] modules have a total of [REDACTED] WS, and theoretically [REDACTED] lots can be processed [REDACTED]
[REDACTED]
[REDACTED]
4. The shipping validation study was performed using [REDACTED] to simulate the APH and Lactated Ringer's Injection, USP (LR) to simulate the final product sipuleucel-T. The shipping route was from Dendreon, [REDACTED] to Dendreon, Morris Plains, NJ. No shipping validation data on APH and the final product was provided, and no other destination was shipped. These issues should be justified by Dendreon.

During the telecon between CBER and Dendreon held on March 16, 2007, I requested the following information as an amendment to BLA for further review.


1. The [REDACTED] study performed in Module [REDACTED]
2. In Item 4, Section 3.2.A.1 Facilities and Equipment, Section 5.0 Other Products, Dendreon states that they plan to manufacture sipuleucel-T and related products for clinical use, and the related products would be prepared [REDACTED] with sipuleucel-T. Please provide the following information:

- 1) Procedures to ensure product segregation and prevention of cross-contamination upon receipt of starting materials through distribution of the final products.
- 2) Procedure for line clearance and cleaning for equipment and the cleanroom modules.
- 3) Procedures to ensure personnel segregation and prevention of cross-contamination, i.e., are operators and verifiers product-specific or will they work on more than one product during a work day?

On March 22, 2007, Dendreon responded to my request by submitting an amendment (STN 125197/8) with a summary report entitled Aseptic Process Validation (APV) Report for Sipuleucel-T for New Jersey, Module [REDACTED] (QVD #51051).




Regarding my first review question on [REDACTED] of commercial and clinical products in the modules, a similar question raised by product reviewers was forwarded to Dendreon, and they responded via email on April 6, 2007.




The rest of the issues in review question #1 have been properly addressed in their email responses to my telecon information requests dated March 16, 2007, and is discussed below. Some of the issues are verified and resolved during the PLI and will not be repeated here.

Regarding my second review question on multi-product issue, Dendreon responded on April 13, 2007 via an email which included an SOP-11168 entitled Policy for Multiproduct Manufacturing in the New Jersey Immunotherapy Manufacturing Facility. This SOP describes the policy and procedures for manufacture of commercial sipuleucel-T and other clinical products, and reflects the discussions between CBER and Dendreon regarding the segregation of commercial and clinical production, as well as the limited capacity for commercial production, i.e., no more than [REDACTED] lots within a module.



This SOP has been reviewed. The specified procedures appear to be adequate and my concerns on this potential product mix-up and cross-contamination have been properly addressed. However, although Dendreon has limited their production of the commercial product to no more [REDACTED] lots [REDACTED] within a single module, it is still not clear to me how the [REDACTED] production of up to [REDACTED] lots of clinical products will affect the production of commercial products. Based on observation during the PLI and the fact that the facility has [REDACTED]



The second review question is related to one of the major 483 observations made during the PLI, which is discussed with more details in the EIR. Without any supporting data to demonstrate that the products can be successfully and reproducibly manufactured in Module [REDACTED] as well as the uncertainty of the potential impact of the [REDACTED] of commercial and clinical products due to the limited sample handling capacity in the QC lab, I would delay the approval recommendation for Module [REDACTED] until it has been fully validated. A satisfactory response from Dendreon to this 483 item and a full validation of the Module [REDACTED] will be expected before an approval recommendation can be made.

As far as the third review question, i.e., the manufacturing capacity of [REDACTED] processing more than [REDACTED] lots for consecutive days, is concerned, it is one of the major 483 discussion items made to Dendreon during the PLI. The validated maximum processing capacity for Module [REDACTED] is [REDACTED] lots. The inspection team has great concerns about Dendreon's capability of [REDACTED] processing more than [REDACTED] lots for [REDACTED] days. This issue will be further discussed in the EIR.

An issue similar to my #4 review question concerning the shipping validation has also been raised by product reviewers. The inspection team has closely followed this shipping validation issue during the PLI. During the PLI, Dendreon has provided us a shipping study with [REDACTED] lots of the final products manufactured from Dendreon's Seattle facility. Detailed evaluation and responses to this issue can be found in EIR.

REVIEW SUMMARY

Introduction

Dendreon Corporation (Dendreon) submitted this Biological License Application (BLA) to seek licensure for its product, sipuleucel-T (APC8015, Provenge[®]), for the treatment of men with asymptomatic, metastatic androgen independent prostate cancer. The product is manufactured at its manufacturing facility located in Morris Plain, New Jersey. Only the DMPQ-related issues in the chemistry, manufacturing and controls (CMC) section have been reviewed. Clinical, product, pharmacological, statistical and other non-DMPQ-related issues are not subjects of this review memo.

Sipuleucel-T, APC8015, is an autologous active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. Sipuleucel-T consists of autologous peripheral blood mononuclear cells, including antigen presenting cells (APCs) that have been activated *in vitro* with a recombinant fusion protein.

The recombinant fusion protein, PA2024, is composed of prostatic acid phosphatase (PAP), an antigen expressed in prostate adenocarcinoma, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator. PA2024 is a critical reagent unique to sipuleucel-T.

Sipuleucel-T is an autologous product and the cells from a single apheresis component, which are obtained from the patient to be treated, yield a single lot of sipuleucel-T. The resultant lot of final product is packaged in a single infusion bag and administered in a single dose. For sipuleucel-T, the biological substance and biological final product are one and the same.

Manufacturing Facility

A. Facility

This review includes the manufacturing facility shown in the following table.

Table 1 Commercial Manufacturing Facilities

Name and Address	Responsibility	Contact
Dendreon 220 East Hanover Ave. Morris Plains, NJ 07950	Manufacture of antigen-loaded antigen presenting cell final products	Ernest Bognar
	QC testing	Plant Manager
	Final product release	ebognar@dendreon.com
	Packaging and shipping	tel. (973) 796-2962
	Raw materials inspection, testing, and release	fax (973) 796-2020
	Raw material kitting	

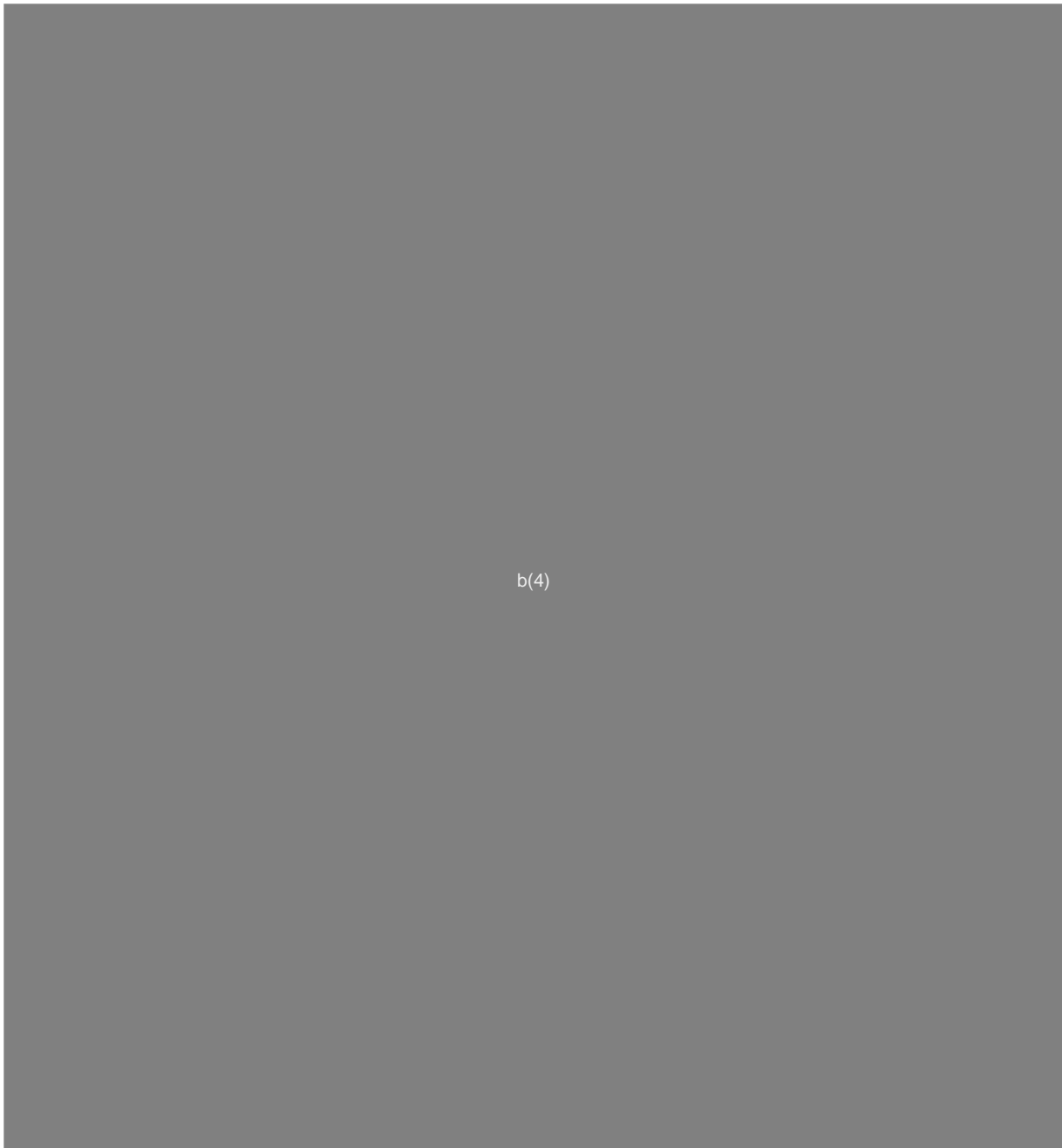
Dendreon's manufacturing facility is housed in a single-story building of approximately 158,000 square feet located at 220 East Hanover Ave., Morris Plains, New Jersey. Dendreon is the sole occupant.

Drawing 1 in Section 6.0 of 3.2.A Appendices shows the overall building plan. Approximately [REDACTED] square feet of the building have been renovated for GMP manufacturing, quality control (QC) laboratories, warehouse, and administrative operations. The un-built areas are available for future construction of additional cleanrooms and expansion of support facilities, which would be a subject of a future BLA supplement.

Drawing 2 in Section 6.0 of 3.2.A Appendices shows an enlargement of the built-out area from Drawing 1. The cleanroom is [REDACTED]

[REDACTED] Outside this core area are the general personnel facilities, QC laboratories, shipping and receiving, mechanical areas, quality assurance (QA) functions, and general office spaces. The following table gives an overview of these areas and their functions.

Table 3 Overview of the NJ Facility



b(4)

The NJ facility is designed to accommodate the [b(4)] manufacture of multiple lots of sipuleucel-T and related autologous APC products. The [b(4)] cleanroom design is based on

[b(4)]

[b(4)] The facility employs procedural controls to prevent contamination and cross-contamination, which will be reviewed specifically in this review memo.

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

The movement of materials and personnel, including incoming material flow, product and sample flow, waste flow, and personnel flow and gowning requirements, and drawings showing the flows, have been described in this BLA. I have reviewed the submitted information and found no major concerns.

Specific Systems

The following systems are described in this section:

- Heating, ventilation, and air conditioning (HVAC) systems
- Environmental monitoring programs
- Key manufacturing equipment
- Computer Systems

[REDACTED]
[REDACTED]. Dendreon states that sterile purified water is [REDACTED]
[REDACTED]

Validation of each of the systems has been addressed, and the validation protocols and summary reports are provided. Dendreon used a risk-based approach to validate the NJ manufacturing facility. All manufacturing equipment and systems planned for the facility were subjected to a risk assessment to evaluate the impact of the operating, control, alarm, and failure conditions on the quality of the final product. The risk assessment was used to determine which systems and equipment would require commissioning or validation, both commissioning and validation, or neither.

The information on risk assessment was not submitted in the original BLA. During the telecon between CBER and Dendreon on December 14, 2006, Mary Padgett requested that Dendreon submit an amendment to include the documentation for the validation of risk assessments that were performed at the NJ manufacturing facility. On December 20, 2007, Dendreon submitted an amendment, including completed assessment forms, to include the information on risk assessment. My evaluation of the risk assessment is discussed in Risk Assessment section of this review memo. The issues have also been followed by Ms. Padgett during the pre-licensure inspection (PLI), and are further discussed in the Establishment Inspection Report (EIR).

A. Heating, Ventilation, and Air Conditioning (HVAC) System

The NJ facility is built on a [REDACTED], where the core production [REDACTED] modules can be replicated to increase capacity as need develops. [REDACTED] modules and the associated product and non-product corridors are supplied with HEPA-filtered air by [REDACTED] air handling units (AHUs), [REDACTED]

All other areas of the facility (administrative, QC laboratories, and warehouse spaces) are supplied or controlled by [REDACTED] additional units as indicated in the following table.

b(4)


The room classifications are summarized in the following table. Drawings that show the classification of the manufacturing areas and the relative room pressurizations are included in the BLA. Room pressurization is designed to ensure the cascade of pressure [REDACTED] the [REDACTED]


[REDACTED] I have reviewed the HVAC section and no major concerns were identified from the information submitted. The information on the HVAC system has also been verified during PLI.



b(4)

The following containment features have been applied to the containment and prevention of contamination of the product at the NJ facility.



The HVAC system was evaluated per Dendreon's risk assessment procedure, which is reviewed in the later section of this review memo. Based on the risk assessment, a number of HVAC systems, such as the HVAC , were commissioned but not validated. Systems such as the cleanroom AHUs have greater impact on product safety, efficacy and quality and thus are validated and the validations have been verified during PLI. No major concerns have been identified.

According to Dendreon, validation of the cleanroom HVAC system is built on a number of elements:



The PQ results for Module ■ are summarized in the following table.



According to Dendreon, Cleanroom Module ■ and the ■ BSCs located in Room ■ were not tested under dynamic conditions and therefore did not fulfill the requirement of protocol QVD 50898. The locations were tested under static conditions and met all acceptance criteria. Dendreon states that the module will not be used for production until the qualification requirements are met. During the PLI, Dendreon presented me with a

PQ study report for Module (b)(4) which showed that the PQ study under both static and dynamic conditions were performed after the BLA was submitted. It appeared that the PQ for Module (b)(4) was successfully executed and no major excursions/deviations occurred during the PQ.

Aseptic Process Validation: (b)(4) was designed to support aseptic processing, and the aseptic process has been validated by means of process simulations similar to standard media fills. The APV program and the results of the studies (Process Validation and/or Evaluation) have been reviewed and discussed in detail in a later section of this review memo. Briefly, the APV program consisted of (b)(4) consecutive successful runs in a module. Each successful run required performing the simulated process in (b)(4), at the intended maximum occupancy. Anticipated interventions such as process disruptions and power interruptions were built into the APV protocol. (b)(4) was used in place of process fluids (cell suspensions, culture media, wash solutions, etc.). The sipuleucel-T manufacturing process steps were performed, resulting in final product bags (b)(4). (b)(4) These bags were required to demonstrate no growth after (b)(4). (b)(4)

B. Environmental Monitoring Programs

The EM programs are designed to ensure that all aspects of manufacturing facility operations are monitored appropriately to detect any excursions and trends that could compromise Dendreon's aseptically-produced products. The programs address the following issues:

- Facility qualification, including the cleanroom PQ and aseptic process validation;
- Routine environmental monitoring programs;
- Qualification of cleaning agents;
- Personnel training and qualification.

Facility Qualification: The cleanroom PQ protocol was executed following equipment IOQ and chemical sanitization of the spaces with disinfectant and sporicidal agents. The PQ protocol was used to perform EM during “static” and “dynamic” conditions to qualify the facility in accordance with FDA, USP, and ISO EM guidelines. (b)(4)

(b)(4)
(b)(4) ISO (b)(4)
(b)(4) The PQ data were used to support initial environmental alert and action levels specific for this facility. The PQ studies for EM in (b)(4) modules have been verified during the PLI and no major concerns were identified.

Dendreon states that the aseptic manufacturing process will be recertified (b)(4) by performing (b)(4) in a representative module at full occupancy. In the event of a major change in the manufacturing process or an APV failure, the full APV (b)(4) successful and (b)(4) runs) will be repeated.

Routine Environmental Monitoring: Dendreon's EM program includes routine monitoring at specified frequencies to cover the production facilities and dynamic monitoring. The program

also encompasses EM trending, the establishment and maintenance of alert and action levels, and investigation of excursions from those levels.

The routine monitoring program evaluates the quality of the air and surfaces in the ISO [REDACTED] module [REDACTED] per week. Support areas immediately adjacent to the cleanroom are also monitored at a regular frequency as specified.

Active airborne viable samples and airborne non-viable particulates are collected throughout the module and adjacent corridors. Cleanroom surfaces that are in close proximity to product manufacturing processes are also monitored routinely. Monitoring locations include:



For dynamic monitoring, Dendreon performs continuous monitoring for air viables within the [REDACTED] by use of [REDACTED] during both Day [REDACTED] manufacturing stages. Non-viable particulates are monitored within the [REDACTED]. Personnel monitoring of operator [REDACTED]



The alert/action levels, which were derived from data obtained during Module qualification studies and/or published guidelines, for dynamic EM have been established, and will be periodically reviewed and adjusted based on ongoing trending. Dendreon states that the procedures for handling of alert and action level excursions, as specified per SOPs, are in place. Based on the outcome of the investigation, appropriate corrective actions to eliminate the cause of the excursion will be taken.

A more detailed review of the EM data for the manufacturing facility will be discussed in the later section of this review memo.

C. Key Manufacturing Equipment

Dendreon states that sipuleucel-T and related immunotherapy products will be manufactured without the use of shared product-contact equipment. Product contact is restricted to [REDACTED] [REDACTED] sterile containers and transfer sets. However, each production module contains [REDACTED] types of equipment that are key to the manufacturing process:



For each of these equipment types, the IOQ protocol and a summary report are provided. One protocol was used qualify each type of equipment; that protocol was repeated to cover each piece

specifications for HVAC parameters, such as differential pressure and temperature, and for equipment in the Modules and QC laboratories. Systems and equipment connected to the [REDACTED] include but are not limited to:



Dendreon has implemented a company-wide [REDACTED] software system and in-house operating procedures to manage data that includes both financial and manufacturing information. Examples of the [REDACTED] functions that support the manufacturing batch record include:



IQ was completed to qualify the computer system equipment and [REDACTED] application installation. OQ confirmed that the configured system operates in accordance with the functional requirements in a consistent and reproducible manner. PQ testing confirmed that the configured system operates in the intended environment by trained users using approved procedures in a reproducible manner. [REDACTED] lots of sipuleucel-T were manufactured using healthy donors to test [REDACTED] performance. Additional testing involved lots that were terminated at various production points to simulate a terminated or failed manufacturing process. These validation studies have been verified during the PLI, and no major problems have been identified. More information about the computer systems can be found in EIR.

Contamination/Cross-Contamination Controls

The manufacturing facility is designed to accommodate the concurrent production of multiple lots of autologous APC products. The facility design features include specified product, material, waste, and personnel flows. In addition to the facility design features, standard operating procedures (SOP) and other controls work together to prevent contamination and cross-

contamination, support product integrity, and protect manufacturing staff as described further in this section.

The manufacturing processes for sipuleucel-T and related APC products employ standard tissue culture techniques, supplies, and equipment. [REDACTED]

[REDACTED] All of these supplies are [REDACTED]. Equipment used during production includes [REDACTED]. None of the equipment has direct product contact. Thus, Dendreon does not dedicate equipment to specific products.

The followings are the systems that Dendreon employs to support contamination precautions:

- Cleaning procedures and disinfectant efficacy
- Product segregation
- Work station clearance and product changeover
- Environmental controls
- Chain of identity procedures
- Personnel considerations

A. Cleaning Procedures and Disinfectant Efficacy

Cleaning procedures are defined for the module and surrounding areas, as well as the WS and associated equipment. Cleaning personnel are appropriately gowned and trained for all cleaning activities. The cleaning procedures and disinfectant efficacy studies as well as the equipment logbooks have been verified during the PLI and are discussed in the EIR. No major concerns were identified.

Modules and Surrounding Areas: Each module has dedicated cleaning equipment. Mop heads are replaced [REDACTED] and all cleaning is documented. Required cleaning activities are defined for 5 specified levels of cleaning. The level and frequency of cleaning required for modules and surrounding areas are established per procedure. The cleaning schedules address daily, bi-weekly, monthly, quarterly, and “as required” cleaning. The cleaning schedules may be revised to address trends in EM or changes in activities.

Cleaning agents are defined for general cleaning and equipment sanitization, room sanitization, or biohazard cleanup. The sanitizing agents [REDACTED]. The disinfectant efficacy studies performed to qualify each cleaning agent are discussed below.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Biohazard Spills: Universal precautions are required for any activities with blood components and cell products in the manufacturing facility. In the event of a biohazard spill, the spill is covered with absorbent material. A [REDACTED] solution is applied to the spill area for a minimum contact time of [REDACTED]. All contaminated materials used in the cleanup procedure are discarded appropriately.

Disinfectant Efficacy Studies: The cleaning agents have been demonstrated to be effective against model infectious agents. In Phase 1 of the microbial disinfectant efficacy study, [REDACTED] indicator organisms were used for disinfectant efficacy studies to demonstrate the suitability of the chosen cleaning agents on representative surfaces used in the NJ facility. In Phase 2 of the study, the routinely used disinfectants will be assessed for effectiveness against normal microbial flora recovered from the facility. This has been verified to be true during the PLI.

Two sets of studies were performed as described below. Protocols and summary reports have been reviewed, which showed that

[REDACTED]

[REDACTED]

B. Product Segregation

Dendreon states that production of APC immunotherapy products is strictly segregated between WSs to prevent cross-contamination and mix-ups. [REDACTED] is permitted in any WS at any given time, and all cell manipulations are confined to [REDACTED] WS. [REDACTED]

Within a WS, all open manipulation of the product occurs within [REDACTED]. All supplies that come in contact with the production lot are sterile [REDACTED]. Product transported or handled outside the [REDACTED] is enclosed within a [REDACTED].

The incubators accommodate multiple product lots segregated by secondary containers. Procedural controls, including a barcode-based labeling, tracking, and verification system, ensure that product identity is maintained while in the common areas.

Prior to and at the completion of processing, the WS undergoes clearance and changeover. All lot-specific labels are verified by QA prior to entry into the cleanroom, and the separation and wash containers and all sample containers are labeled. The WS is also clearly labeled with the lot number and activity. Further product segregation is accomplished through appropriate material and personnel flows. Additional containment features such as airlocks in personnel flows and pass-through are reviewed in above sections.

The SOPs for line clearance, changeover, and other procedural controls have been verified during the PLI, and no major concerns were identified. In addition, per my information request during the telecon dated March 16, 2007, Dendreon has amended their BLA by submitting an SOP-11168 entitled Policy for Multiproduct Manufacturing in the New Jersey Immunotherapy Manufacturing Facility which addresses the policy and procedures for manufacture of commercial sipuleucel-T and other clinical products, and the segregation of commercial and clinical production (Refer to REVIEW QUESTIONS AND COMMENTS section in this review memo for details).

C. Work Station Clearance and Product Changeover

Dendreon states that due to the autologous nature of every product lot, the same procedures are employed for WS clearance and product changeover between different products and changeover between patient lots. According to established SOP, the WS undergoes line clearance and product changeover prior to the initiation and upon completion of each lot. Clearance and changeover procedures require that [REDACTED]

[REDACTED] No new lot may be introduced without documented completion of clearance and product changeover.

The SOPs for WS clearance, product changeover and log sheets have been verified during the PLI, and no major concerns were identified.

D. Environmental Controls

[REDACTED] HEPA-filtered air.

[REDACTED] Environmental controls related to the HVAC system, including air pressure differentials, air supply and return, segregation of air handling units, and the EM program are reviewed in previous sections.

E. Chain of Identity (COI) Procedures

The COI is maintained through extensive use of labeling, operator verification and a barcode system. The barcode system maintains traceability of all manufacturing documentation, in-process containers, and final product back to the starting material and to the patient. Under this system, [REDACTED]

[REDACTED] The COI system checks in and out of each lot and prevents potential product mix-up in each incubator. A more detailed description of the COI system is provided in 3.2.S.2.2, Description of Manufacturing Process and Process Controls in Section 2.3.

During the PLI, the issue of COI system was closely followed by the product reviewers. More detailed discussions can be found in EIR.

F. Personnel Considerations

Facility access is managed by an electronic key card system with controlled access points throughout the facility. These controls limit access to the manufacturing facility to only those individuals who have been authorized for a specific area. Authorized personnel must escort visitors when entering the manufacturing facility, and all visitors will be required to gown appropriately.

Personnel are trained and qualified according to established procedures and such training is documented. The training and qualification program includes:

- Gowning training and certification program.
- Training in aseptic technique, cleanroom behavior, and contamination control.
- Qualification for aseptic processing.

To reduce the potential for cross-contamination, operators are restricted [REDACTED] the operator must don fresh sterile sleeves and a [REDACTED] pair of sterile gloves.

In addition to operators, verifiers are present within the module. Verifiers witness and verify the activities of multiple operators within the module, and do not manipulate the product. All verifiers are trained operators assigned to a witness/verification role.

The training programs including training SOPs and training records for some of the operators have been verified during the PLI. No major problems were observed.

Other Products

Dendreon states that they plan to begin using the NJ facility to manufacture sipuleucel-T and related products for clinical use by the end of 2006. The following table provides a list of the related products manufactured at the NJ facility. The addition of new products or patient populations would be the subject of a BLA supplement. According to Dendreon, clinical products will be prepared [REDACTED] with licensed sipuleucel-T, and clinical manufacturing materials and personnel will adhere to the process flows described in Section 2.3.



Dendreon states that the control procedures for preventing contamination and cross-contamination are not product-specific due to the similarities between products. Instead, they are applied on a lot-to-lot basis as well as a product-to-product basis, and the products will be processed using campaign procedures.

The issues on multiple products and [REDACTED] of commercial and clinical products were discussed with Dendreon and the related questions were forwarded to them. Dendreon has addressed these questions which are discussed in detail in the section of REVIEW QUESTIONS AND COMMENTS in this review memo.

Manufacturing Process and Process Controls

This section of BLA will be reviewed in depth by product reviewers. I only briefly evaluate and comment on those DMPQ-related issues, especially those related to process validations.

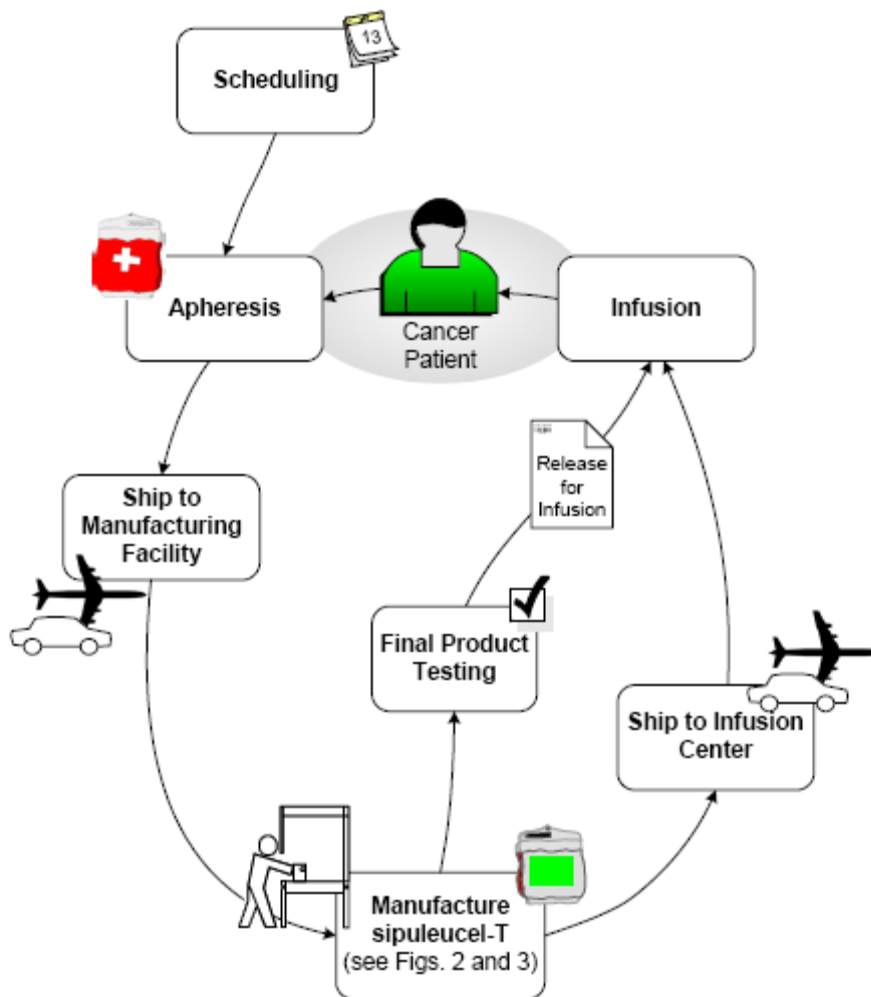
Sipuleucel-T is manufactured from a patient's own peripheral blood cells, which are transported from the apheresis collection center to the Dendreon manufacturing facility in NJ. There, mononuclear cells are aseptically prepared and cultured with the fusion protein, PA2024, to

activate the APCs. The cells are aseptically harvested, washed and suspended in Lactated Ringer's Injection, USP (LR), for delivery to the patient as an intravenous infusion. No reprocessing is performed on sipuleucel-T.

A. Manufacturing Process

The logistics of the manufacturing process are depicted in the following picture.

Figure 1 Sipuleucel-T Manufacturing Overview



The sipuleucel-T manufacturing process is initiated by collecting the patient's peripheral blood mononuclear cells by standard apheresis at a qualified apheresis center. The resultant raw material (APH) is packaged and shipped to Dendreon's manufacturing facility for preparation of sipuleucel-T. The APH shipping package has been validated to maintain the raw material at █ for up to █. The apheresis requirements, procedures, and shipping conditions are discussed in 3.2.S.2.3, Control of Materials, Section 3.0.

b(4)

b(4)

C. Sterility Test

The sterility testing (b(4)) is performed for sipuleucel-T during b(4) final product testing using the b(4) Dendreon states that they have developed and qualified an alternative method, i.e., b(4) sterility test, for sterility and will use this method in place of the 21 CFR § 610.12 method, and the alternate method will be used for routine testing of commercial lots of sipuleucel-T at Dendreon's NJ facility. They claim that the b(4) method has been demonstrated to be at least as effective and sensitive as the CFR method. The information for method validation, Validation of Analytical Procedures, is provided in section 3.2.S.4.3.

b(4)

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

[REDACTED]

[REDACTED]

The issues on the validation studies for the [REDACTED] test and its comparability to the traditional CFR sterility test have been closely followed by product reviewers during the PLI, and their evaluations can be found in their review memo and in EIR.

D. Chain of Identity Controls

The sipuleucel-T COI system consists of procedures and verifications that maintain the COI of sipuleucel-T from apheresis to infusion. The core of the COI system is Dendreon's [REDACTED] computer system, which establishes unique identifiers for the patient and his treatments. These identifiers are used throughout the process to ensure identity and traceability. The [REDACTED] system has been designed and validated to support the COI system.

The COI system is reviewed by product reviewers and have been closely followed during the PLI. More detailed evaluations can be found in EIR.

E. Contain Closure and Packaging Systems

The contain closure study has been performed and the information submitted have been reviewed. The sipuleucel-T container closure system consists of a primary container, a secondary container, and a shipping package, as summarized in the following table.

Table 1 Sipuleucel-T Container Closure System

Primary container	Sealed final product bag, label tethered to bag with a locking nylon tie
Secondary container	Leak-proof, tamper-evident [REDACTED] b(4) pouch containing absorbent material. Pouch bears the international biohazard symbol and the word, "biohazard".
Shipping package	Polyurethane shipping container that: 1) [REDACTED] b(4) [REDACTED] b(4)

The sealed final product bag, [REDACTED] product, has been evaluated by microbial challenge testing, and is summarized in Table 2 in Section 3.2.P.2.4. The results showed that all of the [REDACTED] bags tested maintained their microbial barrier properties following dynamic microbial challenge.

Dendreon states that the bag meets biocompatibility requirements according to [REDACTED], [REDACTED], for an external communicating device, blood path indirect, with limited contact duration [REDACTED]). The biocompatibility testing for [REDACTED], [REDACTED], for the final product bag is summarized in Table 4 in Section 3.2.P.2.4. All tests, except the sensitization that was listed as “pending”, passed.

Dendreon states that as a biological product, sipuleucel-T is exempt from IATA Dangerous Goods Regulations. However, they have designed the packing system in compliance with IATA Packing Instruction 650 to provide added assurance of safe transport. The packaging system, with a different arrangement of gel packs, is also used for shipment of the [REDACTED]. Dendreon states that both package configurations have been validated to ensure that they meet Dendreon’s requirements for shipment of the [REDACTED] and sipuleucel-T final product.

The protocol QVD 50638, Validation of the Apheresis/Provenge Final Product Shipper, is provided. [REDACTED] sets of tests including physical testing, [REDACTED] testing and shipping study were performed for the final product configuration and for the APH configuration. The physical testing was performed by an independent test lab following the [REDACTED] procedures. The [REDACTED] study was also performed by an independent test lab in accordance with protocols QVD 50638 and QCD 50874. The acceptance criteria for physical testing for the final product were met, and the acceptance criteria for [REDACTED] testing were also met (Tables 10 – 11).

The shipper validation study on the packaging system demonstrated that the APH and sipuleucel-T final product shipper is qualified to maintain product temperature for [REDACTED] which is the validated product shelf life, by the pre-specified configurations. The APH configuration met all acceptance criteria in the [REDACTED] test and shipping study, demonstrating the maintenance of product temperature between [REDACTED]. The sipuleucel-T final product configuration also met all acceptance criteria in the [REDACTED] test and shipping study, demonstrating the maintenance of product temperature ([REDACTED]) between 2°C to 8°C for over [REDACTED].

F. Shipping Validation

The protocol for a study that addresses the impact of the shipping procedure on sipuleucel-T has been provided (QVD 50893, Validation of the Sipuleucel-T Shipping Process) and reviewed. This protocol indicates that post-shipment sipuleucel-T samples must meet the product release acceptance criteria, which will be the stability criteria. The actual data from the completed study for the final product is not submitted in this BLA, but will be available at the time of inspection, according to Dendreon.

The shipping study entails monitoring a shipment of simulated product during an actual shipment undergoing normal distribution. The key parameters are listed in Table 9 in Section 3.2.P.2.4. In this study, shipping route [REDACTED] to Dendreon, Morris Plains, NJ, and the simulated product was [REDACTED] for the final product. The APH shipper was tested using [REDACTED] different simulated [REDACTED], which represent the extremes of the accepted range for incoming APH volume. The final

product volume is 250 mL. The acceptance criteria and test results are provided in Tables 13 and 14 for the final product and Tables 18 and 19 for APH. All tests passed.

During the PLI, the issue on shipping validation has been followed by product reviewers. As stated above, the actual shipping route in the shipping study [REDACTED] to Dendreon, Morris Plain, NJ, and the shipping study was performed using [REDACTED] to simulate the final product. No shipping validation has been performed in the NJ facility, and no data is shown on the real final product sipuleucel-T in this BLA. These are my concerns that I have had for this BLA submission. However, during the PLI, the inspection team was presented with data on shipping validation studies performed on three lots of the final product originating from [REDACTED] to Dendreon, Morris Plains, NJ (no APH shipping study was performed). Evaluations of this new shipping study will be discussed in details in EIR.

Process Validation

Dendreon states that process validation (PV) was completed at Dendreon's NJ manufacturing facility, with the production of [REDACTED] lots of sipuleucel-T manufactured from healthy donors. The facility is designed to accommodate the [REDACTED] manufacture of multiple lots of sipuleucel-T and related autologous APC products. As described above, [REDACTED] equivalent WS are housed in [REDACTED] production lots for process validation assured that multiple WSs were in use [REDACTED] and different lots were at different stages in the manufacturing process for part of the validation study. Specifically, the [REDACTED] manufacturing process was initiated for [REDACTED] lots on the [REDACTED] day, and for the remaining [REDACTED] lots on the following day. The PV also includes:

- The cleanroom PQ, which demonstrates that the classified production areas meet the environmental criteria for manufacturing.
- [REDACTED], which provides assurance that the sipuleucel-T manufacturing process can be performed aseptically when challenged with situations such as maximum cleanroom occupancy and process interruptions and interventions. The [REDACTED] is similar to a media fill, in that growth medium is used in place of process fluids in a simulation of process manipulations. A total of [REDACTED] were produced for the [REDACTED].
- Supporting studies encompassing process characterization, product development using healthy donors, and comparability studies, which included [REDACTED] additional lots manufactured in the NJ facility for stability studies (refer to 3.2.P.2.3, Manufacturing Process Development, Section 4.1).

A. Execution of Process Validation



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

b(4)

Although a critical agent, PA2024 is considered as a component of the sipuleucel-T product. It was decided that only the Dendreon NJ facility will be inspected whereas the inspections on other contract manufacturers will be waived given the fact that [REDACTED] have been inspected recently. Dendreon has a vendor audit program that has been reviewed during the PLI, and no major concerns have been identified.

Container Closure System

The container closure system for PA2024 [REDACTED] Component consists [REDACTED]
[REDACTED]

b(4)

The suitability of these components is supported by real time stability studies. During process development, a [REDACTED] physicochemical evaluation of primary packaging and filling materials was initiated by Dendreon and executed by [REDACTED]. This analysis was performed to confirm materials met requirements for [REDACTED] [REDACTED]”. The study included components of the current container closure configuration along with items determined to have significant product contact either during storage or the fill process.

The validation studies for the container closure systems for both PA2024 and the final product have been verified during the PLI. No major concerns were identified.

Risk Assessment

During the telecon between CBER and Dendreon on December 14, 2006, Mary Padgett has requested that Dendreon include in the BLA the documentation for the validation risk assessments that was not included in the original BLA, performed for the New Jersey

manufacturing facility. On December 20, 2007, Dendreon submitted an amendment to include the information on risk assessment including the completed assessment forms.

As noted in Section 3.2.A.1, Facilities and Equipment, Dendreon's risk-based approach to validation requires that systems and equipment be subject to a risk assessment to determine whether Dendreon should perform commissioning or validation, both commissioning and validation, or neither.

Per Dendreon procedure, risk is assessed by three criteria: [REDACTED]
[REDACTED] The criteria are defined on the forms.

[REDACTED]
[REDACTED]

The contents of evaluation forms have been reviewed, and no major concerns have been identified. However, for the [REDACTED] the risk assessment classified the system as Level [REDACTED] which does not require a PQ. Nonetheless, no information or validation study was provided to demonstrate that the sensitivity, specificity, accuracy and reproducibility of the system are comparable to the traditional sterility test.

The following systems and equipment have been assessed for risk (those highlighted system and equipment were validated):





The risk assessment issues have been verified and followed during the PLI. Dendreon's approach for risk assessment for their systems and equipment appear be adequate and the results appear to be acceptable. No major concerns were identified. The issues on [REDACTED] [REDACTED] has been followed by the product reviewers during the PLI, and will be discussed in their review memo.

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