



Our STN: BL 125197/0

May 8, 2007

Dendreon Corporation
Attention: Elizabeth C. Smith
Vice President of Regulatory Affairs
3005 First Avenue
Seattle, WA 98121

Dear Ms. Smith:

We have completed the review of your submission dated November 9, 2006, and all subsequent amendments to your biologics license application (BLA) for sipuleucel-T submitted under section 351 of the Public Health Service Act.

In our review, we find that the information and data submitted are inadequate to support licensure at this time. The deficiencies are summarized as follows:

CMC

1. Outstanding issues from your pre-license inspection, dated February 12-16, 2007, have yet to be resolved.
2. The stability of the --b(4)----- and the potential effect on sipuleucel-T cannot be fully evaluated from the data provided. It is not clear that the data presented in Figure 8 in section 3.2.P.2.3 are representative of the range of clinical experience. Please provide a more detailed explanation of how the stability studies of the -b(4)- were conducted.
3. Additional data are needed to validate shipping of sipuleucel-T during elevated external temperature conditions. Please provide data verifying that sipuleucel-T product attains the specified 2-8°C temperature range within a defined time period and maintains this temperature throughout the remainder of the shipment when exposed to high external temperature shipping conditions. Please provide data showing that product quality is maintained within the limits of the acceptable ranges of temperature and time. These data should be generated from studies conducted at the New Jersey facility.
4. To support the shipping validation studies addressed in item 3, please address the following:
 - a. Please establish a maximum process step time for formulation of the sipuleucel-T product in lactated Ringer's solution before packaging in the shipping container with the gel packs.

- b. Please submit data demonstrating that you can ship sipuleucel-T from the New Jersey facility and infuse it into the patient within the 18 hour shelf life. We recommend that you submit data from all clinical lots manufactured at the New Jersey facility. The data should include the destination and the time from formulation to infusion.
5. Your comparability analysis included data from product manufactured at the Seattle and New Jersey facilities. Please provide additional data from the other manufacturing sites that produced clinical product for the Phase 3 clinical trials. Please provide information on the number of lots manufactured at each manufacturing site.
6. Additional information is needed to assess the validation of the -b(4)---- method as an alternative sterility test method. Please address the following:
 - a. For each of the datasets provided, please clarify where and when the studies were performed and the -b(4)---- model that was used. We note that the -----b(4)---- -- ----- is used in Seattle and the ---b(4)----- is used in New Jersey. Please discuss the differences in the two systems, including any differences in the detection algorithms. If this information is contained in another regulatory file you may submit a letter of cross-reference obtained from the manufacturer authorizing the Agency to refer to information contained in such file.
 - b. We note that you plan to “further demonstrate the suitability of the -b(4)----- using environmental isolates obtained from the NJ facility.” Please submit data from these additional studies.
 - c. If you intend to use the ---b(4)---- method to test sterility of -b(4)----, please submit data to demonstrate that the -b(4)---- formulation does not have any bacteriostatic and fungistatic effects in this method.
7. Additional data or justifications are needed to support your analytical method validations. Please address the following:
 - a. We note that both the --b(4)----- methods are tested in -b(4)--- and that results from each are -b(4)---. For each of these assays, please establish a maximum variability between results of --b(4)----- samples. Please describe what procedures will be followed if the maximum variability is exceeded.
 - b. We note that only gram positive organisms are used for the validation of the gram stain assay. Please include gram negative organisms as part of the validation.
 - c. Please revalidate your -b(4)----- method for accuracy and intermediate precision. Please include precision studies that demonstrate the ability of operators to differentiate between viable and non-viable cells.

CLINICAL

8. We acknowledge the importance of a finding of improved survival, even when it was not the primary study endpoint; however your submission did not provide sufficient evidence to support the effectiveness claim of a prolongation of overall survival of treatment with sipuleucel-T in men with asymptomatic metastatic androgen independent prostate cancer. Both randomized controlled trials, D9901 and D9902A, failed to demonstrate efficacy of sipuleucel-T on the protocol-specified primary endpoint of time to disease progression or on the secondary efficacy endpoints. Since these trials failed to achieve their primary objective, subsequent survival analyses were *post hoc* in nature. Additionally, these survival analyses were performed in a relatively small number of subjects, and a survival difference was seen in only one study. Therefore the submitted clinical data were not sufficiently persuasive to support licensure at this time. Please submit additional clinical data in support of your efficacy claim.
9. The African-American population was underrepresented in the Phase 3 trials submitted and the on-going D9902B, accounting for < 10% of the total trial subjects. Since the biology and prognosis of prostate cancer and cardiovascular diseases in African-Americans may be different from those in the Caucasian population, the trial results may not be applicable to the general prostate cancer population. Therefore, we recommend that you increase the enrollment of African-American subjects in the current D9902B trial, or propose an alternative plan to investigate the safety and efficacy of sipuleucel-T in minority populations.
10. Data submitted did not provide sufficient information about the magnitude and risk factors for cerebrovascular accidents (strokes) in sipuleucel-T- and APC-placebo treated-subjects. In addition, data currently available are insufficient to clarify sipuleucel-T's efficacy and safety in African American men with prostate cancer as described in item 9. If subsequently developed clinical trial data do not provide clarification on these issues, a detailed pharmacovigilance plan should be established to address these and other issues that may be identified.

LABELING

11. We consider the PA2024 protein to be an active ingredient for the purposes of labeling. Please address this in future submissions.
12. We reserve further comment on the proposed labeling until the application is otherwise acceptable.

We recommend that you request a meeting or teleconference with us to address these deficiencies in detail, and to explore possible options to facilitate access to sipuleucel-T for patients following completion of enrollment to your clinical trials. For PDUFA products please submit your meeting request as described in the FDA Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products February, 2000 (<http://www.fda.gov/cber/gdlns/mtpdufa.pdf>). For details, please also follow the instructions

described in CBER's SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants (<http://www.fda.gov/cber/regsopp/81011.htm>).

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application).

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

If you have any questions, please contact the Regulatory Project Manager, Lori Tull, at (301) 827-5102.

Sincerely yours,

Ashok Batra, M.D.
Director
Division of Clinical Evaluation and Pharm/Tox
Office of Cellular, Tissue and Gene Therapies
Center for Biologics Evaluation and Research