

STN: BL 125197/0

6/12/07 1:00 PM telecon with Dendreon.

Dendreon participants: Liz Smith, Connie Spooner

FDA participants: Tom Finn, Keith Wonnacott

Dendreon initiated a call to ask for clarification regarding the CMC issues listed in the CR letter issued to them. They are planning on requesting a formal telecon in the future and wanted to be sure that before they set up the telecon that they understand what it is we are asking.

Most issues were discussed in the order they were presented in the CR letter.

*Item #1. Outstanding issues from your pre-license inspection, dated February 12-16, 2007, have yet to be resolved.*

Dendreon's first question was when they would get feedback on the 483 deficiencies and when they would get a copy of the EIR. They were informed that our office has finished our comments and that DMPQ is in the process of generating a final document, but we do not know when that will be completed. Dendreon feels they have adequately resolved these problems, but they cannot do more until they get some feedback. They have let go of some of their staff but have to maintain some of their manufacturing staff until they know if they need to conduct more studies. They also said they could not be sure all of their staff would stay around for 2 more years until they know the results from the interim trial data. It would be helpful if the FDA could clarify soon what studies they need to do to resolve the outstanding issues. Since Dendreon's original plan was to get approval for (b)(4) manufacturing modules and all (b)(4) workstations, we assumed that now that they would have to wait for the interim data for D9902B that they would change their request for approval of (b)(4) and (b)(4) workstations and producing product at limited capacity to requesting approval for (b)(4) modules and a greater capacity. Dendreon stated that they are interested in planning for greater capacity and wondered whether they could use this as an opportunity to (b)(4) the number of workstations. Our response was that they could use this opportunity to validate for a greater capacity. We stated that our office has finished our comments and that a final version is being generated by DMPQ. We recommend that they contact DMPQ to get an update on when they might receive a response.

*Item #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.*

Dendreon asked for clarification as to the information being requested. They were told that Dendreon should provide more documentation on how the study was designed and

how it was conducted. More information should also be provided on the product lots actually used, preferably in the same format as the other [REDACTED] lots reported in the BLA. Dendreon stated that they did not have %CD54 cell recovery for all lots described in the BLA. They were told that they only need to provide information on those lots that they have collected recovery data. We also pointed out that the [REDACTED] b(4) stability data at the [REDACTED] hour time point is highly variable and they should try to extrapolate the consequence of recovery as low as 12% on the ability to meet lot release specifications for an average production lot. Dendreon responded they will provide those calculations.

Item #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.*

item #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.*

We clarified that though [REDACTED] (b)(4) tests, stability tests, and a shipment of [REDACTED] lots had been performed that these studies were not quite robust enough to demonstrate the stability of the product under conditions the product might be exposed to during actual shipments. It was recommended that the sponsor conduct a small shipping study where they ship product to a destination that is very warm. They could choose a destination that would be a more challenging, stressful representation of what their commercial product would have to withstand. Dendreon commented that it is difficult to design studies using temperature monitors and trying to maintain different temperatures, etc. They stated that they had put a lot of thought into the [REDACTED] (b)(4) tests and the profiles they chose to simulate actual shipping conditions. It was suggested that Dendreon provide more information on the design of these studies and we could potentially re-evaluate the data.

We clarified that one of the concerns was with how long it took to get the product packaged and [REDACTED] to 2-8 degrees as specified. The stability studies conducted at [REDACTED] (b)(4) degrees didn't reflect that very well. Dendreon stated that they will be conducting another stability study at [REDACTED] We agreed that such a study would be very helpful.

Dendreon stated that the shipping data from the NJ facility was limited. They have been manufacturing some clinical product at the NJ facility, but they are still using their contract sites to make product for some of their other destinations, especially the west coast. Currently, they have shipping data to Chicago, Ohio, and some east coast destinations from the NJ facility, but not sure how helpful that will be. We asked if they could provide more information on how long it takes to package the product once it is resuspended in lactated Ringer's solution, how long it takes to get it to the courier, how long it takes to ship the product, when it arrives at the infusion site, and how much time has expired before it is infused into the patient. Dendreon stated that the infusion time is recorded in the clinical case report form, but is not recorded in any of the product databases, so that information is difficult to get. They may be able to get it from some of their clinical sites. Dendreon also stated that they do not plan on setting time controls for the packing and infusion of the product. Their intention is to use the stability studies to establish the 18 hour expiration time. We asked if they could provide projections or estimates from the Seattle Scheduling group on some of the major destinations since we were told during inspection of the NJ facility that these calculations have already been made. Dendreon said they would provide those projections.

*Item #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.*

We clarified that that we did not have issue with the comparability of the lots generated at the NJ facility with the Seattle facility, but that because of the highly variable nature of the product it was difficult to compare production consistency. We ask that they provide a line listing similar to what was provided in the BLA for lots generated at other clinical manufacturing site. Dendreon agreed to provide this information, and may provide some summary data.

*Item #6. Additional information is needed to assess the validation of the [REDACTED] 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 [REDACTED] model that was used. We note that the (b)(4) Model is used in Seattle and the (b)(4) Model 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.*

Dendreon asked about item 6a. They will provide more information about these studies. They also stated that they were getting additional information from the manufacturer about the control software for these two units and would provide additional information. They did not have any questions about items b and c. Dendreon stated that they do not intend to use the (b)(4) system for (b)(4). They will continue to use the CFR/ (b)(4) method for testing (b)(4). We suggest they consider providing a letter of cross-reference from the manufacturer of the (b)(4) system.

*Item #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) and the (b)(4) methods are tested in (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.*

No questions were raised.

Dendreon had concern about including PA2024 as an active ingredient on the product label. They felt it was misleading to include this as an active ingredient because in their opinion (b)(4). They feel that the cells are the active component and not the protein. We agreed that the whole protein is not present, but the therapy relies on the protein being processed and presented on the cell surface, so it could be considered to be part of the product. If they have issue with this point they can try to make their case in the response to the CR letter. Dendreon pointed out that since 2001 that PA2024 has been referred to as either an ancillary component or as a critical raw material, and that these terms were approved by the FDA.

The conversation ended with a notice that they would be sending in a formal request for a telecon to discuss the CMC issues, and that they would be sending in additional CMC amendments in the future.