

# **Exhibit A**

## **Declaration of Frederick J. Sadler**

UNITED STATES DISTRICT COURT FOR THE  
SOUTHERN DISTRICT OF OHIO  
EASTERN DIVISION

CARETOLIVE,	)	
a not-for-profit corp.,	)	
	)	Civil No. 2:08-CV-00005
Plaintiff,	)	
	)	JUDGE FROST
v.	)	
	)	MAGISTRATE JUDGE KING
U.S. FOOD and DRUG	)	
ADMINISTRATION,	)	
	)	
Defendant.	)	

**DECLARATION OF FREDERICK J. SADLER**

I, Frederick J. Sadler, declare as follows:

1. I am the Director of the Division of Freedom of Information ("DFOI"), Office of Management Programs, United States Food and Drug Administration ("FDA"), located in Rockville, Maryland. I have held this position since March 2007. I previously served as the Denials and Appeals Officer in the DFOI Office from July 2000 to December 2006. From December 2006 until March 2007, I served as the Acting Director of DFOI.

2. In my capacity as Director of DFOI, my duties and responsibilities include supervising the office in the receipt and certain aspects of the processing of requests for FDA records under the Freedom of Information Act ("FOIA"), 5 U.S.C. § 552.

3. The statements made in this declaration are based upon my personal knowledge and information about which I have become knowledgeable through my review of official agency records within DFOI's control.

4. I submit this declaration in support of the government's Motion for Summary

Judgment in the above-captioned case. The purpose of this declaration is to set forth DFOI's response to the FOIA request that is the subject of the Complaint in this case.

#### DFOI FOIA PROCESSING

5. Under FDA's regulations at 21 C.F.R. § 20.40(a), all requests for FDA records must be made in writing to the Freedom of Information Staff at FDA, which is currently known as "DFOI," in the Office of Management Programs.

6. When a FOIA request is received by DFOI, a Freedom of Information technician ("FOI technician") on my staff scans the request into a PDF format, logs and uploads the request into the Agency Information Management Systems ("AIMS"), which stores and keeps track of all of the agency's FOIA requests, and assigns the request a reference number.

7. After the FOI technician receives, scans, and logs an incoming request, he or she directs AIMS to forward the request to the FDA office(s) which, based on a preliminary review of the request, is (are) most likely to possess responsive records. I am available to consult with the FOI technicians in the event that the forwarding of a particular request is not clear from the text of the request.

8. Once a FOIA request is logged in, DFOI sends a letter to the requester acknowledging FDA's receipt of the request.

#### PLAINTIFF'S FOIA REQUEST

9. On September 11, 2007, DFOI received a FOIA request from Bellinger & Donahue, dated August 15, 2007.<sup>1</sup> The request sought:

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<sup>1</sup> The delay between the date of Bellinger & Donahue's letter and receipt by DFOI occurred because the requester improperly sent the request to the agency's Cincinnati District Office rather than to DFOI. Per 21 CFR § 20.40(a), all FOIA requests must be received in DFOI

"A copy of all letters written to the FDA (or prepared by the FDA) and purported to be from Dr. Scher, Dr. Hussain and Doctor Fleming in between March 29th 2007 and April 30th of 2007, regarding the BLA submitted for Provenge also known as Sipuleucel-T including the envelope or other means of communication whereby the FDA received such letters and a copy of any record of those letters then being disclosed to any media or other persons or specifically a publication called "The Cancer Letter," including the means of communication to the Cancer Letter of the Scher, Hussain and Fleming letters from the FDA or its employees to outside persons, publications or companies."

See Attachment 1.

10. Consistent with DFOI practice, an FOI technician logged the request into AIMS, and assigned it reference number 2007-8316, reflecting that it was the 8316th FOIA request that FDA received in 2007.

11. On September 11, 2007, DFOI sent an acknowledgment letter to the requesters.

See Attachment 2.

12. DFOI forwarded Plaintiff's request to the Access Litigation and Freedom of Information Branch of FDA's Center for Biologics Evaluation and Research ("CBER") on September 14, 2007. DFOI referred Plaintiff's request to CBER because the request sought correspondence relating to Provenge, an unapproved biological product regulated by CBER. Thus, CBER was most likely to have responsive documents. On November 6, 2007, CBER released all responsive documents, without any redactions, to Bellinger & Donahue.

13. DFOI also forwarded Plaintiff's request to the Office of the Executive Secretariat ("Exec. Sec.") and the Immediate Office of the Commissioner ("Immediate Office") in FDA's Office of the Commissioner. DFOI did so because the request sought agency correspondence, and both Exec. Sec. and the Immediate Office maintain certain agency correspondence in their

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in order to be logged and processed. The request was ultimately forwarded from the Cincinnati District Office to DFOI on or around September 11, 2007.

files.

14. Exec. Sec. responded, through DFOI, on January 24, 2008, indicating that no responsive records had been located. See Attachment 3.

15. The Immediate Office, through DFOI, produced responsive documents, without any redactions, to Plaintiff on February 26, 2008. See Attachment 4.

16. On October 10, 2007, DFOI forwarded Plaintiff's request to the Division of Information Disclosure Policy ("DIDP") in FDA's Center for Drug Evaluation and Research ("CDER"). DFOI did so because, after consultation with CBER, it appeared that CDER was also likely to have the requested correspondence.

17. On January 2, 2008, Plaintiff filed the Complaint in this case (Civil Docket No. 1).

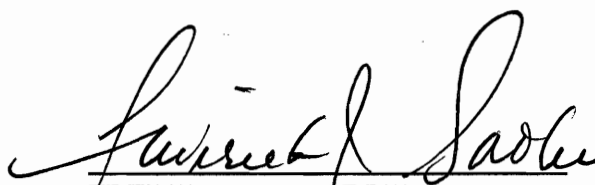
18. In response to Plaintiff's lawsuit, the government filed a Motion to Stay Proceedings (Civil Docket No. 10). As explained in the government's Memorandum in Support of its Motion to Stay Proceedings and the supporting declarations, Plaintiff's request fell into CDER's Complex Track because it could not be answered quickly with readily available documents, and it could require further searching or redacting. Based on the number of FOIA requests ahead of Plaintiff's request in the Complex Track, CDER estimated that Plaintiff's request would not rise to the head of the Complex Track for processing until October 2009.

19. The Court granted the government's Motion to Stay Proceedings on May 22, 2008 (Civil Docket No.23), ordering CDER to provide responsive documents to Plaintiff's request no later than May 18, 2009.

20. CDER responded to Plaintiff's request on May 18, 2009, providing one

unredacted letter. See Attachment 5.

Pursuant to 28 U.S.C. § 1746, I declare under the penalty of perjury that the foregoing is true and correct.



FREDERICK J. SADLER  
Director

Division of Freedom of Information  
Office of Management Programs  
Food and Drug Administration  
U.S. Department of Health and Human Services

Executed on May <sup>18</sup> 2009 in Rockville, Maryland

Scott P. Bellinger  
Kerry M. Donahue\*  
\*Also admitted in Florida

**BELLINGER & DONAHUE**  
Attorneys At Law

6295 Emerald Parkway  
Dublin, Ohio 43016  
Office 614-761-0402  
Fax 614-789-9866

August 15, 2007

RE: CareToLive v. FDA, Southern District of Ohio, case no. 2:07 CV 729

Brenda S. Zimmer  
FDA  
6751 Steger Dr.  
Cincinnati, Ohio 45237-3097

2007-8316  
**RECEIVED**  
SEP 11 2007

Dear Brenda S. Zimmer,

Please consider this a request under the Freedom of Information Act  
**FDA FOI (HF-95)**

We request the following:

- 1) A copy of all letters written to the FDA (or prepared by the FDA) and purported to be from Dr. Scher, Dr. Hussain and Doctor Fleming in between March 29th 2007 and April 30th of 2007, regarding the BLA submitted for Provenge also known as Sipuleucel-T including the envelope or other means of communication whereby the FDA received such letters and a copy of any record of those letters then being disclosed to any media or other persons or specifically a publication called "The Cancer Letter", including the means of communication to the Cancer Letter of the Scher, Hussain and Fleming letters from the FDA or its employees to outside persons, publications or companies.

We are willing to pay the cost.

11502

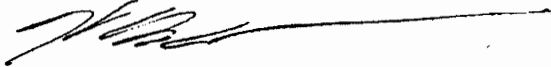
Attachment  
1

- 2 -

August 15, 2007

Please call if you have questions about this request. Thank you.

Sincerely,

A handwritten signature in black ink, appearing to read "Kerry Donahue", with a long horizontal stroke extending to the right.

Kerry Donahue



DEPARTMENT OF HEALTH & HUMAN SERVICES

---

Food and Drug Administration  
Rockville, MD 20857

BELLINGER & DONAHUE ATTY  
KERRY DONAHUE  
6295 EMERALD PKY  
DUBLIN OH 43016 US

09/11/2007

In Reply refer to:  
2007-8316

Dear Requester:

The Food and Drug Administration (FDA) has received your Freedom of Information Act (FOIA) request for records regarding:

PROVENGE (SIPULEUCEL-T) - LTRS 3/29/07-4/30/07

We will respond as soon as possible and may charge you a fee for processing your request. If you have any questions about your request, please call Shera S. Behram, Information Technician, at (301) 827-6552 or write to us at:

Food and Drug Administration  
Division of Freedom of Information  
5600 Fishers Lane, HF1-35  
Rockville, MD 20857

If you call or write, use the reference number above which will help us to answer your questions more quickly.

Sincerely,

Shera S. Behram,  
Information Technician,

Attachment

2



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville, MD 20857

KERRY DONAHUE  
BELLINGER & DONAHUE ATTY  
6295 EMERALD PKY  
DUBLIN OH 43016 USA

01/24/2008  
In Reply refer to:  
2007-8316

Dear Requester:

This is in reference to your request(s) for record(s) from the Food and Drug Administration (FDA) pursuant to the Freedom of Information Act (FOIA).

PROVENGE (SIPULEUCEL-T) - LTRS 3/29/07-4/30/07

The Office of the Executive Secretary, Office of the Commissioner, Food and Drug Administration has received your Freedom of Information Act request. After a diligent search, this office has not located any responsive records. Other agency components may respond to your request under separate cover.

The following charges for this request to date may be included in a monthly invoice:

Reproduction	Search	Review	Fiche	Other	Total
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Reproduction=\$3.10	Search=\$404.75	Review=\$0.00	Fiche=\$0.00	Other=\$0.00	Total=\$407.85
---------------------	-----------------	---------------	--------------	--------------	----------------

All communications concerning this request should be identified with the reference number above and addressed as follows:

Food and Drug Administration  
Freedom of Information Staff, HF1-35  
5600 Fishers Lane (Room 6-30)  
Rockville, MD 20857

Sincerely Yours,

Theola Myo Khin  
Freedom of Information Specialist

Enclosures:  
if indicated

Attachment
3



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville, MD 20857

KERRY DONAHUE  
BELLINGER & DONAHUE ATTY  
6295 EMERALD PKY  
DUBLIN OH 43016 USA

02/26/2008  
In Reply refer to:  
2007-8316

Dear Requester:

This is in reference to your request(s) for record(s) from the Food and Drug Administration (FDA) pursuant to the Freedom of Information Act (FOIA).

PROVENGE (SIPULEUCEL-T) - LTRS 3/29/07-4/30/07

These records were located in the Immediate Office of the Commissioner. Other agency components will review your request and, if responsive records are found, provide them to you under separate cover.

The following charges for this request to date may be included in a monthly invoice:

Reproduction	Search	Review	Fiche	Other	Total
--------------	--------	--------	-------	-------	-------

Reproduction=\$4.30	Search=\$247.00	Review=\$0.00	Fiche=\$0.00	Other=\$0.00	Total=\$251.30
---------------------	-----------------	---------------	--------------	--------------	----------------

All communications concerning this request should be identified with the reference number above and addressed as follows:

Food and Drug Administration  
Freedom of Information Staff, HFI-35  
5600 Fishers Lane (Room 6-30)  
Rockville, MD 20857

Sincerely Yours,

Theola Myo Khin  
Freedom of Information Specialist

Enclosures:  
if indicated

Attachment  
4

**Palmer, Kelly**

**From:** scherh@MSKCC.ORG  
**Sent:** Friday, April 06, 2007 4:59 PM  
**To:** von Eschenbach, Andrew C.  
**Cc:** scherh@mskcc.org  
**Subject:** Concerns with the CBER Dendreon Advisory  
**Attachments:** von eschenbachFDASipuleuceIT.doc

<<von eschenbachFDASipuleuceIT.doc>>

I recognize that this is very controversial, but wanted to share some concerns following the CBER Advisory meeting on Provenge on which I was a voting member. While we all recognize the need for new therapies and options, it is important to make sure that the demonstration of efficacy is consistent with regulatory standards. I appreciate your considerations.

Best wishes for the holiday.

Hard copy will follow.

Thank you.

Howard I. Scher, M.D.  
D. Wayne Calloway Chair in Urologic Oncology  
Chief, Genitourinary Oncology Service  
Memorial Sloan-Kettering Cancer Center  
1275 York Ave.  
New York, N.Y. 10021  
TEL: Administrative: 646-422-4323  
Clinical: 646-422-4330  
FAX: 212-988-0851  
E-mail: Scherh@mskcc.org

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April 5, 2007

Andrew von Eschenbach, MD  
Commissioner  
5600 Fishers Lane  
PKLN RM 1471 HF-1  
Rockville, MD 20857

RE: **CBER Advisory Committee for Sipuleucel-T**  
**March 30, 2007**

Dear Dr. von Eschenbach:

I am writing to express concerns about the recent review of Sipuleucel-T at the FDA Advisory Meeting on March 30, 2007. These concerns are: a recommendation for approval based on data that fall short of the regulatory requirements; an inadequate statistical construct to determine definitive benefit; incomplete data on product safety; and what appear to be different criteria for approval by two Advisory Committees to the Agency. All but the latter were discussed in the open meeting, but warrant further consideration given the outcome. The concerns are based on my experience as a voting member on several ODACs representing the Agency, and separately, as a Presenter to ODAC for Industry Sponsors. I have been one of the Academic Leaders of the Prostate Cancer Clinical Trial Endpoints initiative begun under the joint Sponsorship of the FDA, AACR, ASCO and PCF in 2004, which were presented at the February 2007, Prostate ASCO Meeting in Orlando. The final manuscript is currently under review at the NCI, FDA and the Group of established Prostate Cancer Clinical Trial experts who together, formulated the recommendations. I am also the Principal Investigator of a Multicenter Prostate Cancer Clinical Trials Consortium funded by the Department of Defense that focuses on phase 1 and 2 trials in this disease.

Let me state at the outset that I was one of the four Committee Members who voted "no" to the question whether the trials presented by the Sponsor established the efficacy or demonstrated substantial evidence of benefit to justify an approval recommendation to the FDA. **My vote was based on the fact that neither of the two trials presented met their primary endpoint, which renders the significance of results from any subsequent analyses as "exploratory" and "hypothesis generating".** As such, the

results do not constitute "proof" of benefit or justify a conclusion that they are "reasonably likely" to predict benefit. The trial data were not consistent. Even if one accepts the post-hoc survival analysis results of the larger 127 patient trial (82 men treated with Sipuleucel-T and 45 men treated with a "placebo"), the second trial of 98 patients (65 treated with Sipuleucel-T and 33 with placebo) was not confirmatory. Consequently, the only conclusion that can be reached is that the survival difference observed may have occurred by chance alone, and that the results do not support an approval recommendation. This, and the Sponsor's recognition that an additional prospective study was needed, mandates deferring any decision on whether an approval should be granted until the results of the ongoing 500 patient phase 3 trial that is powered on a primary endpoint of survival, is accrued and analyzed.

Concerns about the validity of the findings were reinforced by the absence of other signals of an antitumor effect. Specifically there were no data provided of a favorable effect on PSA, regression or stabilization of soft-tissue or boney disease radiographically, health related quality of life, or that administration of the product delayed the development of pain. Even the time to the administration of chemotherapy, an indication to the treating Physicians that the clinical course had worsened, was similar between the two groups. Reinforcing the uncertainty was the fact that in response to a direct question at the meeting, none of the Physicians representing the Sponsor could articulate how treatment with the product had "helped" any individual patient.

There were also methodologic concerns. Trial 9901 was designed to show an increase in time to disease progression from 16 weeks for placebo treated to 31 weeks for Sipuleucel-T treated patients (HR = 1.92, alpha = 0.05, two sided, with 80% power). A total of 127 patients were enrolled using a 2:1 randomization in favor of the experimental therapy. The study was double blind and included an independent review of all imaging results. The estimated time to progression on which the trial was powered proved to an overestimate, as the actual observed median time to progression was 9 to 11 weeks for both arms: a difference that was not statistically significant. A summary of the progression events showed that 90% (97/114) were by imaging, 10 were clinical, and 7 were for the new onset of disease related pain. Unrecognized at the time of the design of the trial, was that the eight week interval between disease assessments was too short to observe clinically significant changes by bone scan, and that in many cases, apparent "progressions" eight weeks after the start of a therapy are more a reflection of disease worsening that led to trial entry, and not a failure of the treatment. (CCR 13:1488, 2007) This is similar to what was observed in the trial with the endothelin antagonist, atrasentan, in which a 12 week disease assessment interval was used and a large proportion of patients were withdrawn at the time of scheduled scans in the absence of clinical worsening of disease (ODAC, September 13, 2005). Recognizing this, the Prostate Cancer Working Group 2 has advised that an apparent progression on bone scan at a three month assessment, be confirmed by documenting further progression on a subsequent scan six or more weeks later before considering a patient to have failed the treatment. (ASCO Multidisciplinary Prostate Cancer Symposium, (Abstract #221) February 22-24, 2007, Orlando, FL, 2007). Although the Sponsor suggested that the effect of the product was delayed, this hypothesis could not be explored because serial imaging to assess disease at defined intervals were not performed once a patient was considered to have "progressed" and taken off study. As a result, individual sites of disease were no longer being monitored, so that no statements could be made regarding a possible "delayed effect" of the product on disease status.

At 3-years, a prespecified survival analysis was performed which showed a 4.5 month difference in median survival favoring Sipuleucel-T, and while a significant p-value for the difference was determined, the type I error rate is surely inflated by this additional analysis. Imbalances in disease aggressiveness and disease extent were noted between the Sipuleucel-T and "control" groups including a higher proportion with Gleason 6 disease or less at diagnosis (26.8% vs. 15.6%), and a lower proportion with both bone and soft tissue disease (52% vs. 69%) at the time therapy was started. Both factors favored the Sipuleucel-T arm, predicting a longer survival for the "treated" patients independent of therapy. The 2:1 randomization increased the power of the experimental arm, but it may have

Page 3

inadvertently made the small 43 patient control group more heterogeneous and less representative of the global population of men for whom the indication was proposed. The potential impact of heterogeneity in small patient cohorts was shown when a post-study change in the progression times of two patients (a change not accepted by the Agency), resulted in a change in the significance estimates.

The first question the Agency posed to the Committee was whether the product was "reasonably safe" for the intended population. While the vote was yes, the issue of cerebrovascular events as a potential safety signal was raised. This concern was based on the finding that 4.9% (17/345) of the Sipuleucel-T and 1.7% (3/172) of "placebo" treated patients who were enrolled on randomized trials for the indication, experienced a cerebrovascular event ( $p=0.092$ ). The odds ratio for developing a cerebrovascular event was 2.92, with wide confidence intervals (0.82 to as high as 10 fold). Deaths due to CVA's were recorded in 1.5% of Sipuleucel-T patients and 0.9% of those receiving "placebo". Unclear is why there is no mention of CVA's in the published report of the study in the Journal of Clinical Oncology (JCO 24:3089, 2006). Given that the product is released for administration based on the increase in the proportion of CD54+ cells and not the absolute number of any particular cell type and that CD54+ cells actually represent only 20% of the final product, the contribution of the other cell populations and cytokines that may be present in the administered product on the development of a cerebrovascular event is not known. More important, and perhaps underappreciated during the discussion, is the recognition that the "placebo" used in this trial, a portion of the leukopheresis product that is cultured without the immunizing antigen and reinfused, may not be inert and in itself contributed to a relative worsening of survival for the control group in this trial. To place the frequency of the neurologic events in perspective, no cerebrovascular events were observed in TAX-327, a 997 patient three arm randomized trial that evaluated two different dose schedules of docetaxel in comparison to mitoxantrone (NEJM 351:1052, 2004) or ASCENT1, a 251 patient randomized comparison of docetaxel weekly with or without high dose calcitriol (DN-101)(JCO 25:669, 2007). Neurologic events that were not detailed further were observed in 7% of the 338 patients who received estramustine which is known to be thrombogenic, in combination with docetaxel on the SWOG 99-16 trial (NEJM 351:1513, 2004).

Another concern is that the requirements for regulatory approval appear to differ between the ODAC and CBER Advisory Committee. As an example, ASCENT1 was a prospective randomized phase 2 trial of weekly docetaxel with or without high dose calcitriol (DN-101). The trial was powered to detect a 20% difference in the PSA response rate at six months between the two groups as the primary endpoint, but also included a pre-specified survival analysis, similar to that included in the Sipuleucel-T 9901 trial as one of the secondary endpoints. PSA response was defined as a 50% or greater decline from baseline, according to Consensus Criteria (JCO 17:3461, 1999). A total of 250 patients, 125 per arm were enrolled and followed. The 9% difference in the PSA response rate observed at six months was not statistically significant ( $P<.16$ ), yet here too, the pre-specified survival analysis showed a difference for docetaxel plus DN-101 vs. docetaxel plus placebo: median not reached but estimated to be 24.5 months vs. 16.4 months respectively with a hazard ratio for death of 0.67 ( $p=0.04$ )(JCO 25:669-74, 2007). The safety of the combination was no worse and perhaps better than docetaxel alone. Appropriately in my view, the results were not considered definitive by ODAC, no approval filing was made, and a new 900 patient phase 3 trial powered to test the hypothesis whether the combination of docetaxel in combination with DN-101 conferred a survival advantage relative to docetaxel alone was designed, initiated and continues to accrue. I am the International Principal Investigator on this trial. Contrast this with the regulatory filing history of Sipuleucel-T where the primary endpoint of the registration trial was also not met, yet, it is being considered for approval based on a similar post-hoc analysis with roughly half the total number of patients, and a control arm that is roughly one third the size. Why do the Sipuleucel-T results establish efficacy, while the DN-101 results do not?

An approval recommendation has far reaching implications beyond making the product available that the data simply do not support or justify. For one, it provides the Agency's endorsement of

Page 4

Sipuleucel-T as a "standard of care" treatment for an asymptomatic population of men with androgen independent (castration resistant) disease that represents upwards of 45,000 men in the U.S. The second is that by extension, it elevates Sipuleucel-T to a position of being the new "control" arm for future randomized phase 3 trials that are being designed for the regulatory approval of any new experimental agent or approach. It also opens the door to the premature approval of drugs based on inconclusive data.

Finally, the original question posed by the Agency to the Advisory Committee at the meeting was: "Does the submitted data establish the efficacy of Sipuleucel-T (APC-8015) in the intended population?" The first 4 respondees on the Committee voted "no". The question was then changed to: Do the data show significant benefit. A series of "yes" votes followed.

Consider the conclusion in the manuscript describing the results of trial 9901, published in the Journal of Clinical Oncology in Volume 24, page 3093, in 2006. (JCO 24:3089, 2006) In it, the Investigators state **"that while sipuleucel-T fell short of demonstrating a statistically significant difference in TTP, it MAY provide a survival advantage to asymptomatic HRPC patients. Supportive studies are underway to confirm this effect."** All of the difficulties cited, and the Investigator's own conclusions, show how there are simply too many alternative explanations for the observed survival difference beyond treatment with Sipuleucel-T. Couple this with that fact that were no secondary signals of an antitumor effect and no confirmatory trial however flawed, mandates that any decision for approval be deferred until the phase 3 study, currently underway, has been completed and analyzed.

Thank you for your time and consideration.

Yours sincerely,

Howard I. Scher, M.D.  
Member and Attending Physician

Professor of Medicine  
Joan and Sanford Weill College of Medicine of Cornell University

CC: Janet Woodcock, MD, Deputy Commission of OPE  
Jesse L. Goodman, MD, Director, Center for Biologics Evaluation & Research  
Richard Pazdur, MD, Director, Office of Oncology Drug Products, Center for Drug Evaluation & Research  
Celia Witten, MD, PhD, Director, Office of Cellular Tissues & Gene Therapy, Center for Biologics Evaluation & Research  
James J. Mule, PhD

Page 5

*Multiple endpoints involving different events, FDA Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May 1998*

*Scientific basis for the legal standard, FDA Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May 1998*

**Palmer, Kelly**

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**From:** Maha Hussain [mahahuss@med.umich.edu]  
**Sent:** Monday, April 23, 2007 5:28 PM  
**To:** von Eschenbach, Andrew C.; Witten, Celia (CBER); Woodcock, Janet; Goodman, Jesse; Pazdur, Richard  
**Cc:** Maha Hussain; mulejj@moffitt.usf.edu  
**Subject:** Letter re- recent advisory com. meeting

**Attachments:** FDA Mtg Response 4.23.07.pdf



FDA Mtg Response  
4.23.07.pdf (...)

Dear Drs von Eschenbach, Witten, Goodman, Woodcock, and Pazdur

I am respectfully submitting a letter to you all to share with you some concerns I have regarding the recent advisory committee meeting which reviewed Sipuleucel-T.

Thank you for your consideration

regards

Maha

"Electronic Mail is not secure, may not be read every day, and should not be used for urgent or sensitive issues."

Maha Hussain, M.D., FACP  
Professor of Medicine & Urology  
7314 CCGC  
University of Michigan Comprehensive  
Cancer Center  
1500 E. Medical Center Dr.  
Ann Arbor, MI 48109-0946  
tel: 734-936-8906  
Fax: 734-615-2719

\*\*\*\*\*  
Electronic Mail is not secure, may not be read every day, and should not be used for urgent or sensitive issues.



University of Michigan  
Health System

Comprehensive Cancer Center

Maha Hussain, M.D., F.A.C.P.  
University of Michigan  
1500 E. Medical Center Drive  
7314 CCGC Box 0946  
Ann Arbor, Michigan 48109-0946  
Tel: 734-936-8906  
Fax: 734-615-2719  
[mahahuss@umich.edu](mailto:mahahuss@umich.edu)

April 23, 2007

Andrew C. von Eschenbach  
Commissioner  
5600 Fishers Lane  
PKLN RM 1471 HF-1  
Rockville, MD 20857

Jesse L. Goodman, MD  
Director  
Center for Biologics  
Eval & Res  
8800 Rockville Pike  
N29B RM 5NN02 HFM-1  
Bethesda, MD 20892

Janet Woodcock, MD  
Deputy Commission for OPE  
5600 Fishers Lane  
PKLN RM 1471 HF-2  
Rockville, MD 20857

Richard Pazdur, MD  
Director  
Office of Oncology Drug Products  
Center for Drug Eval & Res  
WO22, Room 2212  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Celia Witten, MD, PhD  
Director  
Office of Cellular  
Tissues & Gene Therapy  
Center for Biologics  
Evaluation & Research  
1401 Rockville Pike  
200N HFM-700  
Rockville, MD 20852

Dear Drs:

It is with concern and professional obligation that I write to you as a member of the FDA's Advisory Committee that recently reviewed Sipuleucel-T on March 29, 2007. My concerns relate to medical, scientific and procedural aspects of the meeting and the precedence that will be set for future reviews.

By way of introduction, I am an academic medical oncologist with expertise in GU oncology, extensive clinical trials experience and have been the PI of several NCI sponsored multi-center trials including randomized phase II and III trials. Currently, I am the PI of a Prostate Cancer Clinical Trials grant funded by the Department of Defense that focuses on phase I and II trials in prostate cancer. My experience also includes co-chairing the prostate cancer subcommittee of SWOG overseeing development of national trials for advanced prostate cancer for the past 13 years. I have served as an adhoc FDA consultant for several years and currently serve as a member of the Oncology Drug Advisory Committee. I was a member of and chaired the ODAC special session on prostate cancer endpoints, March 3rd, 2005 and have been actively involved in the development of



University of Michigan  
Health System

Comprehensive Cancer Center

endpoints for this disease, a summary of which was recently presented at the 2007 Prostate Cancer ASCO meeting.

I was one of the 4 members who voted "No" to whether the submitted data on Sipuleucel-T established "efficacy" or "demonstrated substantial evidence of benefit" in the intended population at the recent advisory committee meeting.

From the medical and scientific aspects the recommendations for approval that may be inferred from the vote are based on data that can only be characterized at best as "suggestive" of possible benefit. As the discussant for Q5 regarding the persuasiveness of the efficacy evidence my comments are public record but to summarize my conclusion was that the data presented is not conclusive. The context here is not "*is the treatment promising*" or "*does it open the door for more immunotherapy research*", the context here is "*is the treatment effective and are the results solid*" such that this therapy should be offered as "*The Standard of Care*" by physicians to thousands of patients with the confidence that their recommendations truly serves the best interest of the patients. First of all the lead trial (study 1) was a small trial by any standard with 127 patients in total of whom only 82 were treated with Sipuleucel-T. The study was not powered for survival nor was survival an end point. A post hoc analysis indicated a significant survival difference but there were no significant differences between the Sipuleucel-T and placebo group with regard to any of the disease manifestations including PSA, time to disease progression (primary endpoint) or pain. This coupled with a clear imbalance in the arms with the control arm having more patients with bone and soft tissue disease thus potentially bulkier disease, more patients with higher Gleason scores, more % with prior chemotherapy and questions regarding the nature of the agent administered as the control (please see comments below), the small sample size, the fact that survival was not powered for and is a post hoc analysis could lead to a plausible conclusion that the observed survival difference may be related to other factors or chance alone and not to the treatment effect. Please contrast this data with the two phase III trials (TAX-327 with 997 patients, SWOG -9916 with 770 patients) that led to the approval of docetaxel. Both of these trials had very consistent results across them and conclusively demonstrated a survival advantage with notable effects on other disease manifestations.

The sponsor presented a second "supportive trial" which was also a small prematurely terminated trial which showed about a 3 month difference in survival which was not statistically significant. The trial results were especially problematic since both arms had a poorer survival (15.7 and 19.0 months) than expected for asymptomatic patients and worse than the survival observed in study 1. This occurred despite similar eligibility criteria to study 1. Furthermore, even the best arm "Sipuleucel-T treated patients" had a median survival of (19 months) which is comparable to the "asymptomatic" subgroup of men treated on the mitoxantrone arm of the Tax327 trial (19.8 months, Berhold et al, ASCO Prostate Cancer Symposium 2007). Please note that mitoxantrone is not considered the standard first line therapy in general or for asymptomatic patients. This clearly raises concern regarding the true efficacy of the agent and reproducibility and reliability of the



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data hence the application in the intended population at large. Furthermore, considering that the "placebo" treated patients had an unexpected poor survival of 15.7 months which is worse than the median survival of patients on mitoxantrone arm of the TAX-327 of 16.4 months (NEJM 04) which also included symptomatic patients, raising questions regarding a negative effect from the placebo thus leading to an apparent survival benefit. Issues regarding CVA's particularly in the intended population are also of concern without mature toxicity data and in the context of inconclusive efficacy data.

As you know a definitive trial is in progress and is within 100 patients of achieving target accrual. This trial will lead to definitive answers as to the true efficacy and safety of this agent. These questions will never be answered if the decision regarding this agent is not deferred at this time until all patients are accrued and data are mature, for obvious reasons.

From the scientific and procedural aspects, in general, it would seem that at the end of the day what should determine a positive verdict in any therapeutic trial is the strength of the evidence as critically reviewed by an Advisory Committee with the proper expertise in the context at hand (ODAC in the case of a therapeutic cancer trial), with clear guidance on the questions posed to the committee within the framework of the regulatory guidelines and requirements of the FDA for approval. This needs to be coupled with an atmosphere that is conducive to an objective discussion and vote.

Another concern, based on this case, is the appearance of discordance in the burden of proof required for regulatory approval between CBER and CDER. In the meeting regarding endpoints in 2005 ODAC reaffirmed the importance of powering trials for endpoints that measure true clinical benefit. But fundamentally here this particular agent did not even meet criteria for its primary endpoint.

In conclusion, as physicians we owe it to our patients to maintain the highest scientific standards and rigor. We owe them our objectivity and the assurance that when we make recommendations for treatment that we are basing our decisions on strong conclusive data. We need your help to ensure maintaining this high standard.

Sincerely,

A handwritten signature in cursive script that reads "Maha".

Maha Hussain, MD  
Professor of Medicine & Urology

cc. James Mule PhD  
Moffitt Cancer Center  
12902 Magnolia Drive SRB-2  
Tampa FL 33612  
[mulejj@moffitt.usf.edu](mailto:mulejj@moffitt.usf.edu)

**Palmer, Kelly**

**From:** scherh@MSKCC.ORG  
**Sent:** Sunday, April 29, 2007 10:16 AM  
**To:** von Eschenbach, Andrew C.  
**Subject:** FW: thank you

Thought you might find the note below of particular interest.

Howard I. Scher, M.D.  
D. Wayne Calloway Chair in Urologic Oncology  
Chief, Genitourinary Oncology Service  
Department of Medicine  
Sidney Kimmel Center for Prostate and Urologic Cancers  
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**From:** Rosenberg, Steven A. (NIH/NCI) [E] [mailto:sar@mail.nih.gov]  
**Sent:** Friday, April 27, 2007 1:12 PM  
**To:** Scher, Howard I./Medicine  
**Subject:** thank you

Howard

A brief note to tell you how much I support and admire your position with respect to the Provenge issue.

You are so clearly correct.

As oncologists, we all stand taller because of your efforts to promote rationale decisions concerning drug approval criteria.

Steve

Steven A. Rosenberg M.D., Ph.D.  
Chief, Surgery Branch  
National Cancer Institute  
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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Public Health Service**

*Food and Drug Administration  
Division of Freedom of Information  
5600 Fishers Lane, HFI-35  
Rockville, MD 20857*

May 18, 2009

File: 07-8316

Kerry M. Donahue, Esq.  
BELLINGER & DONAHUE  
6295 Emerald Parkway  
Dublin, OH 43016

Dear Mr. Donahue:

This is in response to your letter dated August 15, 2007, in which you requested the following:

[A] copy of all letters written to the FDA (or prepared by the FDA) and purported to be from Dr. Scher, Dr. Hussain and Doctor Fleming in between March 29th 2007 and April 30th of 2007, regarding the BLA submitted for Provenge also known as Sipuleucel-T including the envelope or other means of communication whereby the FDA received such letters and a copy of any record of those letters then being disclosed to any media or other persons or specifically a publication called "The Cancer Letter", including the means of communication to the Cancer Letter of the Scher, Hussain and Fleming letters from the FDA or its employees to outside persons, publications or companies.

Your request was received in the Center for Drug Evaluation and Research (CDER) on October 15, 2007.

The records located in CDER's search are enclosed. The following charges may be included in a monthly invoice:

Search: \$0 Review: \$0 Reproduction: \$0.40 TOTAL: \$0.40

The above total may not reflect final charges for this request.

**PLEASE DO NOT SEND PAYMENT UNLESS YOU RECEIVE AN INVOICE FOR THE TOTAL MONTHLY FEE.**

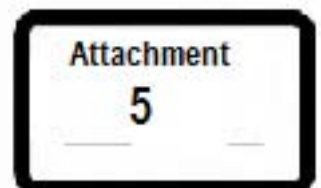
This concludes CDER's response to your request.

Sincerely,

*Howard R. Philips*

Howard R. Philips  
FDA/CDER/Division of Information Disclosure Policy

Enclosure: 4 pages



HF m- A.O 7-2569



*Howard I. Scher, MD*  
*D. Wayne Calloway Chair in Urologic Oncology*  
*Chief, Genitourinary Oncology Service*  
*Sidney Kimmel Center for Prostate and Urologic Cancers*

April 5, 2007

Andrew von Eschenbach, MD  
Commissioner  
5600 Fishers Lane  
PKLN RM 1471 HF-1  
Rockville, MD 20857

RE: CBER Advisory Committee for Sipuleucel-T  
March 30, 2007

Dear Dr. <sup>Andrew</sup> von Eschenbach:

I am writing to express concerns about the recent review of Sipuleucel-T at the FDA Advisory Meeting on March 30, 2007. These concerns are: a recommendation for approval based on data that fall short of the regulatory requirements; an inadequate statistical construct to determine definitive benefit; incomplete data on product safety; and what appear to be different criteria for approval by two Advisory Committees to the Agency. All but the latter were discussed in the open meeting, but warrant further consideration given the outcome. The concerns are based on my experience as a voting member on several ODACs representing the Agency, and separately, as a Presenter to ODAC for Industry Sponsors. I have been one of the Academic Leaders of the Prostate Cancer Clinical Trial Endpoints initiative begun under the joint Sponsorship of the FDA, AACR, ASCO and PCF in 2004, which were presented at the February 2007, Prostate ASCO Meeting in Orlando. The final manuscript is currently under review at the NCI, FDA and the Group of established Prostate Cancer Clinical Trial experts who together, formulated the recommendations. I am also the Principal Investigator of a Multicenter Prostate Cancer Clinical Trials Consortium funded by the Department of Defense that focuses on phase 1 and 2 trials in this disease.

Let me state at the outset that I was one of the four Committee Members who voted "no" to the question whether the trials presented by the Sponsor established the efficacy or demonstrated substantial evidence of benefit to justify an approval recommendation to the FDA. **My vote was based on the fact that neither of the two trials presented met their primary endpoint, which renders the significance of results from any subsequent analyses as "exploratory" and "hypothesis generating".** As such, the

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Page 2

results do not constitute “proof” of benefit or justify a conclusion that they are “reasonably likely” to predict benefit. The trial data were not consistent. Even if one accepts the post-hoc survival analysis results of the larger 127 patient trial (82 men treated with Sipuleucel-T and 45 men treated with a “placebo”), the second trial of 98 patients (65 treated with Sipuleucel-T and 33 with placebo) was not confirmatory. Consequently, the only conclusion that can be reached is that the survival difference observed may have occurred by chance alone, and that the results do not support an approval recommendation. This, and the Sponsor’s recognition that an additional prospective study was needed, mandates deferring any decision on whether an approval should be granted until the results of the ongoing 500 patient phase 3 trial that is powered on a primary endpoint of survival, is accrued and analyzed.

Concerns about the validity of the findings were reinforced by the absence of other signals of an antitumor effect. Specifically there were no data provided of a favorable effect on PSA, regression or stabilization of soft-tissue or boney disease radiographically, health related quality of life, or that administration of the product delayed the development of pain. Even the time to the administration of chemotherapy, an indication to the treating Physicians that the clinical course had worsened, was similar between the two groups. Reinforcing the uncertainty was the fact that in response to a direct question at the meeting, none of the Physicians representing the Sponsor could articulate how treatment with the product had “helped” any individual patient.

There were also methodologic concerns. Trial 9901 was designed to show an increase in time to disease progression from 16 weeks for placebo treated to 31 weeks for Sipleucel-T treated patients (HR = 1.92, alpha =0.05, two sided, with 80% power). A total of 127 patients were enrolled using a 2:1 randomization in favor of the experimental therapy. The study was double blind and included an independent review of all imaging results. The estimated time to progression on which the trial was powered proved to an overestimate, as the actual observed median time to progression was 9 to 11 weeks for both arms: a difference that was not statistically significant. A summary of the progression events showed that 90% (97/114) were by imaging, 10 were clinical, and 7 were for the new onset of disease related pain. Unrecognized at the time of the design of the trial, was that the eight week interval between disease assessments was too short to observe clinically significant changes by bone scan, and that in many cases, apparent “progressions” eight weeks after the start of a therapy are more a reflection of disease worsening that led to trial entry, and not a failure of the treatment.(CCR 13:1488, 2007) This is similar to what was observed in the trial with the endothelin antagonist, atrasentan, in which a 12 week disease assessment interval was used and a large proportion of patients were withdrawn at the time of scheduled scans in the absence of clinical worsening of disease (ODAC, September 13, 2005). Recognizing this, the Prostate Cancer Working Group 2 has advised that an apparent progression on bone scan at a three month assessment, be confirmed by documenting further progression on a subsequent scan six or more weeks later before considering a patient to have failed the treatment.(ASCO Multidisciplinary Prostate Cancer Symposium, (Abstract #221) February 22-24, 2007, Orlando, FL, 2007). Although the Sponsor suggested that the effect of the product was delayed, this hypothesis could not be explored because serial imaging to assess disease at defined intervals were not performed once a patient was considered to have “progressed” and taken off study. As a result, individual sites of disease were no longer being monitored, so that no statements could be made regarding a possible “delayed effect” of the product on disease status.

At 3-years, a prespecified survival analysis was performed which showed a 4.5 month difference in median survival favoring Sipuleucel-T, and while a significant p-value for the difference was determined, the type 1 error rate is surely inflated by this additional analysis. Imbalances in disease aggressiveness and disease extent were noted between the Sipuleucel-T and “control” groups including a higher proportion with Gleason 6 disease or less at diagnosis (26.8% vs. 15.6%), and a lower proportion with both bone and soft tissue disease (52% vs. 69%) at the time therapy was started. Both factors favored the Sipuleucel-T arm, predicting a longer survival for the “treated” patients independent of therapy. The 2:1 randomization increased the power of the experimental arm, but it may have

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inadvertently made the small 43 patient control group more heterogeneous and less representative of the global population of men for whom the indication was proposed. The potential impact of heterogeneity in small patient cohorts was shown when a post-study change in the progression times of two patients (a change not accepted by the Agency), resulted in a change in the significance estimates.

The first question the Agency posed to the Committee was whether the product was "reasonably safe" for the intended population. While the vote was yes, the issue of cerebrovascular events as a potential safety signal was raised. This concern was based on the finding that 4.9% (17/345) of the Sipuleucel-T and 1.7% (3/172) of "placebo" treated patients who were enrolled on randomized trials for the indication, experienced a cerebrovascular event ( $p=0.092$ ). The odds ratio for developing a cerebrovascular event was 2.92, with wide confidence intervals (0.82 to as high as 10 fold). Deaths due to CVA's were recorded in 1.5% of Sipuleucel-T patients and 0.9% of those receiving "placebo". Unclear is why there is no mention of CVA's in the published report of the study in the Journal of Clinical Oncology (JCO 24:3089, 2006). Given that the product is released for administration based on the increase in the proportion of CD54+ cells and not the absolute number of any particular cell type and that CD54+ cells actually represent only 20% of the final product, the contribution of the other cell populations and cytokines that may be present in the administered product on the development of a cerebrovascular event is not known. More important, and perhaps underappreciated during the discussion, is the recognition that the "placebo" used in this trial, a portion of the leukopheresis product that is cultured without the immunizing antigen and reinfused, may not be inert and in itself contributed to a relative worsening of survival for the control group in this trial. To place the frequency of the neurologic events in perspective, no cerebrovascular events were observed in TAX-327, a 997 patient three arm randomized trial that evaluated two different dose schedules of docetaxel in comparison to mitoxantrone, (NEJM 351:1052, 2004) or ASCENT1, a 251 patient randomized comparison of docetaxel weekly with or without high dose calcitriol (DN-101) (JCO 25:669, 2007). Neurologic events that were not detailed further were observed in 7% of the 338 patients who received estramustine which is known to be thrombogenic, in combination with docetaxel on the SWOG 99-16 trial (NEJM 351:1513, 2004).

Another concern is that the requirements for regulatory approval appear to differ between the ODAC and CBER Advisory Committee. As an example, ASCENT1 was a prospective randomized phase 2 trial of weekly docetaxel with or without high dose calcitriol (DN-101). The trial was powered to detect a 20% difference in the PSA response rate at six months between the two groups as the primary endpoint, but also included a pre-specified survival analysis, similar to that included in the Sipuleucel-T 9901 trial as one of the secondary endpoints. PSA response was defined as a 50% or greater decline from baseline according to Consensus Criteria (JCO 17:3461, 1999). A total of 250 patients, 125 per arm were enrolled and followed. The 9% difference in the PSA response rate observed at six months was not statistically significant ( $P<.16$ ), yet here too, the pre-specified survival analysis showed a difference for docetaxel plus DN-101 vs. docetaxel plus placebo: median not reached but estimated to be 24.5 months vs. 16.4 months respectively with a hazard ratio for death of 0.67 ( $p=0.04$ ) (JCO 25:669-74, 2007). The safety of the combination was no worse and perhaps better than docetaxel alone. Appropriately in my view, the results were not considered definitive by ODAC, no approval filing was made, and a new 900 patient phase 3 trial powered to test the hypothesis whether the combination of docetaxel in combination with DN-101 conferred a survival advantage relative to docetaxel alone was designed, initiated and continues to accrue. I am the International Principal Investigator on this trial. Contrast this with the regulatory filing history of Sipuleucel-T where the primary endpoint of the registration trial was also not met, yet, it is being considered for approval based on a similar post-hoc analysis with roughly half the total number of patients, and a control arm that is roughly one third the size. Why do the Sipuleucel-T results establish efficacy, while the DN-101 results do not?

An approval recommendation has far reaching implications beyond making the product available that the data simply do not support or justify. For one, it provides the Agency's endorsement of

Page 4

Sipuleucel-T as a "standard of care" treatment for an asymptomatic population of men with androgen independent (castration resistant) disease that represents upwards of 45,000 men in the U.S. The second is that by extension, it elevates Sipuleucel-T to a position of being the new "control" arm for future randomized phase 3 trials that are being designed for the regulatory approval of any new experimental agent or approach. It also opens the door to the premature approval of drugs based on inconclusive data.

Finally, the original question posed by the Agency to the Advisory Committee at the meeting was: "Does the submitted data establish the efficacy of Sipuleucel-T (APC-8015) in the intended population?" The first 4 respondees on the Committee voted "no". The question was then changed to: Do the data show "substantial evidence". A series of "yes" votes followed.

Consider the conclusion in the manuscript describing the results of trial 9901, published in the Journal of Clinical Oncology in Volume 24, page 3093, in 2006.(JCO 24:3089, 2006) In it, the Investigators state **"that while sipuleucel-T fell short of demonstrating a statistically significant difference in TTP, it MAY provide a survival advantage to asymptomatic HRPC patients. Supportive studies are underway to confirm this effect."** All of the difficulties cited, and the Investigator's own conclusions, show how there are simply too many alternative explanations for the observed survival difference beyond treatment with Sipuleucel-T. Couple this with that fact that were no secondary signals of an antitumor effect and no confirmatory trial however flawed, mandates that any decision for approval be deferred until the phase 3 study, currently underway, has been completed and analyzed.

Thank you for your time and consideration.

Yours sincerely,



Howard I. Scher, M.D.  
Member and Attending Physician

Professor of Medicine  
Joan and Sanford Weill College of Medicine of Cornell University

CC: Janet Woodcock, MD, Deputy Commission of OPE  
Jesse L. Goodman, MD, Director, Center for Biologics Evaluation & Research  
Richard Pazdur, MD, Director, Office of Oncology Drug Products, Center for Drug Evaluation & Research  
Celia Witten, MD, PhD, Director, Office of Cellular Tissues & Gene Therapy, Center for Biologics Evaluation & Research  
James J. Mule, PhD