

May 21, 2009

Rory Kearney, President
CareToLive
P.O. Box 464
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Re: Docket No. FDA-2007-P-0168
(formerly 2007P-0297/CP1)

Dear Ms. Kearney:

This letter responds to your citizen petition dated July 26, 2007, submitted to the Food and Drug Administration (FDA) on behalf of CareToLive (CTL). In its petition, CTL requests that the Commissioner of Food and Drugs (the Commissioner) reconsider the failure of the agency to approve the biologics license application (BLA) submitted by Dendreon Corporation (Dendreon) for Provenge®, a cancer vaccine to treat prostate cancer.¹

Before addressing the specific requests in your petition, we first want to make it clear that we share your concern for men suffering from advanced prostate cancer. Prostate cancer is the most common form of cancer (other than some forms of skin cancer) and the second leading cause of cancer deaths among men in the United States.² Of note, Dendreon announced in April 2009, that it has completed a pivotal phase 3 study of Provenge and that it intends to file an amendment to its existing BLA in the fourth quarter of 2009.³ We are committed to expeditiously reviewing the new information as soon as it is submitted. FDA shares the goal of approving new products, such as Provenge, as soon as they are shown to be safe and effective.

Before a product is approved, there are a number of ways in which individuals can obtain access to an investigational product. FDA has a long history of permitting access to investigational drugs to treat serious and immediately life-threatening diseases without adequate available therapies. Individuals can obtain access by enrolling in on-going clinical investigations of such products, including any existing expanded access protocols. Such investigations can include

¹ We note that there has been previous correspondence and submissions to the docket in connection with this citizen petition. For example, FDA previously sent you an interim response dated January 12, 2008. Moreover, CTL submitted additional correspondence to the docket for this citizen petition dated January 28, 2008, February 14, 2008, and October 7, 2008. Other relevant comments were submitted to the docket dated August 27, 2007 through February 15, 2008.

² U.S. Cancer Statistics Working Group. *United States Cancer Statistics: 1999-2005 Incidence and Mortality Web-based Report*. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2009. Available at: www.cdc.gov/uscs (accessed May 19, 2009).

³ Dendreon's April 14, 2009 press release "PROVENGE Significantly Prolongs Survival in Men with Advanced Prostate Cancer in Pivotal Phase 3 IMPACT Study," is available at <http://investor.dendreon.com/releasedetail.cfm?ReleaseID=376922> (accessed May 19, 2009).

protocols that provide for expanded access for patients with serious or life-threatening diseases who lack other therapeutic options. With regard to Provenge, Dendreon has stated that it will provide patients access to Provenge through its existing on-going clinical trial programs and that there are three actively enrolling clinical trials. The first trial is an open-label study designed to treat patients who were randomized to placebo in the recently completed Phase 3 study. Dendreon has stated that it has two other actively enrolling studies. One of these trials is a single-site trial enrolling 40 patients with localized prostate cancer who are scheduled to undergo a prostatectomy. The other trial is a multicenter trial enrolling approximately 120 patients with metastatic androgen-independent prostate cancer. Patients interested in learning more about prostate cancer studies, including Dendreon's on-going studies, can obtain more detailed information at www.clinicaltrials.gov.

We will now address the specific requests in your petition, which focuses on Dendreon's Provenge BLA submitted in 2006 and FDA's Complete Response Letter issued in 2007, declining to approve the BLA as filed, and requesting additional information. Your statement of grounds includes, among other things, the following assertions:

- (1) FDA designated Provenge for fast track approval indicating that FDA had enough data for approval;
- (2) FDA denied prostate cancer patients who have exhausted FDA approved treatment options the right to life, liberty and the pursuit of happiness; and
- (3) FDA failed to approve the pending BLA because we allowed conflicted doctors to participate in an advisory committee meeting, advocate against Provenge during and after such meeting, and vote in such meeting.

In response to the issues raised in your petition and your specific statement of grounds, we believe that you have misunderstood the meaning of fast track designation. This designation does not necessarily lead to a priority review or accelerated approval. In fact, a product with this designation may not be approved at all.⁴

Moreover, in response to your claim that FDA has denied cancer patients the right to life, liberty, and the pursuit of happiness, we note that there is no constitutional right to an unapproved drug. Further, we believe that you have misunderstood the advisory committee process and its role with respect to the biological approval process. As explained below, the advisory committee is in place to provide advice to the agency and does not make the decision whether to approve a product. The agency makes this decision based upon the review of the data and science available to us.

⁴Fast track refers to the process for interacting with the FDA during drug development while priority review refers to the time frame FDA targets for reviewing a completed application. For general information about the terms "fast track" "priority review," and "accelerated approval," see <http://www.fda.gov/oashi/fast.html> (accessed may 19, 2009) and <http://www.accessdata.fda.gov/scripts/cder/onctools/Accel.cfm> (accessed may 19, 2009).

FDA has carefully considered the issues raised in CTL's petition, the additional correspondence, and the comments submitted to the docket. Given the agency's understanding of CTL's request and for the reasons set forth below, we deny CTL's petition. Please be aware, however, that FDA understands the importance of providing patients with promising new therapies and our denial of this citizen petition has *no* bearing on Dendreon's pending BLA for Provenge. FDA has not made a final decision on whether to license Provenge. As noted above, Dendreon has stated that it has completed its pivotal phase 3 study of Provenge and intends to file an amendment to its existing BLA in the fourth quarter of 2009. We look forward to receiving this information and are committed to expeditiously reviewing the new study data upon submission.

DISCUSSION

I. Members of the Public Cannot Compel the Agency to Render a Final Decision on a BLA

CTL's petition requests the Commissioner to reconsider the decision not to immediately license Provenge. Nothing in the Federal Food, Drug, and Cosmetic Act (FDCA), the Public Health Service Act (PHSA), or FDA's regulations permits a member of the public to obtain, in a separate petition proceeding, a final decision on a pending BLA by relying on the data the sponsor submitted in support of its application. CBER has been and continues to be engaged in a thorough evaluation of the scientific and regulatory issues posed by the Provenge BLA under the legal framework described below. CTL cannot, by means of its petition, circumvent the approval process.

II. As a Legal Matter, CTL May Not Rely on Dendreon's Data

We understand that CTL characterizes itself as an association of "cancer patients, patient families, doctors, investors, and advocates." However, CTL lacks any commercial, financial, associational, fiduciary, or confidential relationships with Dendreon. CTL is not privy to Dendreon's legal, business, or scientific concerns, and therefore cannot represent its interests. Furthermore, without express authorization from Dendreon, which CTL has not provided, CTL may not step into Dendreon's shoes, or rely on Dendreon's data (be it proprietary or otherwise).

In the following sections, we explain the regulatory process for the licensing of a biologic that Dendreon, as the sponsor of the BLA for Provenge, must follow. We hope that this discussion will clarify why the filing of a citizen petition cannot circumvent this process.

III. Legal Framework for Approval of a Biological Product

Provenge is both a biological product under the PHSA and a drug under the FDCA. More specifically, a biological product is defined in the PHSA as any "virus, therapeutic serum, toxin, antitoxin, vaccine ... or analogous product ... applicable to the prevention, treatment, or cure of a disease, or condition of human beings." 42 U.S.C. 262(i). The FDCA defines drug to include, among other things, "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man.: 21 U.S.C. 321(g)(1)(B). A "new drug" is defined as either "any

drug ... the composition of which is such that such drug is not generally recognized ... as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof” or “any drug ... the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.” 21 U.S.C. 321(p).

Under the PHSA, a biological product may not be introduced or delivered for introduction into interstate commerce unless a biologics license is in effect for the product. 42 U.S.C. 262(a). Likewise, an unapproved new drug may not be introduced or delivered for introduction into interstate commerce until an approved new drug application is in effect for the new drug. 21 U.S.C. 331(d), 355(a).

The PHSA and the FDCA provide FDA with the authority to promulgate regulations that establish the requirements for product approvals as well as regulations for clinical investigations of unapproved drugs and biologics. 21 U.S.C. 355(i) and 42 U.S.C. 262(a)(2)(A). The regulations on clinical investigations require the submission of an Investigational New Drug application (IND) describing the protocol, and, among other things, ensuring that human subjects will be protected. These regulations are set out at 21 CFR 312. *See* 21 CFR 312.2 (explaining that the IND regulations apply to clinical investigations of both drugs and biologics).

The regulations addressing investigational new drugs and biologics provide a pathway for the study and approval of unapproved new drugs/biologics. The regulations provide that, once an IND is in effect, the sponsor may conduct a clinical investigation of the product, with the investigation generally being divided into three phases. The first phase involves closely monitored testing for safety in a small group of subjects (Phase 1), followed by testing in more subjects in order to evaluate the effectiveness of the drug for a particular indication, as well as to monitor short-term side effects and risks. 21 CFR 312.21(a). Phase 2 studies generally involve no more than several hundred subjects and are well-controlled and likewise, closely monitored. Phase 3 studies may proceed only after preliminary evidence suggests that the product is both safe and effective. Phase 3 studies gather additional information about effectiveness and safety that may provide the basis for FDA approval. Phase 3 studies typically involve several hundred to several thousand subjects. 21 CFR 312.21 (c).

To obtain a biologics license for a biological product, the manufacturer must submit a BLA pursuant to the PHSA, 42 U.S.C. 262(a), as specified in 21 CFR 601.2, to the Director, Center for Biologics Evaluation and Research (CBER). The BLA must include, among other things, data derived from non-clinical laboratory tests as well as clinical studies demonstrating that the product is safe, pure, and potent, 42 U.S.C. 262(a)(2)(C)(i)(I), and that the facility in which the product is manufactured “meets standards designed to assure that the biological product continues to be safe, pure, and potent.” *Id.* At 262(a)(2)(C)(i)(II). The agency does not consider an application to be filed until the agency determines that all pertinent information and data have been received. 21 CFR 601.2. FDA’s filing of an application indicates that the application is complete and ready for review but does not indicate whether FDA will approve the application.

Dendreon, the sponsor of Provenge, submitted its BLA in late 2006, and FDA considered it to be filed in January 2007. As part of its review, FDA sought the advice of its Cellular, Tissue and Gene Therapies (CTGT) Advisory Committee (see section V.B. for additional information). After reviewing Dendreon's BLA, FDA determined there were deficiencies in the BLA that precluded approval and on May 8, 2007, sent Dendreon a Complete Response Letter declining to approve the BLA as filed, and requesting additional information.⁵ [Footnote: It has long been CBER's practice to issue applicants a Complete Response Letter if CBER determines that it will not approve a BLA or BLA supplement in its present form. This practice is codified at 21 CFR 601.3.] Specifically, FDA requested additional information with respect to chemistry, manufacturing, and controls. This information is needed to help FDA access whether the facility in which the product is to be manufactured "meets standards designed to assure that the biological product continues to be safe, pure, and potent." 42 U.S.C. 262(a)(2)(C)(i)(II). FDA also requested additional information to support Dendreon's effectiveness claim. In response, Dendreon met with FDA and made it clear it intended to continue with an ongoing Phase 3 study designed to measure survival and to submit such data to FDA when they become available. *See* Dendreon, "Dendreon Announces FDA Confirms Data Required for Provenge Licensure," May 31, 2007, available at <http://investor.dendreon.com/releasedetail.cfm?ReleaseID=246500> (accessed May 19, 2009). As discussed above, Dendreon has stated that it has completed this study and that it intends to file an amendment to its existing BLA in the fourth quarter of 2009.

As noted above, issuance of a Complete Response Letter is not a final determination about the merits of an application. In this case, it was a step that the agency took because it did not have sufficient information to determine that the product would be safe and effective, as well as sufficient information to determine that the facility in which the product is manufactured, processed, packed, or held would ensure the continued safety, purity, and potency of the product. 42 U.S.C. 262(a)(2)(C). Without this information, FDA could not make an approval determination. Thus, the administrative action sought by CTL's petition, to have the agency reverse its decision not to immediately approve Provenge, is premature.

Issuance of a Complete Response Letter is *not* final agency action. Instead, it indicates that there are deficiencies remaining that preclude approval of an application or supplement. A Complete Response Letter usually summarizes all the deficiencies that the agency has identified in an application and, where appropriate, describes actions necessary to place the application in a condition for approval. Rather than being final agency action on the application, it is an invitation to the sponsor to amend and complete the application so that a determination with respect to the application can be made. As discussed above, Dendreon has stated that it has completed this study and that it intends to submit the results of the study in an amendment to its existing BLA in the fourth quarter of 2009.

IV. FDA's Fast Track Designation Does Not Equate to Fast Approval

⁵ It has long been CBER's practice to issue applicants a Complete Response Letter if CBER determines that it will not approve a BLA or BLA supplement in its present form. This practice is codified at 21 CFR 601.3.

CTL contends in its petition that FDA invited the BLA and designated Provenge for fast track status “approval” and by doing so, FDA indicated that it had enough data to decide if Provenge was safe and “substantially” proven to be effective. As explained more fully below, CTL has mistakenly assumed that by designating Provenge for fast track, FDA necessarily made a substantive determination that Dendreon’s BLA “had enough data” to allow the agency to make a final decision without requesting more information. CTL also mistakenly implies that FDA’s designating Provenge for fast track was somehow connected with Dendreon’s submitting its BLA and with the Prescription Drug User Fee Act (PDUFA) due date of May 15, 2007.⁶

FDA developed initiatives to speed evaluation of the safety and effectiveness of certain drugs and biologics, in response to the Food and Drug Administration Modernization Act of 1997. These initiatives include our fast track program.⁷ Such initiatives are intended to foster collaborative efforts of the agency with researchers, patients, industry experts, and health care providers and to help sponsors of new drugs that treat cancer and other life-threatening diseases develop their products more efficiently so that they can be made available to patients as quickly as possible. *See generally* FDA, “Fast Track, Accelerated Approval and Priority Review,” available at <http://www.fda.gov/oashi/fast.html> (accessed May 19, 2009).⁸ A drug is eligible for

⁶ Under PDUFA (21 U.S.C. 379(h)(Public Law 102-571), FDA agreed to specific goals for improving the drug review time and created a two-tiered system of review times – standard review and priority review. See <http://www.fda.gov/oc/pdufa/default.htm> (accessed May 19, 2009). A biological product is subject to priority review if the product, if approved, would be a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a serious or life-threatening disease. An applicant must make a request for priority review. All other applications are subject to standard review. For additional information, see <http://www.fda.gov/oashi/fast.html> (accessed May 19, 2009).

The Food and Drug Administration Modernization Act of 1997 (the Modernization Act), as well as the Food and Drug Administration Amendments Act of 2007, reauthorized and expanded PDUFA. In conjunction with the reauthorization of PDUFA, FDA agreed to meet specific performance goals (PDUFA goal). These goals include reviewing and acting on 90 percent of standard original NDA and BLA submissions within ten months of receipt, and 90 percent of priority original NDA and BLA submissions within six months of receipt. See <http://www.fda.gov/oc/pdufa4/pdufa4goals.html> (accessed May 19, 2009). These six-month and ten-month dates are referred to as the PDUFA due dates. FDA designated the Provenge BLA for priority review and the PDUFA due date was May 15, 2007, six months after receipt of the BLA. FDA issued its Complete Response Letter on May 8, 2007, thus meeting the PDUFA due date.

⁷ Section 112 of the Modernization Act amended the FDCA by adding new section 506 (codified at 21 U.S.C. 356). Section 506 authorizes FDA to take actions appropriate to facilitate the development and expedite the review of an application for a fast track product. These actions are not limited to those specified in the fast track provision but also encompass existing FDA programs to facilitate development and review of products for serious and life-threatening conditions. A critical feature of fast track is that it emphasizes close, early communication between FDA and the sponsor to improve the efficiency of drug development.

⁸ FDA’s “subpart E” regulations are an integral part of FDA’s fast track programs. *See* <http://www.fda.gov/cder/guidance/5244fnl.htm> (accessed May 19, 2009). These regulations provide for procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. 21 CFR 312.80. The procedures recognize that the agency should exercise the broadest flexibility in applying the

fast track designation if “it is intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for such a condition.” 21 U.S.C. 356(a)(1). Because this approach implies speed, there can be no confusion about the specific meaning of fast track. This designation is not related to the data in a BLA, but to the condition the biologic is intended to treat. In fact, fast track designation can be requested at the time of original submission of an IND or at any time thereafter prior to receiving marketing approval.⁹

As noted in the “Guidance for Industry, Fast Track Drug Development Programs-Designation, Development, and Application Review, January 2006,” available at <http://www.fda.gov/cber/gdlms/fsttrk.htm> (accessed May 19, 2009), a drug that receives fast track designation is eligible for more frequent meetings with FDA to discuss the development plan for the biologic or drug; more frequent written correspondence from FDA about such things as the design of the proposed clinical trials; and rolling review, which means that an applicant can submit completed sections of its BLA for review by FDA, rather than waiting until every section of the application is completed before the entire application can be submitted for review. 21 U.S.C. 36(c)(1).

Although FDA processes applications designated for “fast track” more expeditiously than other applications, it must apply the same substantive standard of approval to all drugs and biological. In addition, *a fast track designation is independent of, and does not necessarily lead to, a priority review or accelerated approval.* Therefore, the correct term is fast track designation, not fast track “approval,” as mistakenly stated in your petition. Although the hope is that fast track designation will speed the development of such products, the approval process depends on the sponsor’s submitting sufficient data demonstrating safety and effectiveness for the product.

FDA granted Dendreon’s request for fast track designation in late 2005. *See* Dendreon, “Dendreon Announces FDA Grants Fast Track Status for Provenge,” Nov. 7, 2005, available at <http://investor.dendreon.com/releasedetail.cfm?ReleaseID=178878> (accessed May 19, 2009). Dendreon submitted its BLA for Provenge in late 2006. FDA thus granted fast track designation more than a year *before* Dendreon submitted its BLA. Thus, FDA’s fast track designation could not have been based on a prediction about whether Dendreon’s BLA, which FDA had not yet received, would contain sufficient data for FDA to issue a final approval decision without requesting more information. Also, the May 15, 2007 PDUFA date was not connected with the granting of fast track designation.

V. Advisory Committee Process; FDA Final Determinations

CTL objects to FDA’s denying immediate approval of Provenge even though the advisory committee voted 17-0 that Provenge was safe and 13-4 that there was evidence of efficacy. CTL

statutory standards to these therapies. *Id.* The expedited procedures include, for example, early meetings with the FDA to discuss study design and FDA monitoring of the progress of clinical studies. 21 CFR 312.82d and 312.87.

⁹ If such a request is made, FDA will respond within 60 calendar days of receipt. 21 U.S.C. 356(a)(2) and (3).

also contends that at least two of the four “no” votes were by doctors who had both disclosed and undisclosed conflicts of interest, and argues that the “no” votes of Drs. Howard Scher and Maha Hussain should be stricken from the record. In addition, CTL alleges that Drs. Scher and Hussain, along with Dr. Richard Pazdur, engaged in a conspiracy to derail the Provenge approval. Further, CTL accuses FDA of being pressured into its decision.

As explained more fully below, although FDA takes advisory committee recommendations under advisement; only the agency can make the decision to approve a drug or biologics application. In addition, members of an advisory committee are thoroughly screened for compliance with rules governing conflicts of interest and may be granted waivers when appropriate.

A. Advisory Committees

In some instances, FDA seeks advice from advisory committees comprised of various outside experts, whose primary role is to provide independent expert advice that will contribute to the quality of the agency’s decision-making. *See generally* 21 CFR Part 14. Voting members of advisory committees, with limited exceptions not applicable here, are appointed as FDA “special government employees” (SGEs). 21 CFR 14.95(a)(1). As such, they are subject to 18 U.S.C. 208, which generally prohibits executive branch employees, including SGEs, from participating personally and substantially in any manner in which they, or any persons whose interests are imputed to them, have a financial interest. However, an SGE serving on an advisory committee may obtain a waiver that allows him or her to participate in a matter with which he or she has a *potential* conflict when the appointing official certifies in writing that “the need for the individual’s services outweighs the potential for a conflict of interest created by the financial interest involved.” 18 U.S.C. 208(b)(3).

At the time of the advisory committee meeting addressing Provenge, 21 U.S.C. 355(n)(4) (since rescinded and superceded) required each member of an advisory committee reviewing drug or biologics applications to disclose all conflicts of interest the member may have had with the work to be undertaken by the committee, and prohibited the member from voting on any matter where he or his immediate family could gain financially from the advice given to the FDA.¹⁰ [Footnote: Since that time, the Food and Drug Administration Amendments Act of 2007 amended the FDCA by adding new section 712, codified at 21 U.S.C. 379d-1, which now governs conflicts of interest for FDA advisory committee members.] This provision also stated that FDA (by delegation from the Secretary of Health and Human Services) could grant a waiver if such waiver was “necessary to afford the panel essential expertise,” except that a waiver could not be granted for a member of an advisory committee when the member’s own scientific work was involved. See former 21 U.S.C. 355(n)(4) (rescinded and superceded by 21 U.S.C. 379d-1 as enacted by FDA Amendments Act of 2007).

¹⁰ Since that time, the Food and Drug Administration Amendments Act of 2007 amended the FDCA by adding new section 712, codified at 21 U.S.C. 379d-1, which now governs conflicts of interest for FDA advisory committee members.

FDA recruits advisory committee members who are recognized authorities in their areas of expertise. The people who have this kind of expertise are widely sought by the government, by patients, and by medical product developers, and they often are just as widely employed. Many academic experts engaged in research relevant to the issues addressed at FDA advisory committee meetings have some scientific ties to industry that potentially raise conflicts of interests. For the guidance that was in place at the time of the advisory committee meeting here, see “FDA Guidance on Conflict of Interest for Advisory Committee Members, Consultants and Experts,” available at <http://www.fda.gov/oc/advisory/conflictinterest/guidance.html> (accessed May 20, 2009). An updated guidance, reflecting the conflict of interest requirements set out in the FDA Amendments Act of 2007, is available at <http://www.fda.gov/oc/advisory/GuidancePolicyRegs/ACWaiverCriteriaFINALGuidance080408.pdf> (accessed May 19, 2009).

Conflict of interest screening is conducted on a meeting-by-meeting basis. The scope of conflicts that may preclude participation changes with the subject matter of each meeting. Individuals may not participate in specific meetings for which they have a potential conflict unless they obtain an appropriate waiver.

Although FDA carefully considers the advice and recommendations of its advisory committees as part of the overall review process, such advice is not binding, and decisions, such as whether to approve a BLA, are made by FDA alone. *See* 21 CFR 14.5 (the purpose of an advisory committee is “to conduct public hearings on matters of importance that come before FDA, to review the issues involved, and to provide advice and recommendations to the Commissioner;” however, “[t]he Commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee.”).

B. March 29, 2007 Cellular, Tissue and Gene Therapies Advisory Committee Meeting

As part of its review of the BLA, CBER sought the advice of its Cellular, Tissue and Gene Therapies (CTGT) Advisory Committee. In addition, CBER determined that it would benefit from review by prostate cancer experts. Also, at CBER’s request, Dr. Pazdur from FDA’s Office of Oncology Drug Products (OODP), Center for Drug Evaluation and Research (CDER) participated in the advisory committee meeting. Dr. Pazdur has extensive experience in OODP evaluating other prostate cancer therapies. On March 29, 2007, the CTGT Advisory Committee held a public meeting to discuss the safety and efficacy data submitted by Dendreon. Prior to the meeting, FDA screened all participants, including Drs. Scher¹¹ and Hussain, for conflicts and granted waivers in accordance with 18 U.S.C. 208(b)(3) and 21 U.S.C. 355(n)(4). CTGT Advisory Committee Meeting, March 29, 2007, Transcript (Transcript), at 8-10, available at <http://www.fda.gov/ohrms/dockets/sac/07/transcripts/2007-4291T1.pdf> (accessed May 19, 2009). In addition, prior to the meeting, both Dendreon and FDA staff members prepared briefing documents which were forwarded to the advisory committee members and made publicly available on FDA’s website before the meeting. See Dendreon Briefing Document, and FDA Clinical Briefing Document, Statistical Briefing Document, and Chemistry, Manufacturing,

¹¹ Dr. Scher was an advisory committee member and SGE.

and Controls Briefing Document, available at <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4291B1-00-index.htm> (accessed May 19, 2009).

At the meeting, both Dendreon representatives and FDA staff members discussed their analyses of the Provenge BLA, including the clinical trial data. As evidence of effectiveness, Dendreon presented two Phase 3 clinical studies (D9901 was the first study, and D9902A, the second), each of which was designed to evaluate the effect of the drug on time to disease progression., with such progression being measured by radiologic scans, new onset of cancer-related pain, and other significant disease-specific events. Transcript, at 22, 29, 32, 152-53, 162; FDA Clinical Briefing Document, at 13-14. Neither Phase 3 study demonstrated that the drug had a treatment effect of delaying disease progression. Transcript, at 22, 43, 155-157, 164, 169; FDA Clinical terminated prematurely after the first study's negative results indicated that the second study would not meet its designated endpoint of delaying time to disease progression, and as a result only 98 patients were enrolled in the second study. Transcript at 162-63; FDA Clinical Briefing Document, at 16-17, 30.

Dendreon presented *post hoc* analyses of the data from the first study. According to Dendreon's interpretation, that data showed a statistically significant difference (approximately 4.5 months) in a different endpoint, survival, in patients treated with Provenge as compared to placebo. Transcript, at 37, 42, 151, 169; FDA Clinical Briefing Document, at 37. By contrast, the second study did not show a statistically significant difference in survival. Transcript at 151, 164, 169; FDA Clinical Briefing Document, at 35, 37. Moreover, neither study was designed prospectively to measure survival as an endpoint, *see* FDA Clinical Briefing Document, at 14 (noting statement in Dendreon's protocol that “[t]his study is not powered to show a survival effect”), and, as FDA staff observed, the survival analyses had limitations that affected their reliability. Transcript, at 170-71; FDA Clinical Briefing Document, at 4 (“doubts remain about the persuasiveness of the efficacy data”).

Specifically, FDA staff noted that the survival analyses were *post hoc*, making the results difficult to interpret, that the studies had small sample sizes (even the first study had only 127 patients), and that a statistically significant survival difference was seen in only one of the two studies. Transcript, at 151, 170-71, 177-182. In their Clinical Briefing Document, FDA staff further explained:

[I]nterpretation of this survival difference should be made with caution. The lack of a pre-specified primary method for survival analysis renders it difficult to estimate the Type 1 [false positive] error of this survival analysis. Thus, it is difficult to estimate the persuasiveness of the submitted survival results. The small size of the study makes it more likely that this finding could have occurred by chance. Consequently, the confidence on this survival evidence for the efficacy claim must be weighed against above-mentioned caveats of the post hoc nature of the survival analyses.

FDA Clinical Briefing Document, at 30; *see also* FDA Statistical Briefing Document, at sections 3.1.1, 3.2 (“The key efficacy evidence (difference between the two arms in overall survival) for this BLA is based on post-hoc analyses and the efficacy evidence is not substantial from a statistical perspective.”)

With respect to safety, FDA staff noted that there was a higher incidence of cerebral vascular accident (CVA) events (strokes) in Provenge, as compared to placebo. Transcript, at 166; FDA Clinical Briefing Document, at 3 (“approximately three times as many subject experienced CVA's in the treatment group compared with controls”). Although the FDA staff members recognized that the difference was not statistically significant, they indicated that the data showed a potential safety signal. *Id.* At 169; FDA Clinical Briefing Document, at 45.

After presentation and discussion of the data, the advisory committee members were asked to vote on whether the evidence established that the drug was safe and effective. They voted unanimously that the product was safe. Transcript, at 364-69. the committee then voted 13-4 in the affirmative of efficacy. *Id.* At 370-89.

Although the Advisory Committee voted favorably on the questions of safety and efficacy, such votes were simply advisory in nature. Moreover, the FDA staff members' clinical briefing documents, along with the advisory committee transcript, show shortcomings of Dendreon's data, including the failure of both of Dendreon's studies to meet their intended endpoints, the *post hoc* nature of Dendreon's survival analysis, the inconsistency of survival results between Dendreon's two studies, the small size of the studies, and the potential safety signal related to strokes. These documents provide ample support for FDA's decision not to grant approval at the time and to request more data. In reaching this decision, FDA considered all available data and information before us at the time and based its decision on a rigorous scientific and statistical analysis.

C. No Evidence of Conspiracy

Contrary to CTL's conspiracy allegations concerning certain members of the advisory committee, FDA staff members had identified all the deficiencies in Dendreon's effectiveness data prior to the advisory committee meeting, as is evident from FDA's Clinical and Statistical Briefing Documents prepared *before* the meeting, and from the fact that the FDA staff members' presentation at the meeting occurred *prior to* discussion and vote by the advisory committee members, including Drs. Hussain and Scher. *See generally* Transcript, available at <http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4291T1.pdf> (accessed May 19, 2009). Dr. Hussain's and Dr. Scher's agreement with the FDA staff members' analysis, as expressed at the advisory committee meeting and in letter to FDA afterward, does not provide evidence of a conspiracy. There is no merit to the assertion that we were pressured into our decision by Drs. Hussain, Scher, or Pazdur.

It is important to remember that as discussed above, FDA is not bound by the recommendations of its advisory committees. FDA seeks such input to ensure that it has the benefit of diverse perspectives among those with expertise in particular areas. As their name suggests, however,

advisory committees are formed to provide *advice* regarding matters of importance that come before FDA. Whatever recommendations a committee may put forth, the authority is FDA's alone to determine whether a drug meets the statutory requirements for approval: "The Commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee." 21 CFR 14.5; *see also* 21 U.S.C. 355(n)(7) (providing that FDA officials responsible for any matter reviewed by a scientific advisory committee shall review the panel's recommendations and shall notify affected persons of the final decision or the reasons that a final decision has not been reached); *Animal Def. Council v. Hodel*, 840 F.2d 1432, 1438 (9th Cir. 1988) (fact that particular recommendations of subordinates and advisory committees ultimately may have been rejected, perhaps in favor of recommendations offered by other participants in the decision-making process, is not indicative of bad faith); *Public Citizen Health Research Group v. FDA*, 740 F.2d 21, 33 (D.C. Cir. 1984) (court would not bind Secretary to the advice and recommendations of his subordinates and advisory committees).

FDA acted reasonably in considering the scientific evidence and concluding that it could not approve the Provenge BLA in 2007. The BLA did not demonstrate the evidence of effectiveness required for approval or provide the chemistry, manufacturing and controls necessary for the facility in which Provenge was to be manufactured, also required for approval.

VI. FDA's Decision Did Not Deny Patient the Right to Life, Liberty, and the Pursuit of Happiness

CTL's petition alleges that FDA's decision not to approve Provenge immediately has denied patients with advanced prostate cancer their right to life, liberty, and the pursuit of happiness. This broad sweeping claim fails to allege a cognizable constitutional violation and therefore fails to provide grounds for granting of the citizen petition. Further, the allegation does not explain how any of these general rights has been violated by FDA's decision not to approve Provenge. CTL has not—and cannot—reasonably allege the violation of any constitutional right.

What CTL specifically objects to is that FDA did not grant Dendreon immediate approval to market Provenge. Carefully described, the right CTL seeks to assert is not the right to life, liberty, or the pursuit of happiness but the right of terminally ill patients to have access to an unapproved product.

Every appellate court to consider whether patients have a substantive due process right to bypass FDA's drug approval requirements and obtain unapproved products has rejected such claim. Moreover, the Supreme Court denied certiorari in the most recent such case after the appellate court found that there is no fundamental right of access to experimental drugs for the terminally ill. *Abigail Alliance for Better Access to Developmental Drugs v von Eschenbach*, 495 F.3d 695, 697 (D.C. Cir. 2007) (en banc), *cert. denied*, 128 S.Ct. 1069 (2008).

Specifically, the United States Court of Appeals for the District of Columbia, sitting *en banc*, considered the claims of terminally ill patients arguing for unfettered access to experimental drugs based on a fundamental constitutional right of access to potentially life-saving drugs. The Court of Appeals explained that there is no fundamental right to patients who claimed violations of privacy and liberty rights. The appellate court determined that the claims were properly

dismissed. See *Abigail Alliance*, 495 F.3d 695, 703-07 (surveying the Nation’s history of drug regulation and holding that based upon that history, terminally ill patients have no “deeply rooted” due process right of access to investigational new drugs that have undergone some testing, but that FDA has not approved, citing *Washington v. Glucksberg*, 521 U.S. 702, 720-21 (1997); *Mitchell v. Clayton*, 995 F.2d 772, 775 (7th Cir. 1993) (“a patient does not have a constitutional right to obtain a particular type of treatment or obtain treatment from a particular provider”); *United States v. Burzynski Cancer Research Inst.*, 819 F.2d 1301, 1313-14 (5th Cir. 1987) (holding cancer patients had no “constitutional right to obtain medical treatment that is encompassed by their right to privacy”); *Carnohan v. United States*, 616 F.2d 1120, 1122 (9th Cir. 1980) (“Constitutional rights of privacy and personal liberty do not give individuals the right to obtain [an unapproved drug] free of the lawful exercise of government police power.”); *Rutherford v. United States*, 616 F.2d 455, 457 (10th Cir. 1980) (rejecting terminally ill cancer patients’ asserted constitutional right of access to unapproved drugs, and holding that “the patient[‘s]...selection of a particular treatment, or at least a medication, is within the area of governmental interest in protecting public health”), *on remand* from 442 U.S. 544 (1979), *cert. denied*, 449 U.S. 937 (1980)).

CTL’s petition reveals a misunderstanding of the scientific and regulatory processes underlying review of a BLA by FDA. CTL contends that the U.S. Government has a moral and legal obligation to administer its regulation of drugs for life-threatening and terminal diseases in a compassionate and timely manner. FDA has deep sympathy for the plight of patients who have exhausted their treatment options, but Congress requires FDA to make approval decisions based solely upon scientific data. FDA cannot disregard the clear statutory requirements set out by Congress, which require that every drug approval be based on rigorous scientific evidence, including drugs intended to treat a life-threatening disease. FDA reviewed the existing BLA for Provenge in a timely fashion, and its Complete Response Letter appropriately requested additional scientific data to satisfy the statutory requirements for approval. See, “Dendreon Receives Complete Response Letter from FDA for Provenge® Biologics License Application,” May 9, 2007, available at <http://investor.dendreon.com/ReleaseDetail.cfm?ReleaseID=241649> (accessed May 19, 2009).

VI. Conclusion

FDA shares the concerns raised by CTL regarding the need for treatment options for advanced prostate cancer. The agency has implemented programs designed to expedite the review and approval of promising new treatments for cancer and other life-threatening diseases, and continues to work to improve those programs. In addition, through the Office of Special Health Issues¹² (OSHI) [Footnote: Information is available at <http://www.fda.gov/oashi/home.html>], FDA has a longstanding practice of interacting with prostate cancer patients. Through these communications, FDA continues to learn about the needs and preferences of the prostate cancer community.

¹² Information is available at <http://www.fda.gov/oashi/home.html>

After careful consideration of the issues raised in CTL's petition, we decline to reconsider our decision to not immediately approve Provenge. As explained in CBER's Complete Response Letter to Dendreon, the scientific data in the Provenge BLA were not sufficient to conclude that Provenge is safe and effective for the treatment of prostate cancer, or that its manufacturing plant satisfies the relevant chemistry, manufacturing and control requirements. FDA's decision not to approve Provenge at this time was proper and in accordance with the biologics license approval requirements under the PHSA.

We remain committed to working with Dendreon to facilitate its activities in pursuit of licensure for Provenge. We look forward to receiving Dendreon's amendment to its existing BLA so that we may review this information expeditiously.

Sincerely,

/s/ David Horowitz

David J. Horowitz, J.D.
Assistant Commissioner for Policy

Cc: Division of Dockets Management (HFA-305)