

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

CARETOLIVE, et al.,	:	
	:	
Plaintiffs,	:	Case No. C2-07-729
	:	
v.	:	JUDGE FROST
	:	
ANDREW VON ESCHENBACH, et al.,	:	Magistrate Judge King
	:	
Defendants.	:	

**DEFENDANTS' MEMORANDUM IN OPPOSITION TO PLAINTIFF'S
MOTION FOR EMERGENCY PRELIMINARY INJUNCTIVE RELIEF**

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INTRODUCTION

Plaintiff CareToLive (“CTL”), which characterizes itself as an association of cancer patients, patient families, doctors, investors and advocates (Amended Complaint (“Am. Compl.”) at 2), brought suit against various officials of the Food and Drug Administration (“FDA”) challenging the agency’s failure to grant immediate approval to a biologics license application (“BLA”) for Provenge, a biological product intended to treat a particular type of metastatic prostate cancer. CTL seeks preliminary injunctive relief enjoining FDA to allow the immediate marketing and distribution of Provenge.

As discussed below, FDA has reasonably determined that the scientific data are not currently sufficient to conclude that Provenge is safe and effective for the treatment of prostate cancer. FDA has therefore issued a so-called Complete Response Letter to the drug’s sponsor, Dendreon Corp., requesting additional data. Dendreon has not challenged FDA’s decision to issue the letter and is currently in the process of gathering the requested data. The issuance of a Complete Response letter, with a request for additional data, does not signal the end for a product. Rather, it is an intermediate step that the agency sometimes must take to assure it has sufficient data to establish efficacy and/or safety prior to licensure. While FDA is sympathetic to the fact that there are very limited treatment options for the type of prostate cancer Provenge is intended to treat, FDA cannot disregard the clear statutory requirements set out by Congress, which mandate that every drug approval be based on rigorous scientific evidence, even if the drug is intended to treat a life-threatening disease.

Under these circumstances, CTL’s lawsuit is both meritless and premature. FDA’s decision to issue a Complete Response Letter seeking additional data, rather than granting

immediate approval to the Provenge BLA, was plainly reasonable, and there is no basis for the Court to intervene on CTL's behalf in an ongoing administrative process involving FDA and Dendreon, the drug's sponsor. Indeed, CTL fails to provide *any* legal analysis in support of its claims, relying instead upon testimonials regarding the supposed efficacy of Provenge, editorials advocating a different standard for drug approvals, wild conspiracy theories that lack a shred of supporting evidence, and reckless, *ad hominem* attacks on reputable scientists which border on defamatory and have no place in a court of law. For all of its intemperate and inflammatory allegations, baseless assertions, and bald speculation, CTL's complaint fails to state a cognizable legal claim, and its motion for preliminary injunction is utterly without foundation.

As will be demonstrated in the defendants' forthcoming motions to dismiss,¹ this Court lacks subject matter jurisdiction over CTL's claims and, even if it had jurisdiction, those claims fail to state a cause of action upon which relief can be granted. As such, this Court need not, and should not, even reach CTL's motion for preliminary relief because this action has no jurisdictional basis and it should be disposed of promptly under Rule 12 of the Federal Rule of Civil Procedure. In any event, FDA's decision to issue a Complete Response Letter with respect to Dendreon's Provenge BLA was not arbitrary and capricious, an abuse of discretion, or contrary to law. CTL therefore cannot prevail on a claim under the Administrative Procedure Act ("APA"), the only applicable waiver of sovereign immunity that would permit CTL's official capacity claims to go forward. Nor has CTL demonstrated that it or its members would suffer irreparable harm in the absence of preliminary injunctive relief, that the issuance of injunctive

¹ Defendants will file one motion to dismiss CTL's official capacity claims, and a simultaneous motion on behalf of defendants Pazdur and Scher to dismiss the individual capacity claims CTL improperly seeks to assert against them.

relief would not harm others, or that such relief would serve the public interest. Accordingly, its motion for preliminary injunction must be denied.

BACKGROUND

1. Statutory and Regulatory Scheme

Biological products are defined under the Public Health Service Act (“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). They have been subject to federal licensing requirements and regulation for over a century. Biological products can also be drugs, and are generally subject to the same statutory and regulatory requirements that apply to all drugs.²

The Food, Drug and Cosmetic Act (“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* (1) a drug that is “not generally recognized, among experts qualified by scientific training and experience . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof,” *or* (2) a drug that, “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).

² See 42 U.S.C. § 262(j) (stating that the FDCA applies to biological products subject to regulation under 42 U.S.C. § 262, except that a product required to have an approved BLA under § 262(a) need not have an approved new drug application (“NDA”) under the FDCA); *United States v. Pro-Ag., Inc.*, 796 F. Supp. 1219, 1224 (D. Minn. 1991) (“all biologics by definition are drugs”).

a. Drug and Biological Product Approval Process

Under the FDCA, a “new drug” cannot be distributed in interstate commerce until the drug’s sponsor submits a New Drug Application (“NDA”) to FDA and obtains the agency’s approval. *See* 21 U.S.C. §§ 331(d), 355(a). If the new drug is a biological product, the drug’s sponsor must seek FDA’s approval by filing a BLA for the product, pursuant to the PHSA. 42 U.S.C. § 262.

Clinical testing on humans is usually a prerequisite for the approval of a new drug. Because clinical testing would otherwise be barred by the FDCA’s general prohibition on the distribution of unapproved new drugs, the FDCA permits FDA to promulgate regulations that allow the distribution of unapproved drugs “intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs.” 21 U.S.C. § 355(i)(1).

Before testing a new drug on humans – whether a biologic or another type of drug – the drug’s sponsor must submit an investigational new drug application (“IND”) to FDA. *See* 21 C.F.R. § 312.2 (specifying that IND regulations apply to clinical investigations of drugs to be approved under the FDCA and to biologics to be licensed under the PHSA). Among other things, the IND must describe the protocols for the planned clinical tests. *Id.* § 312.23(a)(6). FDA regulations describe the steps that must be taken for IND clinical trials as a three-phase process. *Id.* § 312.21.

Generally, Phase 1 involves the initial experiments introducing the new drug into human subjects. A Phase 1 study involves a small number of subjects, and is “designed to determine the metabolism and pharmacologic actions of the [new] drug in humans, the side effects associated

with increasing doses, and, if possible, to gain early evidence on effectiveness.” *Id.*

§ 312.21(a)(1). Phase 2 typically involves a well-controlled, closely monitored evaluation of the drug. *Id.* § 312.21(b). Phase 2 trials evaluate “the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug.” *Id.* Phase 3 usually involves the evaluation of the drug in a large clinical trial or trials, “to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling,” as a predicate to approval of the drug. *Id.* § 312.21(c).

Once the sponsor of a biological product has completed the clinical trial process, it can submit a BLA in accordance with 21 C.F.R. § 601.2(a). The required documentation in a BLA provides critical information for FDA’s evaluation of the biological drug, including the results of clinical trials, the composition of the drug, manufacturing information, and sample labeling. *Id.* FDA will not consider a BLA to be filed until all pertinent data have been received by the agency. *See id.* The fact that FDA considers a BLA to have been filed does not mean that there is sufficient evidence for FDA to approve it. A team of experts at FDA reviews the complex information submitted in the BLA, weighing the benefits and risks of the drug.

FDA will approve a BLA application for a new biological drug if, among other things, the BLA demonstrates that the drug 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.* § 262(a)(2)(C)(i)(II) – so-called “CMC” or chemistry, manufacturing, and controls. FDA’s regulations further define these

standards. “Safety” means “the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.” 21 C.F.R. § 600.3(p).

“Purity” means “relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product.” *Id.* at § 600.3(r). Finally, “potency” means the “specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.” *Id.* at § 600.3(s).

The “potency” requirement for a biological product under the PHS Act thus requires evidence of effectiveness. As part of the Food and Drug Administration Modernization Act of 1997, Congress instructed FDA to “take measures to minimize differences in the review and approval of products required to have approved biologics license applications under section 351 of the [PHSA] (42 U.S.C. 262) and products required to have approved new drug applications under section 505(b)(1) of the [FDCA] (21 U.S.C. 355(b)(1)).” Pub. L. No. 105-115, § 123(f), 111 Stat. 2296, 2324 (1997), *reprinted at* 21 U.S.C. § 355 note. The following year, FDA issued an industry guidance citing this provision and discussing “the quantitative and qualitative standards for demonstrating effectiveness of drugs *and* biologics.” FDA, “Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,” May 1998, at 2, 3 (emphasis added) (hereinafter, FDA, “Providing Clinical Evidence of Effectiveness”), *available at* <http://www.fda.gov/cder/guidance/1397fnl.pdf>.

As indicated in the industry guidance, FDA applies the same general efficacy standards to BLAs and NDAs. Under those standards, FDA rejects NDA approval if, *inter alia*, the

investigation reports submitted with the application fail to include “adequate tests . . . to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling,” or if the information available to FDA regarding the drug under consideration is “insufficient . . . to determine whether such drug is safe for use.” 21 U.S.C. § 355(d)(1) & (d)(4). Likewise, FDA must reject approval of an NDA if “there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have,” as established by “adequate and well-controlled investigations, including clinical investigations,” conducted by qualified experts. 21 U.S.C. § 355(d) & (d)(5).³ *See also* FDA, “Providing Clinical Evidence of Effectiveness, at 3 (stating that with respect to the quantity of evidence needed to establish a drug’s effectiveness by substantial evidence, “it has been FDA’s position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own.” The guidance goes on to state that while FDA has been flexible in its interpretation, in cases in which it has relied on one study, that study was “of excellent design [and] provided highly reliable and statistically strong evidence of an important clinical benefit.”).

³ FDA regulations for new drugs at 21 C.F.R. § 314.126(b) describe an “adequate and well-controlled study” as having *all* of the following characteristics: (1) a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the study protocol; (2) a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect; (3) a subject selection method that provides adequate assurance that subjects have the disease being studied; (4) a method of assigning patients to treatment and control groups to minimize bias; (5) adequate measures to minimize bias on the part of subjects, observers, and data analysts; (6) well-defined and reliable methods of assessing subjects’ responses; and (7) an analysis of the results which is adequate to assess the effects of the drug and a description of the results and the analytical method in the report of the study. These regulations must be rigorously followed. *See, e.g., Warner-Lambert Co. v. Heckler*, 787 F.2d 147 (3d Cir. 1986) (upholding Commissioner’s rejection of all 31 studies submitted by drug’s sponsors for failure to fulfill regulatory criteria).

i. “Fast Track” Processing

FDA has developed initiatives to speed its evaluation of the safety and effectiveness of certain drugs, including its “Fast Track” program. Such programs 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 who 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> (May 2006).⁴ A drug is eligible for “Fast Track” review 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). “Fast Track” review has no relation to the sufficiency of a sponsor’s complete product approval application. In fact, “Fast Track” designation can be requested and granted at any time during (or after) the investigational stage, long before an approval application is ever filed. 21 U.S.C. § 356(a)(2) & (3). Moreover, FDA can review *portions* of the product approval application for a fast track product before the sponsor submits a *complete* application. 21 U.S.C. § 356(c)(1). Although FDA processes drug applications in the “Fast Track” program more

⁴ FDA’s “subpart E” regulations are an integral part of FDA’s “Fast Track” programs. *See* <http://www.fda.gov/cder/guidance/5244fnl.htm>. 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 C.F.R. § 312.80. The procedures recognize that the agency should exercise the broadest flexibility in applying the statutory standards to these therapies. *Id.* The expedited procedures include, for example, early meetings with FDA to discuss study design and FDA monitoring of the progress of clinical studies. 21 C.F.R. §§ 312.82, 312.87.

expeditiously than other applications, it must apply the same standard of approval to all drugs. *See* 21 U.S.C. §§ 355b-d.

ii. Advisory Committees

In some instances, FDA seeks advice from advisory committees comprised of various outside experts, the primary role of which is to provide independent expert advice that will contribute to the quality of the agency's decision-making. *See generally* 21 C.F.R. Pt. 14. Voting members of advisory committees, with limited exceptions not applicable here, are appointed as FDA "special government employees" ("SGEs"). 21 C.F.R. § 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 matter 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).

In addition, 21 U.S.C. § 355(n)(4) requires each member of an advisory committee reviewing drug or biologics applications to disclose all conflicts of interest the member may have with the work to be undertaken by the committee and prohibits the member from voting on any matter where he or his immediate family could gain financially from the advice given to FDA. However, FDA (by delegation from the Secretary of Health and Human Services) may grant a waiver if such waiver is "necessary to afford the panel essential expertise," except that a waiver

may not be granted for a member of an advisory committee when the member's own scientific work is involved. 21 U.S.C. § 355(n)(4).

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 also by medical product developers and often 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 implicate government conflict of interest rules. *See* FDA, "Policies and Procedures for Handling Conflicts of Interest with FDA Advisory Committee Members, Consultants, and Experts," *available at* <http://www.fda.gov/oc/advisory/conflictinterest/policies.html>.

Conflict of interest screening is conducted on a meeting-by-meeting basis. The scope of conflicts that may preclude SGE participation changes with the subject matter of each meeting. Individuals are not "removed" from a committee because of a conflict of interest, but unless they obtain the proper waivers, they are prohibited from participating in the relevant meeting discussion because of such conflicts with particular matters before the committee. *Id.*

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 C.F.R. § 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. FDA Responses to a BLA

In response to a BLA, FDA may refuse to file it if it is incomplete, 21 C.F.R. § 601.2; FDA, “Refusal to File Procedure for Biologics License Applications,” SOPP 8404, *available at* <http://www.fda.gov/cber/regsopp/8404.htm>; approve it, 21 C.F.R. § 601.4(a); deny it and provide the applicant the opportunity for a hearing, *id.* § 601.4(b); or, if there are deficiencies in the BLA, send a “Complete Response” letter declining to approve the BLA in its current form and requesting additional information from the sponsor, *Applications for Approval to Market a New Drug*, 69 Fed. Reg. 43351, 43352 (July 20, 2004). As discussed below, FDA’s May 8, 2007 letter regarding Dendreon’s BLA for Provenge was a “Complete Response” letter. Such letters “ensure a consistent approach to informing sponsors of needed changes before we can approve an application, *with no implication as to the ultimate approvability of the application.*” *Id.* (emphasis added.)

2. Statement of Facts

Provenge is a biological product intended to treat a particular type of metastatic prostate cancer. Am. Compl. ¶ 15. Dendreon has been studying its safety and effectiveness in clinical trials pursuant to an IND submitted to FDA in 1996. *See* Cellular, Tissue and Gene Therapies (“CTGT”) Advisory Committee Meeting, March 29, 2007, Transcript (“Transcript”), at 20, *available at* <http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4291T1.pdf>.⁵ FDA granted Dendreon’s request for “Fast Track” designation in late 2005. *See* Dendreon Corp., “Dendreon Announces FDA Grants Fast Track Status for Provenge,” Nov. 7, 2005, *available at*

⁵ The March 29, 2007, Advisory Committee Meeting Transcript is already before the Court as Exhibit C to Plaintiff’s Motion for Emergency Preliminary Injunctive Relief.

<http://investor.dendreon.com/ReleaseDetail.cfm?ReleaseID=178878>. Dendreon submitted its BLA for Provenge in late 2006, and FDA considered it to be filed in January 2007. *See* Am. Compl. ¶ 27. Because Provenge is a therapy that uses a patient's own cells to prepare a final product designed for infusion back into the patient to activate his immune system against the cancer cells, the regulatory responsibility for reviewing and, ultimately, approving or denying approval of the BLA rests with the Office of Cellular, Tissue and Gene Therapies ("OCTGT") in FDA's Center for Biologics Research and Evaluation ("CBER"). *Id.* ¶¶ 14, 16, 29.

As part of its review, CBER sought the advice of its CTGT Advisory Committee. Am. Compl. ¶¶ 29, 33. CBER decided to augment this standing advisory committee with prostate cancer experts. To do so, it sought recommendations from FDA's Office of Oncologic Drug Products ("OODP"), directed by defendant Dr. Richard Pazdur, in a different product center at FDA, the Center for Drug Evaluation and Research ("CDER"); OODP evaluates other prostate cancer therapies and works with its own advisory committee. *See id.* ¶ 33. 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 individual defendant Dr. Howard Scher, for conflicts and granted waivers in accordance with 18 U.S.C. § 208(b)(3) and 21 U.S.C. § 355(n)(4). Transcript, at 8-10. In addition, both Dendreon and FDA prepared briefing documents, which were circulated to the advisory committee members before the meeting and made publicly available on FDA's website. *See* Dendreon Briefing Document, and FDA Clinical Briefing Document, Statistical Briefing Document, and Chemistry, Manufacturing, and Controls ("CMC") Briefing Document, available at <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4291B1-00-index.htm>.

At the meeting, both Dendreon and FDA discussed their analyses of the Provenge BLA, including the clinical trial data. As evidence of efficacy, 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 succeeded in showing that the drug had a treatment effect of delaying disease progression. Transcript, at 22, 43, 155-57, 164, 169; FDA Clinical Briefing Document, 4, 24, 35-36. In fact, the second study was terminated prematurely after the first study's negative results indicated that the second study would not meet its designated endpoint, delaying time to disease progression, resulting in enrollment of only 98 patients for that 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 had shown a statistically significant difference in survival (approximately 4.5 months) in patients treated with Provenge as compared to placebo. Transcript, at 37, 42, 151, 169; FDA Clinical Briefing Document, 37. However, the second study did not show a statistically significant survival difference. Transcript, at 151, 164, 169; FDA Clinical Briefing Document, 35, 37. Moreover, neither study was designed *a priori* to measure survival as the 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 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 noted that the survival analyses were *post hoc* in nature, making the results difficult to interpret, that the studies were performed with a small sample size (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 its Clinical Briefing Document, FDA 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 for the survival analyses.

FDA Clinical Briefing Document, at 30; *see also* FDA Statistical Briefing Document, at §§ 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 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 subjects experienced CVA’s in the treatment group compared with controls”). While FDA recognized that the difference was not statistically significant, it indicated that the data showed a potential safety signal. *Id.* at 169; FDA Clinical Briefing Document, at 45.

After discussion, the advisory committee members were asked to vote on whether the evidence established that the drug was safe and effective. They voted unanimously in the affirmative with respect to safety. After some debate over the standard for establishing efficacy, CBER explained that the question was whether there was “substantial evidence” that the drug was effective, but provided no further explanation as to what “substantial evidence” means under the FDCA. The committee then voted 13-4 in the affirmative on efficacy. *Id.* at 370-89.

CBER continued its review and, on May 8, 2007, issued a Complete Response Letter to Dendreon declining to approve the BLA in its current form because of various deficiencies.⁶ *See* Am. Compl. ¶ 43; Dendreon Corp., “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&Header=News>. FDA requested that Dendreon submit additional information with respect to the CMC section of the BLA. *Id.* In addition, FDA asked Dendreon to submit additional clinical data in support of its efficacy claim. *Id.* Dendreon has since met with FDA to discuss the additional data required to support licensure and indicated that it intends to proceed with its new Phase 3 study designed to

⁶ Defendants are not attaching the Complete Response Letter to this memorandum because it is part of a BLA file for an unapproved product and is, therefore, unavailable for public disclosure under FDA regulations. 21 C.F.R. § 601.51(d). In addition, the letter may contain trade secret and confidential commercial information belonging to Dendreon, which FDA is likewise prohibited from disclosing to the public. 21 C.F.R. § 20.61. Defendants cannot provide the letter or any other part of the administrative record to CTL unless and until a protective order is in place prohibiting further disclosure of Dendreon’s proprietary information. *See* 21 C.F.R. § 20.86. Defendants will provide the Complete Response Letter to the Court, *in camera* and under seal, should the Court wish to review it at this time. However, defendants believe that there are sufficient grounds to defeat CTL’s motion for preliminary injunction in the publicly available advisory committee documents and on Dendreon’s website, and that the Court need not review the Complete Response Letter itself in order to rule on CTL’s motion.

measure survival and to submit such data to FDA when it becomes available. *See* Dendreon Corp., “Dendreon Announces FDA Confirms Data Required for Provenge Licensure,” May 31, 2007, *available at*

<http://investor.dendreon.com/ReleaseDetail.cfm?ReleaseID=246500&Header=News>.⁷

Plaintiff CTL submitted a Citizen Petition to FDA dated July 26, 2007. *See* Original Complaint (“Compl.”), Exhibit B. FDA’s Docket Branch received the Citizen Petition on July 27, 2007, just three days before CTL initiated this lawsuit, and assigned it docket number 2007P-0297. Under FDA regulations, a Citizen Petition is the mechanism for formally asking the agency to take a particular action, and is a prerequisite to filing suit on the subject. *See* 21 C.F.R. §§ 10.25, 10.30, 10.45. In its Citizen Petition, CTL urges the Commissioner of Food and Drugs to “reverse [FDA’s] decision to deny immediate approval to Provenge.” Compl., Exhibit B. FDA regulations require the Commissioner, within 180 days of receipt of a Citizen Petition, to either approve the petition, deny the petition, or, if more time is required, issue a tentative response. 21 C.F.R. § 10.30(e)(2). On July 30, 2007, FDA issued an acknowledgment of the receipt of CTL’s Citizen Petition, but has not yet otherwise responded. *See* <http://www.fda.gov/ohrms/dockets/dockets/07p0297/07p-0297-ack0001-vol11.pdf>.

On July 30, 2007, CTL brought this suit, alleging a host of claims against various FDA officials in both their official and individual capacities. Compl. (Dkt #2). CTL’s complaint also purported to seek preliminary injunctive relief but, following a Local Rule 65.1 informal

⁷ At the advisory committee meeting, even before FDA’s decision to issue a Complete Response Letter, Dendreon stated its intention to complete an additional Phase 3 study with a significantly greater patient population of 500 and powered to measure survival as the primary endpoint. Transcript, at 84.

conference on August 29, 2007, the Court denied CTL's motion without prejudice for failure to comply with Local Rule requirements. *See* Order (August 31, 2007) (Dkt # 20). The Court also ordered CTL to file an amended complaint "that clearly and specifically sets forth its causes of action so that both the Court and Defendants can understand the nature of the claims Plaintiff seeks to pursue." *Id.* CTL filed an amended complaint on September 5, 2007, once again purporting to assert a variety of constitutional, statutory and declaratory claims, and naming as defendants FDA Commissioner Andrew von Eschenbach and Department of Health and Human Services Secretary Mike Leavitt, in their official capacities, as well as Richard Pazdur, an FDA employee, and Howard Scher, an advisory committee member (and SGE), both of whom are named in their official and individual capacities. Am. Compl. (Dkt # 22).

Subsequently, on September 10, 2007, CTL, filed a renewed motion for a preliminary injunction. *See* Plaintiff's Motion for Emergency Preliminary Injunctive Relief (and supporting Memorandum) (Dkt # 23) (hereafter "Pl. Mem."). In its motion, CTL seeks an order from this Court "enjoining the FDA from denying the marketing and distribution of Provenge," and/or declaring "that the FDA must correct the ongoing due process denial of CareToLive by immediately providing them their due process rights as afforded them by being citizens of these United States of America heretofore denied." Pl. Mem. at 54.

ARGUMENT

In determining whether to issue a preliminary injunction, a court must consider the following four factors: "(1) whether the movant has a 'strong' likelihood of success on the merits; (2) whether the movant would otherwise suffer irreparable injury; (3) whether issuance of a preliminary injunction would cause substantial harm to others; and (4) whether the public

interest would be served by issuance of a preliminary injunction.” *Leary v. Daeschner*, 228 F.3d 729, 736 (6th Cir. 2000) (quoting *McPherson v. Mich. High Sch. Athletic Ass’n*, 119 F.3d 453, 459 (6th Cir. 1997) (*en banc*)); *see also* *Gonzales v. Nat’l Bd. of Med. Exam’rs*, 225 F.3d 620, 625 (6th Cir. 2000); *Am. Sys. Consulting, Inc. v. Devier*, No. 2:07-cv-818, 2007 WL 2670049, at *2 (S.D. Ohio Sept. 7, 2007) (Frost, J.).

These factors are to be balanced against one another rather than considered as prerequisites to the entry of preliminary relief. *Abney v. Amgen*, 443 F.3d 540, 546-47 (6th Cir. 2006); *Leary*, 228 F.3d at 736. This does not mean, however, that where the asserted harm is great, a movant need only prove a “substantial case” on the merits, as CTL erroneously asserts. Pl. Mem. at 22-24. Notwithstanding the Eleventh Circuit caselaw on which CTL relies, the Sixth Circuit has never adopted a standard under which a movant can obtain preliminary relief without demonstrating probable success on the merits. “Although no one factor is controlling, a finding that there is simply no likelihood of success on the merits is usually fatal.” *Gonzales*, 225 F.3d at 625; *see also* *Abney*, 443 F.3d at 547.

Moreover, “[t]he moving party must demonstrate a right to injunctive relief by clear and convincing evidence.” *Am. Sys. Consulting*, 2007 WL 2670049, at *2; *see also* *Leary*, 228 F.3d at 739 (“the proof required for the plaintiff to obtain a preliminary injunction is much more stringent than the proof required to survive a summary judgment motion”). As the Sixth Circuit has explained, this heightened standard of proof is required “because a preliminary injunction is ‘an extraordinary remedy involving the exercise of a very far-reaching power, which is to be applied only in [the] limited circumstances which clearly demand it.’” *Id.* (quoting *Direx Israel, Ltd. v. Breakthrough Med. Corp.*, 952 F.2d 802, 811 (4th Cir. 1991)) (internal citations omitted)

(alteration in original); *see also Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 215 (D.D.C. 1996) (“Injunctive relief is an extraordinary remedy and must be sparingly granted.”).

In this case, CTL has wholly failed to meet its burden of demonstrating a “strong” likelihood of success on the merits. Indeed, it has no likelihood of success whatsoever. As will be demonstrated in the defendants’ forthcoming motions to dismiss, this Court lacks subject matter jurisdiction over CTL’s claims and, even if it had jurisdiction, those claims fail to state a cause of action upon which relief can be granted. In any event, FDA’s action in issuing a Complete Response Letter with respect to Dendreon’s BLA for Provenge was not arbitrary and capricious, an abuse of discretion, or contrary to law, and CTL’s attempts to assert tort and constitutional claims are woefully deficient. Nor has CTL demonstrated that it or its members would suffer irreparable harm in the absence of preliminary injunctive relief, that the issuance of injunctive relief would not harm others, or that such relief would serve the public interest. Accordingly, its motion for preliminary injunction must be denied.

I. CTL HAS NO LIKELIHOOD OF SUCCESS ON THE MERITS

A. CTL’s Claims Are Subject to Dismissal for Lack of Jurisdiction and Failure to State a Claim Upon Which Relief Can be Granted

CTL has no likelihood of success on the merits because, as will be explained in greater detail in the defendants’ forthcoming motions to dismiss, CTL’s complaint is subject to dismissal in its entirety due to lack of jurisdiction and failure to state a claim upon which relief can be granted. Although defendants will not burden the Court with an exhaustive recitation of those arguments in this brief, the principal grounds for dismissal can be summarized as follows.

First and foremost, CTL's challenge to FDA's failure to grant immediate approval to Provenge is premature under the ripeness, finality, and exhaustion of administrative remedies doctrines. The three doctrines overlap and are all "designed, in part, to permit an agency of the Executive Branch to decide issues of administrative law fully before a court intervenes." *Ayuda, Inc. v. Thornburgh*, 948 F.2d 742, 754 (D.C. Cir. 1991), *vacated on other grounds*, 509 U.S. 916 (1993). CTL's primary grievance – that FDA did not grant immediate approval for Provenge, but instead requested more information – implicates the ripeness and finality doctrines because the agency is still in the process of working with the drug sponsor to determine whether further data can be developed that will satisfy the BLA approval standard. FDA's Complete Response Letter was an intermediate step in the BLA administrative process.

In addition, FDA regulations provide that a member of the public must file a citizen petition to request that FDA "take or refrain from taking any form of administrative action," and receive a final response to that petition, before seeking redress in the courts. 21 C.F.R. § 10.45(b). Because CareToLive filed a citizen petition with the FDA just three days before it initiated this lawsuit, it has failed to exhaust the administrative remedy required by FDA regulations. CTL's lawsuit is therefore premature under all of these doctrines and must be dismissed. Furthermore, CTL lacks standing because it has not established that it has suffered an injury-in-fact that is actual or imminent, not conjectural or hypothetical, caused by FDA, and redressable by the Court. Accordingly, this Court lacks jurisdiction over CTL's claims.

CTL's due process and equal protection claims under Count I are deficient also because they fail to state a claim for relief. To establish a due process interest in unfettered access to an unapproved biologics product, CTL has the burden of showing that this interest is "objectively,

deeply rooted in this Nation's history and tradition" and "implicit in the concept of ordered liberty, such that neither liberty nor justice would exist if [it] were sacrificed." *Washington v. Glucksberg*, 521 U.S. 702, 721 (1997) (internal quotation marks and citations omitted). CTL has not and cannot begin to meet this standard. Indeed, every appellate court to consider whether there is a substantive due process right to bypass FDA's approval requirement and obtain unapproved products has squarely rejected such a claim, including a recent decision by the *en banc* D.C. Circuit. *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695, 697 (D.C. Cir. 2007) (*en banc*); *Rutherford v. United States*, 616 F.2d 455, 457 (10th Cir.), *cert. denied*, 449 U.S. 937 (1980). *See also 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 to obtain treatment from a particular provider"); *United States v. Burzynski Cancer Research Inst.*, 819 F.2d 1301, 1313-14 (5th Cir. 1987) (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.").

CTL's equal protection allegations fare no better. CTL alleges defendants "conspired to . . . deny equal protection of law to [prostate cancer patients] with the intent to harm this classification of persons for their own benefit." Am. Compl., Count II, ¶ N. But a conspiracy claim must be dismissed if it merely alleges in conclusory terms that a conspiracy exists and that the alleged conspirators had economic incentives to conspire together, but "does not set forth a single fact in a context that suggests an *agreement*." *Bell Atlantic Corp. v. Twombly*, 550 U.S.

___, 127 S. Ct. 1955, 1969 (2007) (emphasis added). “A plaintiff’s obligation to provide the ‘grounds’ of his ‘entitle[ment] to relief’ requires more than labels and conclusions, and a formulaic recitation of the elements of a cause of action will not do.” *Id.* at 1964-65 (citations omitted). Any claim of an equal protection conspiracy therefore must be dismissed for utter lack of supporting factual allegations.

CTL’s claims in Count II under the post-Civil War statutes against civil rights conspiracies likewise fail. Sovereign immunity bars §§ 1985(3) and 1986 suits brought against the United States and its officers acting in their official capacity. *Davis v. U.S. Dep’t of Justice*, 204 F.3d 723, 726 (7th Cir. 2000); *Affiliated Prof’l Home Health Care Agency v. Shalala*, 164 F.3d 282, 286 (5th Cir. 1999).

Because all of CTL’s claims are thus subject to dismissal on their face, CTL has *no* likelihood of success on the merits and its motion for emergency preliminary injunctive relief should be denied for that reason alone.⁸

B. CTL’s Claims Are Meritless

Even if this Court were to allow some portion of CTL’s claims to proceed to the merits, CTL still has no likelihood of success because its claims are wholly meritless. CTL challenges FDA’s failure to grant immediate approval to Dendreon’s BLA for Provenge and seeks an order

⁸ Although the preliminary injunctive relief CTL seeks is directed solely at FDA itself, the individually named defendants also have numerous defenses available to them which pose an absolute bar to the claims CTL seeks to assert against them and which will be raised in their motion to dismiss to be filed on October 5, 2007. CTL’s motion does not – and indeed, cannot – seek equitable relief against any defendant sued in his individual capacity, as any relief ordered by the Court could only be effectuated by FDA itself. Accordingly, this memorandum is filed solely on behalf of the defendants sued in their official capacities and does not purport to speak to the claims for damages asserted against Drs. Pazdur and Scher in their individual capacities.

from this Court preliminarily enjoining FDA from denying the marketing and distribution of Provenge. *See* Pl. Mem. at 4, 54. Thus, at its core, this action centers on the merits of FDA's decision not to grant immediate approval to the Provenge BLA. FDA's decision was based on the agency's scientific judgment after considering all relevant factors and is entitled to great deference. Accordingly, even if CTL could establish this Court's jurisdiction, which it cannot, CTL cannot demonstrate that it is likely to succeed on the merits of its claim.

1. FDA's Administrative Decision Not To Immediately Approve the Provenge BLA Is Entitled to Deference

CTL's likelihood of success on the merits of its claim must be considered in light of the applicable standard of review. FDA's administrative decisions are subject to review by the Court under the APA, and may be disturbed only if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). This standard is highly deferential to the agency. *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971). Indeed, "there is a presumption in favor of the validity of the administrative action." *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 216 (D.D.C. 1996) (quoting *Ethicon, Inc. v. FDA*, 762 F. Supp. 382, 386 (D.D.C. 1991)). The reviewing court must consider whether the agency's decision was based upon consideration of the relevant factors and whether there has been a clear error of judgment. *Overton Park*, 401 U.S. at 416. However, "under this narrow scope of review, '[t]he court is not empowered to substitute its judgment for that of the agency.'" *Bristol-Myers Squibb Co.*, 923 F. Supp. at 216 (quoting *Overton Park*, 401 U.S. at 416). In applying the arbitrary and capricious standard, the court reviews the administrative record

assembled by the agency and does not undertake its own fact finding. *See, e.g., Camp v. Pitts*, 411 U.S. 138, 142 (1973).

When, as here, an agency's decision is based upon an evaluation of scientific information within the agency's area of technical expertise, its decisions are traditionally accorded great deference. *Southwestern Pa. Growth Alliance v. Browner*, 121 F.3d 106, 117 (3d Cir. 1997); *Fed. Power Comm'n v. Fla. Power & Light Co.*, 404 U.S. 453, 463 (1972). Courts "review scientific judgments of the agency 'not as the chemist, biologist, or statistician that [they] are qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to certain minimal standards of rationality.'" *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) (quoting *Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976)); *see also Int'l Fabricare Inst. v. EPA*, 972 F.2d 384, 389 (D.C. Cir. 1992) ("The rationale for deference is particularly strong when [the agency] is evaluating scientific data within its technical expertise."). Affording the highest level of deference to an agency's scientific judgments is particularly apt when the judgment relates to a choice of an appropriate scientific methodology. *See Solite Corp. v. EPA*, 952 F.2d 473, 489-90 (D.C. Cir. 1991); *see also Nat'l Ass'n of Metal Finishers v. EPA*, 719 F.2d 624, 657 (3d Cir. 1983) ("the choice of scientific data and statistical methodology to be used is best left to the sound discretion of the [agency]"), *rev'd on other grounds*, 470 U.S. 116 (1985).

Such deference has repeatedly been applied in cases under the FDCA. *See, e.g., Serono Labs, Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998) (FDA's determination of whether the active ingredient in a generic was the same as in a brand-name drug for purposes of the FDCA rests on "the 'agency's evaluations of data within its area of expertise,' and hence is entitled to a

‘high level of deference’ from this court”) (quoting *A.L. Pharma v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995)); *Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996) (“FDA possesses the requisite know-how to conduct such [scientific] analyses, by sifting through the scientific evidence to determine the most accurate and up-to-date information regarding a particular drug We therefore defer to its reasonable findings”); *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995) (FDA’s “judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA’s expertise and merit deference from us.”); *Tri-Bio Labs., Inc. v. United States*, 836 F.2d 135, 142 (3d Cir. 1987) (“in evaluating scientific evidence in the drug field, the FDA possesses an expertise entitled to respectful consideration by this court”), *cert. denied*, 488 U.S. 818 (1988).

2. FDA’s Decision Not To Immediately Approve Provenge Was Proper

Although the full administrative record is not presently before the Court, the public advisory committee documents provide more than sufficient support for FDA’s decision not to grant immediate approval to the Provenge BLA. These documents reflect FDA’s reasoned decision-making involving the application of highly scientific and technical statistical principles. Even this limited portion of the administrative record demonstrates that FDA’s decision was not arbitrary and capricious.

FDA can approve a biological product, such as Provenge, only if the BLA demonstrates that it is safe, pure, and potent. 42 U.S.C. § 262(a)(2)(C)(i)(I). Potency is a determination of effectiveness, and requires adequate evidence. 21 C.F.R. § 600.3(s). FDA evaluates effectiveness as set out in its industry guidance on the topic. FDA, “Providing Clinical Evidence of Effectiveness,” at 2-4, available at <http://www.fda.gov/cder/guidance/1397fnl.pdf> (applying

same effectiveness standards to biological product BLAs and new drug NDAs). *See also* FDAMA, Pub. L. No. 105-115, § 123(f), 111 Stat. 2296, 2324 (1997), *reprinted at* 21 U.S.C. § 355 note (instructing FDA to minimize differences in review and approval of biological products required to have BLAs and drugs required to have NDAs); 21 U.S.C. § 355(d) and (d)(5) (requiring FDA to reject NDAs where “there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have,” as established by “adequate and well-controlled investigations, including clinical investigations,” conducted by qualified experts).

Prior to the advisory committee meeting, FDA prepared briefing documents, which provided detailed analyses of Dendreon’s clinical trial data. Those documents, along with the advisory committee transcript, provide ample support for FDA’s finding that the evidence presented in the Provenge BLA did not meet the statutory standard for approval. There is no dispute that both of Dendreon’s Phase 3 clinical trials failed to meet their designated endpoints, *i.e.*, they failed to show that Provenge was effective in delaying disease progression. Transcript, at 22, 43, 155-57, 164, 169; FDA Clinical Briefing Document, 4, 24, 35-36. In addition, Dendreon admitted that the second study was terminated prematurely after the first study’s negative results indicated that the second study would not meet its designated endpoint, resulting in enrollment of only 98 patients for that study, which FDA deemed an insufficient sample size. Transcript, at 162-63; FDA Clinical Briefing Document, at 16-17, 30.

FDA’s industry guidance on clinical effectiveness discusses at length “FDA’s position that Congress generally intended to require at least *two* adequate and well-controlled studies, *each convincing on its own.*” FDA, “Providing Clinical Evidence of Effectiveness,” at 3, *available at* <http://www.fda.gov/cder/guidance/1397fnl.pdf> (emphases added). In FDA’s view,

the sole evidence supporting Dendreon's claim of efficacy was its *post hoc* analysis of the first study showing a statistically significant difference in survival (approximately 4.5 months) in patients treated with Provenge as compared to placebo. Transcript, at 37, 42, 151, 169; FDA Clinical Briefing Document, 37. The second study, however, did not support such a conclusion. Transcript, at 151, 164, 169; FDA Clinical Briefing Document, 35, 37. Moreover, even the analysis of the first study was severely limited from a statistical perspective. Transcript, at 170-71; FDA Clinical Briefing Document, at 4 ("doubts remain about the persuasiveness of the efficacy data"). First, Dendreon admitted that neither of its studies was *a priori* designed to measure survival as the 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").

Second, FDA noted that the survival analyses were *post hoc* in nature, making the data difficult to interpret, and the studies were performed with a small sample size (even the first study had only 127 patients). Transcript, at 151, 170-71, 177-182; FDA Clinical Briefing Document, at 30 (warning that "interpretation of this survival difference should be made with caution" because the "lack of a pre-specified primary method for survival analyses renders it difficult to estimate the Type 1 [false positive] error of this survival analysis" and noting that "[t]he small size of the study makes it more likely that this finding could have occurred by chance").⁹ Indeed, FDA's statistician concluded that "[t]he key efficacy evidence (difference between the two arms in overall survival) for this BLA is based on post-hoc analyses and the

⁹ Dendreon's decision, even prior to FDA's issuance of the Complete Response Letter, to proceed with a new Phase 3 study powered to measure survival and including 500 patients, demonstrates that even Dendreon recognized the weaknesses in its existing clinical trial data. Transcript, at 84.

efficacy evidence is not substantial from a statistical perspective.” FDA Statistical Briefing Document, at § 3.2.

With respect to safety, FDA noted that there was a higher incidence of CVA events (strokes) in Provenge, as compared to placebo. Transcript, at 166; FDA Clinical Briefing Document, at 3 (“approximately three times as many subjects experienced CVA’s in the treatment group compared with controls”). Although FDA recognized that the difference was not statistically significant, it nevertheless viewed such data as a potential safety signal. *Id.* at 169; FDA Clinical Briefing Document, at 45. When weighing the benefits and risks of the drug, FDA was entitled – indeed, expected to – consider this potential safety risk against the questionable efficacy data.

In light of the foregoing factors, FDA’s decision not to approve Provenge at this time, pending the receipt and analysis of additional data, was plainly reasonable. This Court should reject CTL’s invitation to substitute its judgment for FDA’s.

3. CTL’s Allegations Are Unfounded and Immaterial

CTL fails to provide *any* legal analysis in support of the merits of its claims. Instead, its motion is full of testimonials regarding the supposed efficacy of Provenge, citations to editorials and patients’ pleas for a different standard for drug approvals, and conspiracy theories that are not supported by a shred of evidence.

For example, rather than address the shortcomings in the data cited by FDA in its Clinical Briefing Document and during the advisory committee meeting, CTL presents transcripts of interviews with patients who claim that Provenge has benefited them. *See* Pl. Mem. at 9, 13-15. However, anecdotal and testimonial evidence from doctors or patients regarding the safety and/or

efficacy of a new drug is insufficient to meet the standards of the FDCA with respect to establishing safety and effectiveness. As the Supreme Court has observed:

[The FDA drug approval standards] barring anecdotal evidence indicating that doctors “believe” in the efficacy of a drug, [is] amply justified by the legislative history. The hearings underlying the 1962 [Amendments to the FDCA] show a marked concern that impressions or beliefs of physicians, no matter how fervently held, are treacherous.

Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609, 618-19 (1973). The Supreme Court further explained that “[t]he ‘substantial evidence’ requirement reflects the conclusion of Congress . . . that clinical impressions of practicing physicians and poorly controlled experiments do not constitute an adequate basis for establishing efficacy.” *Id.* at 630. The Court also recognized that it is Congress’ policy that underlies the drug approval regulations which provide that “[i]solated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.” *Id.* See *Upjohn Co. v. Finch*, 422 F.2d 944, 951 (6th Cir. 1970) (upholding regulations interpreting “substantial evidence” as a “correct application of the Congressional definition” and finding that testimonial documents do not constitute substantial evidence). See also *Glasser v. Thompson Med. Co.*, 32 F.3d 969, 987-88 (6th Cir. 1994) (characterizing anecdotal drug experience reports as “inherently unreliable, unscientific . . . [and] unhelpful” and “the rankest type of anecdotal evidence”); *Simeon Mgmt. Corp. v. FTC*, 579 F.2d 1137, 1142 (9th Cir. 1978) (anecdotal evidence or statements by doctors that they “believe” a drug is effective do not constitute substantial evidence); *United States v. Sene X Eleemosynary Corp.*, 479 F. Supp. 970, 977 (S.D. Fla. 1979) (general recognition of safety and effectiveness cannot be established by anecdotal evidence or the fact that a number of physicians throughout the country prescribe the drug).

CTL's assertions regarding the substantial demand for the drug and the public criticism of FDA's decision are likewise irrelevant with respect to the merits of CTL's claim. Rather than question FDA's scientific conclusions, a substantial number of the authorities cited by CTL advocate that FDA disregard the statutory and regulatory requirements and apply a different standard of approval to drugs intended to treat life-threatening diseases such as cancer. *See, e.g.*, Pl. Mem. at 7 (quoting Dr. Moyad: "If Provenge is delayed or rejected for several years than not only will I be disappointed but I have to believe some of the opposition to this vaccine will have allowed the science of medicine to completely cloud the human side of medicine."); 20 (quoting Dr. Gottlieb: "[T]he FDA should not be asking for more and more data until the agency finally reaches a comfort level, They [sic] need to make decisions based on the small amounts of data that are typically available when you are studying a rare and terminal disease); 21 (quoting Dr. Schlom: ("[T]he scientific community and regulatory committees ought to rethink the design of clinical vaccine trials and our current approach to measuring the effectiveness of a cancer vaccine."); 24 (citing a "thesis written with the help of a professor at Harvard who would state that when it comes to treatments for serious life threatening conditions that safety alone should be enough for approval").

While FDA is sympathetic to the fact that there are very limited treatment options for the type of prostate cancer Provenge is intended to treat, the arguments advanced above do not provide a basis for FDA to disregard the clear statutory requirements set out by Congress. The FDCA mandates that every drug approval be based on "substantial evidence," even if the drug is intended to treat a life-threatening disease, and FDA properly made its decision by applying that standard to the evidence presented by Dendreon. *See United States v. Rutherford*, 442 U.S. 544,

552 (1979) (there is no exemption from the FDCA’s approval requirements for drugs intended to treat terminal illnesses). CTL’s arguments are thus better addressed to Congress than FDA or this Court. While CTL may believe that FDA has “unjustly erred on the side of safety in balancing the risks and benefits” of new cancer treatments, “arguments about morality, quality of life, and acceptable levels of medical risk” are best aired “in the democratic branches, without injecting the courts into unknown questions of science and medicine.” *Abigail Alliance*, 495 F.3d at 713. Indeed, “[o]ur Nation’s history and traditions have consistently demonstrated that the democratic branches are better suited to decide the proper balance between the uncertain risks and benefits of medical technology, and are entitled to deference in doing so.” *Id.*

Finally, while CTL baldly alleges that Drs. Scher and Pazdur, along with Dr. Maha Hussain (who is not named as a defendant) and others, engaged in a conspiracy to derail the Provenge approval, CTL provides absolutely no support for such allegations. Indeed, its claims are contradicted by the facts here. First, CTL mistakenly implies that by designating Provenge for “Fast Track” review, FDA necessarily made a substantive determination that Dendreon’s BLA had enough data to let the agency make a final decision without requesting more information. Am. Compl. ¶ 45 (“[b]y encouraging and accepting the BLA and placing it on Fast Track status, the FDA had already determined it had sufficient data . . . yet the issuance of the Complete Response Letter . . . was supposedly issued due to a ‘lack of data.’”); Pl. Mem. at 32 (alleging that FDA’s decision to require more data was not sincere given its decision that there was sufficient data to meet the “Fast Track” requirements). But “Fast Track review” designation can be requested and granted at any time during (or after) the investigational stage, long before an approval application is ever filed. 21 U.S.C. § 356(a)(2). In this instance, Dendreon

announced FDA's grant of "Fast Track" designation for Provenge in November 2005, over a year *before* Dendreon submitted its BLA. Dendreon Corp., "Dendreon Announces FDA Grants Fast Track Status for Provenge," Nov. 7, 2005, <http://investor.dendreon.com/ReleaseDetail.cfm?ReleaseID=178878>. Thus, FDA's "Fast Track" designation could hardly have been based on a prediction about whether Dendreon's BLA, which had not yet submitted, would contain sufficient data for FDA to issue a final approval decision without requesting more information.

Second, CTL ignores the fact that FDA had identified all of the flaws in Dendreon's efficacy data prior to the advisory committee meeting, as is evident from FDA's Clinical and Statistical Briefing Documents prepared *before* the meeting, and the fact that FDA's presentation at the meeting occurred *prior to* discussion and vote by the advisory committee members, including Drs. Hussain and Scher. *See generally* Transcript. That Drs. Hussain and Scher happened to agree with FDA's analysis and shared their views both at the advisory committee meeting and in letters to FDA afterward is hardly evidence of a conspiracy. CTL's accusation that FDA was pressured into its decision by the actions of Drs. Hussain and Scher, and Dr. Pazdur (who notably did not speak at the advisory committee meeting and who, as a member of CDER and not CBER, had no regulatory authority over Provenge) rings false.

Moreover, although CTL would prefer otherwise, FDA is not bound by the recommendations of its advisory committees. FDA seeks such input to ensure that it has the benefit of all 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 recommendation a committee may put forth, it is ultimately up to FDA alone to determine whether or not 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 C.F.R. § 14.5; *see also* 21 U.S.C. § 355(n)(8) (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 no final decision has been reached); *Animal Def. Council v. Hodel*, 840 F.2d 1432, 1438 (9th Cir. 1988) (fact that particular recommendations of subordinates and advisory committees may have ultimately 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 at this time because it did not demonstrate the “substantial evidence” of efficacy required for approval.¹⁰ For this reason alone, CTL has no likelihood of success on the merits, and its motion for preliminary injunction should be denied.

II. THE BALANCE OF HARMS AND THE PUBLIC INTEREST MANDATE THE DENIAL OF PRELIMINARY INJUNCTIVE RELIEF

Because CTL has no likelihood of success on the merits of its claims, the Court need not even address the other three preliminary injunction factors – irreparable injury, harm to others, and the public interest. *See Leary*, 228 F.3d at 739 (district court is not required to make findings

¹⁰ This Court should reject CTL’s attempt to set forth its own definition of “substantial evidence,” Pl. Mem. at 37-38, as that term is explicitly defined by statute and further explained in FDA regulations. *See* 21 U.S.C. § 355(d); 21 C.F.R. § 314.126.

on factors that are not dispositive to issuance of preliminary injunction) (*citing Am. Imaging Servs., Inc. v. Eagle-Picher Indus., Inc.*, 963 F.2d 855, 862 (6th Cir. 1992)); *see also Abney*, 443 F.3d at 547 (finding of no likelihood of success is usually fatal); *Gonzales*, 225 F.3d at 625 (same). Nevertheless, the Sixth Circuit has described it as “generally useful” for a district court to analyze all four factors. *Leary*, 228 F.3d at 739. Here, as demonstrated below, the remaining factors likewise weigh against the entry of preliminary injunctive relief.

A. CTL Will Not Suffer Irreparable Harm Absent Preliminary Injunctive Relief

Not only has CTL failed to make the requisite showing of likely success on the merits, it has also failed to demonstrate that it will suffer “immediate and irreparable harm” absent injunctive relief. *Abney*, 443 F.3d at 551. Because CTL’s likelihood of success on the merits is exceedingly slim, CTL “would have to make a very substantial showing of severe irreparable injury” to prevail on its motion. *Nat’l Pharm. Alliance v. Henney*, 47 F. Supp. 2d 37, 41 (D.D.C. 1999). Irreparable injury is a “very high standard,” *Bristol-Myers*, 923 F. Supp. at 220 (quoting *Am. Coastal Line Joint Venture, Inc. v. United States Lines, Inc.*, 580 F. Supp. 932, 936 (D.D.C. 1983)), and requires a showing that, absent relief, the plaintiff “will suffer ‘actual and imminent’ harm rather than harm that is speculative or unsubstantiated.” *Abney*, 443 F.3d at 552 (quoting *Monsanto Co. v. Manning*, 841 F.2d 1126, 1988 WL 19169, at *6 (6th Cir. Mar. 8, 1988)). As the D.C. Circuit has explained:

[T]he injury must be both certain and great; it must be actual and not theoretical. Injunctive relief “will not be granted against something merely feared as liable to occur at some indefinite time,” *Connecticut v. Massachusetts*, 282 U.S. 660, 674, 51 S. Ct. 286, 291, 75 L. Ed. 602 (1931); the party seeking injunctive relief must show that “[t]he injury complained of [is] of such imminence that there is a ‘clear and present’ need for equitable relief to prevent irreparable harm.” *Ashland Oil*,

Inc. v. FTC, 409 F. Supp. 297, 307 (D.D.C.), *aff'd*, 548 F.2d 977 (D.C. Cir.1976) (citations and internal quotations omitted).

Wisc. Gas Co. v. FERC, 758 F.2d 669, 674 (D.C. Cir. 1985). Moreover, “the movant must show that the alleged harm will directly result from the action which the movant seeks to enjoin.” *Id.*

1. The Preliminary Relief CTL Seeks Is Unavailable to It

In its motion, CTL asks that the Court “issue an order enjoining the FDA from denying the marketing and distribution of Provenge as there is clear and convincing evidence that it is safe and effective and/or declare that the FDA must correct the ongoing due process denial of CareToLive by immediately providing them their due process rights as afforded them by being citizens of these United States of America heretofore denied.” Pl. Mem. at 54. Although it is unclear precisely what relief CTL thereby seeks from the Court – whether it be an order requiring FDA to approve Dendreon’s BLA for Provenge (which would be unprecedented) or something less extreme – it appears that what CTL ultimately seeks through this motion is immediate access to the drug for any patient who desires such treatment. Pl. Mem. at 4 (“Plaintiffs seek injunctive relief that would allow the [prostate cancer] patients immediate reasonable access to the immunotherapy Provenge with the advice and consultation from state licensed doctors . . .”).

Such relief, however, is beyond this Court’s ability to grant – not only because the manufacturer of Provenge, Dendreon Corp., is not a party to this case, but also because the only remedy available to CTL, in the event the Court should find merit in its claims, would be to remand the matter back to FDA for further proceedings on Dendreon’s BLA – proceedings that have continued unabated since the issuance of FDA’s Complete Response Letter and that remain

ongoing at this date. The denial of preliminary relief in such circumstances would have no appreciable impact on CTL and cause it no harm whatsoever.

Indeed, it is well established that, even if the administrative record does not support the agency action under review, or the agency did not consider all the relevant factors, or the reviewing court cannot evaluate the challenged agency action on the basis of the record before it, “the proper course, except in rare circumstances, is to remand to the agency for additional investigation or explanation. The reviewing court is not generally empowered to conduct a *de novo* inquiry into the matter being reviewed and to reach its own conclusions based on such an inquiry.” *Fla. Power & Light Co. v. Lorion*, 470 U.S. 729, 744 (1985). As the D.C. Circuit recently explained:

When a final agency action is challenged in the district court, that court “sits as an appellate tribunal [If it] determines that [the] agency made an error of law, the court’s inquiry is at an end: the case must be remanded to the agency for further action consistent with the corrected legal standards.” *PPG Indus., Inc. v. United States*, 311 U.S. App. D.C. 214, 52 F.3d 363, 365 (D.C. Cir. 1995) (internal quotation marks omitted); *see also Esch v. Yeutter*, 278 U.S. App. D.C. 98, 876 F.2d 976, 993 (D.C. Cir. 1989) [**13] (court should not “make the substantive decision” itself).

Neb. HHS v. HHS, 435 F.3d 326, 331 (D.C. Cir. 2006). *See also Kamargo Corp. v. FERC*, 852 F.2d 1392, 1398 (D.C. Cir. 1988) (if court determines that agency has a statutory duty that it failed to exercise, the court should not decide the issue but, instead, should remand the issue to the agency to resolve in the first instance); *Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976) (*en banc*) (courts review scientific judgments of federal agencies “not as the chemist, biologist, or statistician that we are qualified neither by training nor experience to be, but as a reviewing

court exercising our narrowly defined duty of holding agencies to certain minimal standards of rationality”).

This principle is echoed in FDA’s own regulations, which provide that, “upon judicial review of administrative action,”

(1) If a court determines that the administrative record is inadequate to support the action, the Commissioner shall determine whether to proceed with such action. (i) If the Commissioner decides to proceed with the action, the court will be requested to remand the matter to the agency to reopen the administrative proceeding and record, or on the Commissioner’s own initiative the administrative proceeding and record may be reopened upon receipt of the court determination. . . .

(2) If a court determines that the administrative record is adequate, but the rationale for the action must be further explained: (i) The Commissioner shall request either that further explanation be provided in writing directly to the court without further administrative proceedings, or that the administrative proceeding be reopened in accordance with paragraph (i)(1)(I) of this section

21 C.F.R. § 10.45(i).

CTL has cited no authority (and none exists) for the proposition that a court, upon finding that FDA’s refusal to approve a particular drug was arbitrary and capricious, may exercise the equivalent of *de novo* review and direct the agency to approve the drug.¹¹ At most, the Court could remand the matter back to the agency, either to provide a better or more detailed explanation for its decision to issue a Complete Response Letter, or else to reconsider that decision upon an expanded or reopened administrative record.

¹¹ This is especially true where, as here, relief is being sought by way of an emergency motion for preliminary injunctive relief, and there is no administrative record before the Court.

As noted above, FDA is continuing to work with Dendreon in pursuit of its BLA as the parties await the receipt and analysis of additional data from the ongoing Phase 3 trial. In these circumstances, with an administrative process already in place, a remand to the agency would serve little additional purpose and no harm will come to CTL should the Court decline to enter such preliminary relief.

2. CTL's Claim of Harm is Speculative and Unsubstantiated

In any event, even if the Court were empowered to enter the specific injunctive relief against FDA that CTL seeks, it is speculative, at best, whether Dendreon would choose to make Provenge available to patients before the ongoing Phase 3 clinical trial is completed or whether, given the mixed evidence of its efficacy adduced thus far, any member of CTL or any other prostate cancer patient would actually benefit from access to Provenge.¹² Thus, CTL's claim of irreparable harm is far too speculative and unsubstantiated to support the entry of preliminary injunctive relief. *See Abney*, 443 F.3d at 551-52.

As noted above, CTL seeks to enjoin FDA "from denying the marketing and distribution of Provenge." Pl. Mem. at 54. In order to demonstrate irreparable harm, CTL must establish that FDA's refusal to allow the marketing and distribution of Provenge is directly causing "actual and imminent" harm to its members and, conversely, that compelling FDA to permit the marketing of Provenge would redress that harm. *Abney*, 443 F.3d at 552. In other words, CTL must show not only that its members will suffer irreparable harm in the absence of injunctive relief, but also that

¹² As noted above, Dendreon, which manufactures Provenge, is not a party to this litigation and is, by all accounts, committed to pursuing FDA approval of its BLA through the ongoing administrative process. It seems highly unlikely that Dendreon would risk marketing Provenge without awaiting the results of the Phase 3 clinical trial presently under way and without formal FDA approval of its BLA.

the relief it requests from the Court will prevent that harm from occurring. As discussed below, CTL cannot make such a showing.

In support of its claim of irreparable harm, CTL alleges that some of its members are “terminal stage prostate cancer patients,” including those with Androgen Independent Prostate Cancer (“AIPC”) or Hormone Refractory Prostate Cancer (“HRPC”), which, CTL explains, are “interchangeable and mean exactly the same thing.” Pl. Mem. at 4. CTL further describes AIPC patients as “those men that have already either had their prostates removed or undergone chemotherapy or radiation therapy.” Pl. Mem. at 8. To qualify for Provenge, according to CTL, “AIPC recipients must have already undergone either the removal of their prostates, and [sic] have failed hormone therapy.” Pl. Mem. at 8. CTL claims that AIPC or HRPC patients live 20 months on average (Pl. Mem. at 8), and argues that “[i]f this court does not grant this injunctive relief being sought many of these men will needlessly die early deaths awaiting a trial in this matter.” Pl. Mem. at 12.

Despite its claims in its complaint and motion papers, CTL has produced no evidence that any member of its association is in fact an AIPC or HRPC patient or that any member of CTL would be eligible for treatment with Provenge if it were available. Indeed, among the hundreds of pages of exhibits attached to CTL’s motion, there is only a single affidavit from a prostate cancer patient who identifies himself as a member of CTL. *See* Pl. Mem., Exhibit D at 1 (Affidavit of John Fish). That patient, however, Mr. John Fish, states only that he has “late stage prostate cancer” and that he is “hopeful that Provenge will become available.” *Id.* There is no indication what treatments Mr. Fish has already undergone and no basis for determining whether or not he would qualify for treatment with Provenge, were it available, let alone whether he

would benefit from it. A similar, unsigned affidavit from a Mr. Howard Cassell, included as part of the same exhibit, suffers from the same flaw. *See id.*, Ex. D at 5.¹³

Assuming *arguendo* that there are additional as yet unidentified members of CTL who are AIPC or HRPC patients and who would qualify for treatment with Provenge were it available, CTL's claim of irreparable harm still falls well short of the standard set forth above. Far from demonstrating that it or its members would suffer "actual and imminent harm" in the absence of preliminary injunctive relief, *Abney*, 443 F.3d at 552, CTL's claim that patients will "needlessly die" without access to Provenge is utterly speculative and unsubstantiated. While defendants have the utmost sympathy for patients suffering from prostate cancer and do not question the legitimacy of their desire for alternative treatments or the sincerity of their belief that they would benefit from treatment with Provenge, the current scientific record simply does not bear out that belief. Indeed, as noted above, the current evidence of Provenge's efficacy is mixed at best. It is thus purely speculative whether access to Provenge can or would help any member of plaintiff's organization or any other cancer patient.¹⁴

¹³ CTL's brief purports to identify a third prostate cancer patient, Ted Girgus, as a member of its organization. *See* Pl. Mem. at 9, 13, 16. However, CTL has submitted no affidavit or other evidence to confirm this claim. A transcript of a radio interview with Mr. Girgus, identified as Exhibit A to CTL's motion, has yet to be served on defendants or filed with the Court.

¹⁴ In support of its claim of irreparable harm, CTL relies heavily upon press accounts and interviews with individuals purporting to have benefited from treatment with Provenge. *See, e.g.*, Pl. Mem. at 9, 13-16. As noted above, however, these anecdotal expressions of belief do not provide valid scientific evidence of Provenge's efficacy. *See supra*, section I.B.3 (citing cases); *see also Burzynski*, 819 F.2d at 1314 ("[W]hen the subject of investigation is the existence of cancer, the personal testimony of the lay sufferer is entitled to no weight.") (quoting *United States v. Hoxsey Cancer Clinic*, 198 F.2d 273, 280 (5th Cir. 1952)).

In these circumstances, CTL's claim of irreparable harm must be rejected. In fact, the Sixth Circuit recently affirmed the denial of a motion for preliminary injunction in a situation remarkably similar to this one – holding that a group of patients had not established irreparable harm when, as in this case, it was uncertain whether they would actually benefit from the drug to which they sought access. *Abney*, 443 F.3d at 552. The patients in that case, all of whom suffered from Parkinson's disease, had participated in a clinical trial of a promising new treatment for the disease – a protein known as GDNF. *Id.* at 542-44. After Amgen, the drug's manufacturer, terminated the drug study and refused to allow further access to GDNF, the patients brought suit and sought a preliminary injunction requiring Amgen to continue making the drug available. *Id.* at 545. The district court denied the motion and the Sixth Circuit affirmed. *Id.* at 542, 546.

In *Abney*, as in this case, the plaintiffs contended that “absent a preliminary injunction they would suffer immediate, irreparable harm because without GDNF they allege that their health will continue to deteriorate as a result of their Parkinson's disease.” *Id.* at 551. Although the court found that there was evidence in the record that supported the plaintiffs' claim, it determined that the district court did not abuse its discretion in concluding that the plaintiffs had failed to show that they would suffer irreparable harm absent a preliminary injunction. *Id.* As the court explained:

To demonstrate irreparable harm, the plaintiffs must show that unless GDNF treatments resumed immediately, they will suffer “actual and imminent” harm rather than harm that is speculative or unsubstantiated. . . . Here there is no question that the plaintiffs' health will continue to deteriorate as a result of their Parkinson's disease. Nonetheless, there is no guarantee that the plaintiffs' condition will improve or at least deteriorate at a slower rate if they are prescribed GDNF.

Id. at 552 (internal citations omitted).

The court noted that the plaintiffs had provided evidence suggesting that GDNF was effective, including evidence that patients who had received GDNF subjectively felt an improvement in their condition, and that doctors who had administered it believed it to be safe and effective. *Id.* At the same time, however, the record contained evidence rebutting the plaintiffs' claims, including, most importantly, "evidence in the record suggesting that even if the plaintiffs were provided with GDNF their health might not improve." *Id.* In the end, the court concluded that "there is simply conflicting evidence as to whether GDNF would really prevent irreparable harm to the plaintiffs if immediately administered. Therefore the district court did not abuse its discretion in concluding that the plaintiffs failed to establish they would suffer irreparable harm absent a preliminary injunction." *Id.*

Here, as in *Abney*, it is purely speculative whether treatment with Provenge would actually benefit any member of CTL or any other prostate cancer patient – either by slowing the progression of the disease or prolonging their period of survival. Moreover, even if injunctive relief were entered against FDA, it is far from certain that Dendreon would choose to make Provenge available to patients before the ongoing clinical trial is completed. Under these circumstances, CTL cannot demonstrate that the relief it seeks from this court would actually redress the harm it claims it would suffer in the absence of preliminary injunctive relief. Because CTL has not met its burden of showing that a preliminary injunction is necessary to prevent irreparable harm, its motion must be denied. *Cf. Abney*, 443 F.3d at 551-52.¹⁵

¹⁵ CTL's claim of irreparable harm fares no better in conjunction with its alternative request for a declaration that FDA "correct the ongoing due process denial of CareToLive." Pl. Mem. at 54. CTL seems to be contending that, if the Advisory Committee were reconstituted

B. Injunctive Relief Would Cause Substantial Harm to Others

CTL blithely asserts that “[n]o harm to others will occur if the request for injunctive relief is granted.” Pl. Mem. at 17. But, as noted above, Provenge has not been shown to be a safe and effective treatment for prostate cancer. While the results of the ongoing Phase 3 clinical study may well establish the drug’s safety and efficacy, it is also quite possible that the study could reveal heretofore unexamined safety concerns or demonstrate that the drug has no material impact on survival and thus prove to be an ineffective therapy.

Under the circumstances, the potential harm to others is significant indeed. Should this Court grant the relief CTL requests, it would be ordering FDA to allow the marketing of an unproven and inadequately studied drug, the actual safety and efficacy of which is still unknown. The risk to others in such event is twofold. First, and most obviously, if Provenge turns out to have previously unknown safety issues, any patient who takes the drug will be exposed to those risks. Indeed, as discussed above, the preliminary data currently available showed a higher incidence of CVA events (strokes) in Provenge, as compared to placebo. Transcript, at 166; FDA Clinical Briefing Document, at 3 (“approximately three times as many subjects experienced CVAs in the treatment group compared with controls”). While FDA recognized that the

without Drs. Pazdur and Scher, it would vote overwhelmingly in favor of recommending that FDA approve Provenge and that FDA would adopt its recommendation and act accordingly. *See* Pl. Mem. at 24. This is, of course, rank speculation. Even if the Advisory Committee were to reconvene in such circumstances, there is no way to know what recommendations it would issue and no reason to believe that FDA would reverse its previous decision to await additional clinical data from Dendreon before acting on its BLA. In any event, CTL’s citizen petition seeking FDA reconsideration of its Provenge decision is currently pending before the agency and, if FDA were to find merit in CTL’s arguments and allegations, the agency would presumably decide for itself to re-open the Advisory Committee proceedings or simply grant the petition and promptly approve the Provenge BLA.

difference was not statistically significant (and the Advisory Committee voted unanimously that Provenge was safe), the data nevertheless contain a potential safety signal that may or may not prove to be significant and that merits further study in any event. *See* Transcript at 169; FDA Clinical Briefing Document, at 45.

Second, and equally important, making Provenge available before it has been adequately tested and shown to be efficacious could potentially cause harm to the very population it is intended to help – late-stage prostate cancer patients – many of whom would no doubt forego other, proven treatments in order to try this new alternative. Should this occur, and Provenge turns out to be an ineffective remedy, the ultimate effect of its premature marketing could be to hasten the course of the disease, and shorten lives rather than extend them. As the Supreme Court has observed: “An otherwise harmless drug can be dangerous to any patient if it does not produce its purported therapeutic effect. But if an individual suffering from a potentially fatal disease rejects conventional therapy in favor of a drug with no demonstrable curative properties, the consequences can be irreversible.” *Rutherford*, 442 U.S. at 556 (citations omitted); *see also Abigail Alliance*, 495 F.3d at 713 (“Although terminally ill patients desperately need curative treatments . . . their deaths can certainly be hastened by the use of a potentially toxic drug with no proven therapeutic benefit.”).

Compounding the problem, allowing the premature marketing of Provenge could also make it more difficult to obtain the data necessary to determine whether or not Provenge is a safe and effective cancer agent. As noted above, the drug’s manufacturer, Dendreon, is currently conducting a Phase 3 clinical trial of the drug to answer that very question. However, Dendreon would undoubtedly find it difficult to continue the trial should the drug be available to any

patient who desired it. Indeed, few late-stage cancer patients would be willing to participate in a drug study in which they might be administered a placebo if the drug itself were readily available outside the clinical trial setting. Nor would Dendreon have much incentive to continue the trial when it could, instead, sell the drug directly to patients at a substantial profit. *See Abigail Alliance for Better Access to Developmental Drugs v. McClellan*, No. 03-1601, 2004 WL 3777340, at *12 (D.D.C. Aug. 30, 2004) (“The FDA has found from experience ‘that it has often been difficult to obtain [studies of drugs after their release into the market], which would mean that a product approved on the basis of almost no data would have prolonged distribution without knowledge of who is likely to benefit and how to manage toxicity.’”) (citation omitted) (alteration in original), *aff’d en banc*, 495 F.3d 695 (D.C. Cir. 2007).

Thus, contrary to CTL’s contention, the requested preliminary injunctive relief would potentially cause substantial harm to others.

C. The Public Interest Would Not Be Served by the Entry of Injunctive Relief

CTL has also failed to show that the preliminary injunctive relief it seeks would serve the public interest. *See Abney*, 443 F.3d at 552-53; *Leary*, 228 F.3d at 736. About all CTL has to say on this subject is that “[t]he public has a great interest in seeing a rational, reasonable and realistic approach to cancer treatments by the FDA” (Pl. Mem. at 22), a sentiment with which no one would disagree. However, it is Congress that has set the standards by which FDA is to evaluate new cancer treatments – whether they be drugs, devices, or biologics – and those standards require that the agency find by substantial evidence that the proposed new treatment is safe and effective before it can be approved for use. *See* 21 U.S.C. §§ 355(a), (d); 42 U.S.C. § 262(a)(2)(C)(i)(I); *see also Abigail Alliance*, 495 F.3d at 713 (“prior to distribution of a drug

outside of controlled studies, the Government has a rational basis for ensuring that there is a scientifically and medically acceptable level of knowledge about the risks and benefits of such a drug.”); *Rutherford*, 442 U.S. at 551-54 (holding that there is no exemption from the FDCA’s approval requirements for drugs intended to treat terminal illnesses).

As noted above, determining the safety and efficacy of a new drug is a task within the province of the FDA – not the judiciary or the public. *See Schering*, 51 F.3d at 399 (“The FDA is the agency charged with implementing the Food, Drug and Cosmetic Act as amended. Its judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA’s expertise and merit deference from us.”); *Serono Labs, Inc. v. Shalala*, 158 F.3d 1313, 1324 (D.C. Cir. 1998) (same). Congress has entrusted FDA to make such evaluations because it has the expertise and experience to analyze scientific data and weigh the relevant risks and benefits. *See id.* at 1320 (FDA’s “evaluations of scientific data within its area of expertise” are entitled to “high level of deference” from the court) (quoting *A.L. Pharma*, 62 F.3d at 1490). It would be unwise in the extreme, and contrary to the public interest, for FDA’s expert determinations to be overturned based upon the wishes of consumers or anecdotal experience.

Terminally ill patients are understandably desperate for new and alternative treatments, but that very desperation makes them uniquely vulnerable to exploitation by unscrupulous peddlers of the latest “cure,” and puts them in perhaps the least advantageous position to objectively evaluate the safety and efficacy profile of an unproven new drug. *See Rutherford*, 442 U.S. at 558 (“Since the turn of the century, resourceful entrepreneurs have advertised a wide variety of purportedly simple and painless cures for cancer . . .”); *Cowan v. United States*, 5 F.

Supp. 2d 1235, 1242 (N.D. Okla. 1998) (“to permit terminally ill patients to seek any type of treatment regardless of the effectiveness of such treatment would create a cottage industry existing solely to provide potential panaceas to highly vulnerable patients”).

Evaluating the safety and efficacy of new therapies is FDA’s mission, and its alone. It would be a grave disservice to the public interest to override FDA’s considered judgment and order a drug onto the market prematurely. In *Abney v. Amgen*, discussed above, the Sixth Circuit found that the public interest weighed against the entry of preliminary injunctive relief in very similar circumstances, agreeing with Amgen’s argument that “it is up to the FDA, and not doctors or their patients, to determine whether a drug is safe and effective.” *Abney*, 443 F.3d at 553. As the court explained:

[T]he plaintiffs’ claim that physicians should be the sole arbiter of patient care wholly undermines the purpose and value of the FDA. The public has a strong interest in ensuring that the FDA rather than individual doctors has the power to decide what drugs meet baseline levels of safety and efficacy. Thus, the district court did not abuse its discretion by concluding that the public interest would not be served by granting the plaintiffs’ motion for preliminary injunction.

Id.

So too here, the injunctive relief CTL seeks in this case is contrary to the public interest. Accordingly, its motion for preliminary injunction should be denied.

CONCLUSION

For the forego reasons, CTL's Motion for Emergency Preliminary Injunctive Relief should be denied.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that the foregoing Memorandum in Opposition to Plaintiff's Motion for Emergency Preliminary Injunctive Relief was filed on the 1st day of October, 2007, using the Court's CM/ECF system, which will serve all counsel of record electronically.

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