

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

CareToLive, et al.,

Plaintiffs,

Case No. 2:07 CV 729

vs.

Judge Frost

Andrew von Eschenbach,

et al.,

Magistrate Judge King

Defendants.

**PLAINTIFF'S REPLY TO DEFENDANT'S MEMORANDUM CONTRA  
PLAINTIFF'S MOTION FOR  
EMERGENCY INJUNCTIVE RELIEF**

Now comes the Plaintiffs and hereby offer the following Reply to the Defendant's Memorandum Contra Plaintiff's Emergency Motion for Injunctive Relief.

**Procedural introduction**

Plaintiff properly requested a hearing in its motion for emergency injunctive relief. Plaintiff plans to present all evidence stipulated and unstipulated at that hearing. Defendant's memorandum contra makes assumptions that are contrary to the Plaintiff's understanding of the manner in which this Court will proceed on the injunction. Consistent with the agency's attitude towards due process rights of cancer patients, the apparent goal of the Defendant's memorandum is to persuade this Court to deny the Plaintiff a hearing, something this Court should not consider.

It makes little sense, considering the emergency nature of the injunctive relief sought, for the parties to waste 4 to 6 months of the Court's valuable time arguing over what the record should and should not contain considering that 90% of "the record" is at the fingertips of the agency, retrievable by them with a minimum of keystrokes. The

additional 10% of the evidence that will explain the administrative actions sought to be presented by Plaintiffs to this Court can be quickly, readily, and easily compiled with very little effort by the agency. Defendant's goal clearly, is to exclude that 10% of the evidence. Considering that one of the goals of Plaintiffs in this case has been to obtain simple and open due process of law and to obtain a *complete* record from a government agency that has consistently demonstrated an inability to respond to, if not an overt attempt to thwart, a timely response to Plaintiff's Freedom of Information Act (FOIA) requests (see Plaintiffs pending motion for enforcement of FOIA, dckt no. 29), and attempts to obtain discovery, even though this is in an emergency situation. The argument now that the Plaintiff be denied further due process from another branch of government, seems egregiously insensitive and uncaring with respect to Patient Rights. With very little effort, the entire remaining evidence to be assembled by Plaintiff can be quickly and conveniently assembled. Any evidence this Court did not wish to consider at the hearing would simply not need to be considered at that time (but, importantly, it would be available and/or could be proffered) as this Court is free to use its discretion to consider what the Court does or does not deem appropriate at the time of the hearing. However, to have an effective hearing, to proceed in a timely manner, and to ensure that this matter does not waste the Court's valuable time, the evidence must be available. The evidence will in large part comprise evidence already possessed by Plaintiffs, combined with the administrative record and the easily ascertainable testimony of a few agency employees who would merely be inconvenienced for a few hours on a single day in order to provide testimony. The Defendants have taken the unusual stance that they will spend hundreds of legal hours in an attempt to defend and hide a "procedure" together with a few

documents it would rather not disclose. That eleven (11) attorneys seek to stop Plaintiffs from obtaining information from a public agency rather than inconvenience just a couple of the thousands of employees that work at the FDA defies reason and common sense. Eighty (80) people die every day of prostate cancer. Considering the emergency nature of this action, an extremely slight inconvenience to the FDA could be tolerated by them to ensure that the evidence this Court requires to make a decision is, at a minimum, available at the hearing and disclosed to the public.

Because the Defendants now have filed their announced motions to dismiss, the argument counter thereto will be presented to this Court by way of a memorandum contra those motions so that this Court will not have to read repetitive Plaintiff documents on the same topic. However it suffices for current purposes that Plaintiffs respectively ask the Court to immediately schedule an injunctive hearing on its docket so that Plaintiffs can prepare for a date certain and because this Court should at the very least review this matter under the APA, which excludes the possibility that the Court would dismiss the entire case for any reason. Because even evidence outside the administrative record that explains the administrative record is admissible for review in unusual cases, such as here, where the FDA has not offered an explanation for ignoring the pronouncements of 17 experts of its own choosing who participated in the FDA's Advisory Committee (AC) meeting of March 29, 2007, and who voted 17-0 that Provenge was "safe" and 13-4 that it demonstrated "substantial evidence of efficacy," and has at least apparently acted capriciously, and that evidence is offered in support of a procedural challenge to the administrator's decision and an alleged lack of due process, some discovery and a hearing is the minimal short-term direction required. Delaying discovery and progress towards a

hearing in an emergency case, considering the likelihood of the hearing proceeding, would not make sense and would serve only the purpose of delay at the expense of terminally ill patients who have so little time left.

**Legal argument**

In accordance with Southern District of Ohio Local Rule 7.1(2) a request for oral argument on this matter has properly been made. Local Rule 7.1 PROCEDURE FOR DECIDING MOTIONS section (b)(2) states:

In all other cases, if oral argument is deemed to be essential to the fair resolution of the case because of the public importance *or* the complexity of the factual or legal issues presented, counsel may apply to the court for argument.....

Since the proposition is an “or”, this Court should schedule a hearing if either the fair resolution is of public importance or because of the legal or factual complexity of the matter. It is understood that the Defendants do not disagree that this matter is factually complex, which assumption is implicit in their position that it is so complex that only the FDA can possibly understand the issues. Additionally it is *legally* complex as even counsel for Defendants have previously indicated to this Court, so the Plaintiffs likely have to present no additional argument for this Court to schedule the matter for hearing under the courts local rules. That said, out of an abundance of caution in this important matter, if the Court also wants to proceed to determine the issue of whether this is a matter of public importance before it renders a decisions with regards to the immediate scheduling of a hearing, it can proceed to the arguments set forth below in that regards.

The Court is reminded that procedurally under Federal Rule of Civil Procedure 65, the Court can also consolidate the hearing with a trial on the merits. Civil Rule 65 states:

Before or after the commencement of the hearing of an application for a preliminary injunction, the court may order the trial of the action on the merits to be *advanced and consolidated* with the hearing of the application. Even when this consolidation is not ordered, any evidence received upon an application for a preliminary injunction which would be admissible upon the trial on the merits becomes part of the record on the trial and need not be repeated upon the trial.

This Court should schedule the matter for hearing and allow very brief, simple, to the point and very easily accumulated basic discovery, as that is all that is required for Plaintiff to prove its entire case.

**This matter is of great public importance**

The Public importance of Public accountability, by a Public agency to the Public cannot be understated. Where such an agency presents one face to the public and acts completely differently behind its closed doors, the public's outrage is understandable. The FDA (also intermittently referred to as "the agency") convened an open hearing (an advisory committee or "AC") for the public to openly discuss the positives and negatives regarding the Provenge BLA. *The FDA was free to question any of the 17 experts it selected to participate in this AC regarding any questions and or concerns they may have had regarding the safety and efficacy of Provenge.* The public was invited to this hearing and discussions occurred. There was dialogue between the FDA staff members and the experts. Questions, comments, and an extensive, highly technical exchange took place, and finally after approximately 5 hours, two votes were taken. For the first time now, after 4 months has passed since the agency requested additional data, the FDA has attempted to suggest very general, non specific, and speculative explanations as to why Dr. Andrew von Eschenbach did not listen to his own committee of experts (17 in all), which rationalizations ring insincere and places him in an untenable position, considering that no such concerns were raised by the FDA or the agency's own panel of experts

during the 5 hour meeting. Worse, the explanation now being proffered is not presented as the overarching reasons for not approving Provenge but rather as *possible* reasons. In other words even now the FDA's is attempting to keep the agency's options open with regard to a public explanation using concocted post hoc concerns that seemingly appear to have evolved out of thin air, given that the concerns apparently were not present at the time of the AC meeting. The context of that meeting can be seen in the advisory transcript at <http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4291T1.pdf> (or is attached to the Plaintiffs motion for inj. Relief as Ex.C).

"(8) Within 90 days after a scientific advisory panel makes recommendations on any matter under its review, the Food and Drug Administration official responsible for the matter shall review the conclusions and recommendations of the panel, and notify the affected persons of the final decision on the matter, or of the reasons that no such decision has been reached. Each such final decision shall be documented including the rationale for the decision."

No reason or explanation has been provided to the public to date. The public has a right to know. The FDA is supposed to already have the rationale documented. The 483 issues are severable and indeed are not part of what is sought. The AC Briefing documents, the AC hearing, and the AC transcript formed a due process. If there is other information key to the rationale, it should have been on the table then, and it should be on the table now.

After approximately \$1billion dollars has been spent by Dendreon during a decade of research and clinical testing of Provenge, and upon the conduct of FDA-mandated and controlled Phase I, Phase II, and Phase III (two) trials (and based on the current extended quality of life enjoyed by those who received Provenge many years ago, including Messrs. Bruce Tower, Eduardo Garcia, and Ray Matyshyn), the approval by the FDA of fast track status, the later acceptance by the FDA and conformance of the

sufficiency of the data from the Provenge BLA, the oral comments from the FDA to Dendreon confirming that there were sufficient data to evaluate Provenge, the positive statistical briefing document generated by the FDA prior to the hearing, the positive tone of the FDA advisory committee that was summed up with the extremely positive AC panel votes on safety and efficacy; the public rightfully believed Provenge would be approved by the PDUFA date of May 15, 2007. Provenge was going to be approved and the world would be introduced to a new era of immunotherapy for the treatment of cancer. Doctors, their patients, scientists, advocates, investors, and the public at large were excited about the FDA's acceptance of this new treatment, which was expected to spawn the research and development of similar biological products (something that should have been accelerated following the mapping of the human genome) for the treatment of cancer. It appeared, as preached by Dr. Andrew von Eschenbach in the months before Black Wednesday that the FDA was in the process of building the "bridge" that would eventually lead to cancer becoming a treatable condition, rather than the dreaded killer that it is. Everything that had occurred in the public's eye was positive towards the approval of Provenge for AIPC patients. The world stood by, waiting for the wall to fall and the bridge building to begin. Following the March 29<sup>th</sup> advisory meeting Dendreon was receiving the congratulations of the world for their achievement, something that was met with the exuberance of the public.

Was it irrational exuberance? Not the way the FDA, a public tax dollar supported agency, which must answer to the public, handled the matter in the public eye. Most of the public that followed the Provenge story, who were without the privilege of inside information from the FDA, believed approval, or at least conditional approval, was

imminent. Rational members of the public were led to believe approval or conditional approval was imminent. Was it rational considering what was happening off the record, behind closed doors, out of the sight and sound of the public? While the FDA has refused to give a specific explanation for the decision or even procedurally explain how and when the decision not to approve was made, the Plaintiffs as well as the public are left to in general believe it was not and that will not change as the FDA refuses to offer an explanation why it acted in private so differently then it did in public. What *is* important at this point is that neither the Plaintiffs, the public at large, nor this Court can make further judgment in this matter until a full and complete record is before it and before the Defendants meet *their burden* to publicly explain its apparent nonsensical decision. Because the FDA refuses to provide a complete record (and refuses to abide by FOIA requests to provide the requisite information), it is indeterminable by a fair and impartial tribunal. Neither the public nor this Court can properly evaluate the decision without a full and complete record. Whether the record is full and complete cannot be determined until the FDA presents that full record, which it refuses to do.

The public has a right to know why the agency painted a certain face on a subject, only to do something else behind closed doors. To argue what should or should not be in the record prior to even having the “proposed record” seems a waste of time and energy of all (the failure to explain should place this burden of producing the record on the Defendants as they have made it *per se capricious*). The FDA is showing little regard or respect for the Court’s time by its continued refusals to provide information that, by law, it is required to provide. For full public accountability the record should include the letters written by the two AC experts, Drs. Howard Scher and Maha Hussain (now

admittedly placed on the AC by Dr. Pazdur), who, by their actions both during and after the AC clearly were there to sabotage the decision to approve Provenge. Does the record now include the minutes of the meetings wherein the discussion to approve or deny approval occurred behind closed doors. Does the record contain the additional COI's that were undisclosed on the waivers of Drs. Scher and Hussain? The FDA admits that Dr. Pazdur placed Drs. Scher and Hussain on the AC. They don't admit that he did it to sabotage Provenge, but that he did so will be clear to this Court once it knows of all the behind the scenes actions, some of which exceeded the scope of authority of both the FDA employees and the "special government employees" involved. The actions outside the scope of employment are unlikely to be part of the voluntary record the FDA presents. It's inconceivable to argue that it is coincidence that Dr. Pazdur hand picked two conflicted doctors who would personally benefit, by Provenge's non-approval and thus had inherent biases rendering them negative towards Provenge, and that they then both acted as expected at the hearing (considering their conflicts), and just coincidentally wrote similar letters to the FDA that were both leaked to the same publication. Point being; is this part of the record? The Defendants should pick their poison. Were these actions taken by Dr. Pazdur (an FDA employee) and Dr. Scher (a special government employee during the AC proceedings) outside the scope of their employment and thus not part of the record, or were these actions taken within the scope of employment and by agreement between Drs. Pazdur and Dr. Scher and thus, part of the administrative record for review by the public and this Court

The Agency wants to limit the record for review by this Court. Contrary to Defendants assertions, Plaintiffs are confident that this Court would find in favor of

Plaintiff even if it just reviewed the administrative record (even as assembled by the FDA). If the Court considers the entire and full record and examines the process actually afforded the Provenge BLA on and off the record, the Court will clearly find that the actions of the FDA were arbitrary and capricious. The Defendants arguments are directed towards the goal of preventing this Court seeing what really happened just as they have attempted to hide their unlawful activities from the public. The FDA's argument that the record favors their actions, rings false, and it is. They make such a claim for the single purpose of persuading this Court that it need not look at the full record and at the circumstances that occurred, even though that evidence is simple and concise in its content. What the FDA really wants, in the strongest terms, is that the Court and the public not be given an opportunity to consider the entire record and thus, not have the opportunity make a determination regarding the capriciousness of their decision in this case. The problem for the Defendants is that they know that this Court, with a full understanding of the personnel involved and of their motives at the AC meeting combined with the nefarious and unlawful post-AC activities on the part of both FDA government and special government employees, would become angered in the manner than many in the public who are familiar with this case have become.

When the Agency acts *one way in public and one way in private, the public has even more right than usual to demand an open review*. It actually is an invitation to litigation for the FDA to operate in both a dysfunctional *and* secretive manner. If there is a better way to raise the ire of the public, the FDA has not discovered it.

The undisclosed outside the record conflicts are important because a review of the AC transcript by this Court, knowing about these undisclosed conflicts, causes the AC

transcript to be read in a completely different manner and helps to explain why certain doctors, who, again, are both employees and special government employees, took actions that they did and that they did *knowingly* because they had a certain agenda in mind.

Should this Court be concerned that if it reviews the actions of the FDA in this matter, then everyone who is unhappy about an immunotherapy not being approved in the future will challenge through the courts the decision by the FDA? No, particularly not if the FDA conducts its business in a forthright, honest and open manner, and does not do one thing in the public eye and another behind closed doors. More importantly, this FDA action is unprecedented and unlikely to regularly occur. The Defendants (although incorrectly) state in their memorandum that the agency has been regulating in this manner for 100 years. If that were true, then this is the first time in 100 years that the FDA has acted privately, differently than it has acted publicly with regards to a life threatening illness. *Stated otherwise, this is the first time the FDA has ever overruled a positive advisory recommendation in support of a life saving treatment for a terminal group of patients.* If this is a once-in-a-hundred-year event in which the FDA has acted contrary to the public face it put on an issue, then the FDA can certainly spend a couple of hours in a deposition to answer as to why they did this, and then, the Court can judge the arbitrary and capricious nature of the agency's actions based on some available documents and direct testimony.

The public has a right to accountability. They have a right to know why the FDA overruled its very own panel of seventeen (17) experts. How was this decision made, when was it made, and who participated in the decision? Was the decision made before

or after the AC meeting? This is not just a routine decision in the regular course of business, *as it has never happened in a hundred years, and it involves terminal patients.*

Because the agency on its own determined the make up of the advisory panel, it basically chose its own weapon. The agency, using its own discretion and own resources, decided that these 17 people (five more than in a jury and recognized *experts* to boost) were among the best, if not *the* best, in the world to make this decision. Because the agency afforded its own due process to itself, any action taken behind closed doors before or after the hearing contrary to that process in a public hearing is per se arbitrary and capricious. The agency decision being per se arbitrary and capricious (because the panel determined under the proper statutory guidelines substantial evidence that Provenge is safe and effective) the burden should be shifted to Defendants to prove that not following the expert advisory opinion was the proper action to take or at least was not arbitrary and capricious. In other words, it should be the agency's burden to prove that what was done in public was wrong and that what occurred in private, secretively, behind closed doors, was in fact the right determination and/or was not arbitrary and capricious. There must be some accountability or some explanation for their seemingly incorrect actions. The public demands it and it is due.

The FDA is a public agency that must answer to the public. From the FDA website, <http://www.fda.gov/opacom/morechoices/mission.html>.

### **FDA's Mission Statement**

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more

affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

The Courts have frequently articulated the “great principle of public policy, applicable to all governments alike, which forbids that the public interests should be prejudiced by the negligence of the officers or agents to whose care they are confided.” *United States v. Nashville, C. & St. L.R. Co.*, 118 U.S. 120, 125, 6 S.Ct. 1006, 1008, 30 L.Ed. 81 (1886). See also *Guaranty Trust Co. v. United States*, 304 U.S. 126, 58 S.Ct. 785, 82 L.Ed. 1224 (1938); *Stanley v. Schwalby*, 147 U.S. 508, 515, 13 S.Ct. 418, 421, 37 L.Ed. 259 (1893).

A complainant adversely affected by the Secretary's failure to act on a complaint can bring an action in the district court. The court would have the authority to “compel agency action unlawfully withheld or unreasonably delayed,” § 706(1). *Brock v. Pierce County* 476 U.S. 253, \*260, 106 S.Ct. 1834, \*\*1839 (U.S.,1986). The Supreme Court has recognized, the role of public agencies often sets them apart. Public agencies by their very nature represent the public interest and, as such, have a duty to protect both the public fisc. and the integrity of the government programs they represent. *Brock v. Pierce County*, 476 U.S. 253, 259-60, 106 S.Ct. 1834, 1839 (1986). The FDA does not just owe a duty to the companies that manufacture drugs, they owe a duty to the American people. The public had few complaints about how the FDA handled this matter, (though truth be known, there were concerns about Drs. Scher’s and Hussain’s behavior and statements at the AC), until the leaked letters appeared and until the agency took the matter of approval behind closed doors and came out with an answer that is illogical and unexplainable on the basis of the information chosen by the FDA to be disclosed to the public. Why specifically does the FDA believe the 17 experts were wrong, and if they believed that they were, why were the reasons not brought up for discussion at the AC hearing. The

public understanding of the matter after the AC meeting concluded was further underscored by all the press releases throughout the country that confirmed some of what the public believed. The following is just a very small sample of excerpts of press articles and is offered not for the truth of the matter asserted but for the effect that they had, and continue to have, on the public perception of this matter, which further explains the fundamental unfairness of the procedure, at least in the eyes of the public.

Bristol-Myers Squibb  
Taxol

A Food and Drug Administration advisory committee recommended in a unanimous vote that paclitaxel be approved for a new indication involving the treatment of breast cancer.

The FDA usually follows the recommendations of its advisory panels, which are not binding.

[http://findarticles.com/p/articles/mi\\_m0CYD/is\\_21\\_34/ai\\_61621152](http://findarticles.com/p/articles/mi_m0CYD/is_21_34/ai_61621152)

**APPROVED!**

Merck  
Gardasil

An advisory panel to the U.S. Food and Drug Administration (FDA) unanimously recommended the approval of a new vaccine against cervical cancer.

The FDA, which usually follows the panel's recommendations, will make a final decision on whether to approve the vaccine for use in the United States in June 2006.

<http://www.imaginis.com/cervical-cancer/news/news6.04.06.asp>

**APPROVED!**

Nitro-Med  
BiDil

A Food and Drug Administration advisory panel recommended the approval of a heart-failure drug specifically for African-Americans yesterday, after a discussion about race, genetics and medicine.

The F.D.A. usually heeds the advice of its advisory panels, meaning that the drug, called BiDil, is likely to become the first treatment ever designed and marketed for one racial group

The company has said it was prepared to begin marketing the drug almost immediately.

<http://www.nytimes.com/2005/06/17/business/17drug.html?n=Top/Reference/Ti>

mes%20Topics/People/S/Saul,%20Stephanie

**APPROVED!**

Idec - Genentech

Rituxan

An advisory panel to the Food and Drug Administration today unanimously recommended approval of a biotechnology drug produced by Idec Pharmaceuticals Corporation and Genentech Inc. for the treatment of a form of non-Hodgkin's lymphoma that is a slow-growing but fatal and incurable cancer of the immune system.

The F.D.A. is expected to follow the recommendation of its advisory panel and approve Rituxan by the end of the year.

<http://query.nytimes.com/gst/fullpage.html?res=9503EED8173AF935A15754C0A961958260&n=Top%2FNews%2FHealth%2FDiseases%2C%20Conditions%2C%20and%20Health%20Topics%2FCancer>

**APPROVED!**

Acambis Plc

Acambis

An expert FDA advisory panel has unanimously approved a smallpox vaccine made by Acambis Plc.

The FDA still has to approve the vaccine, however they tend to side with their advisory panels when it comes to approving new drugs and medical devices.

[http://www.dogflu.ca/05182007/13/advisory\\_panel\\_approves\\_smallpox\\_vaccine](http://www.dogflu.ca/05182007/13/advisory_panel_approves_smallpox_vaccine)

**APPROVED!**

Searle

Celebrex

An FDA advisory panel's recommendation to allow Celebrex to be marketed for children suffering from juvenile rheumatoid arthritis (JRA) has some experts concerned over long-term health effects.

While the issue of short-term efficacy and safety did not seem a big issue with the FDA panel, long term safety was a matter of concern.

<http://www.medicalnewstoday.com/articles/58458.php>

**APPROVED!**

GlaxoSmithKline

Xenical

A joint FDA advisory committee voted 11-3 to recommend approval late Monday following a daylong hearing.

The agency usually follows the recommendations of its outside panels of experts, but its final decision could take months.

"We know that being overweight has many adverse consequences, including an increase in the risk of heart disease and type 2 diabetes," said Dr. Douglas Throckmorton, deputy director for the FDA's Center for Drug Evaluation and Research.

<http://www.cbsnews.com/stories/2006/01/23/health/main1232164.shtml>

**APPROVED!**

Merck  
Zostavax

According to an FDA advisory panel, studies show that an experimental vaccine to prevent shingles can cut the rate of infection by about half in people 60 and older and help curb related pain. But drug company Merck's data also showed the vaccine, Zostavax, did not significantly reduce rates of death or hospitalization and became less effective after three years.

The advisory panel of outside health experts say that Zostavax showed no serious side effects and they will consider whether to recommend approval.

The FDA usually follows its advisory panels advice.

<http://www.news-medical.net/?id=15054>

**APPROVED!**

Eli Lilly  
Evista

ROCKVILLE, Md., July 25 -- An FDA advisory panel has recommended that the agency approve raloxifene (Evista) for prevention of breast cancer in high-risk postmenopausal women.

For that indication, the panel voted 10 to 4. By a closer vote -- 8 to 6 -- the panel said raloxifene's label should be amended to allow its use for prevention of breast cancer in women with osteoporosis.

The FDA is expected to act by the end of September. Although the agency is not required to follow the advice of its advisory panels, it generally does.

<http://www.medpagetoday.com/ProductAlert/Prescriptions/tb/6258>

**APPROVED!**

<http://www.healthday.com/Article.asp?AID=608270>

Genentech  
Herceptin

An advisory panel for the U.S. Food and Drug Administration (FDA) today recommended approval of the breast cancer drug Herceptin, the first cancer drug to successfully treat a specific genetic alteration. The FDA's Oncologic Drugs Advisory Committee recommended Herceptin for approval as a single agent and for use in combination with Taxol.

The final decision rests with the head of the FDA, who usually follows the advice

of the panel of doctors.

<http://www.newswise.com/articles/view/?id=herceptn.ucl>

**APPROVED!**

Biogen Idec

Tysabri

A panel advising the Food and Drug Administration yesterday said the multiple sclerosis drug Tysabri, sold by Biogen Idec Inc. of Cambridge and Elan Corp. of Ireland, should be approved to treat Crohn's disease.

The FDA does not have to follow the recommendation, although the agency tends to follow the advice of its medical panels.

[http://www.boston.com/business/globe/articles/2007/08/01/fda\\_panel\\_backs\\_tysabri\\_for\\_crohns/](http://www.boston.com/business/globe/articles/2007/08/01/fda_panel_backs_tysabri_for_crohns/)

**APPROVED!**

Biogen

Amevive

A U.S. Food and Drug Administration advisory panel has given its recommendation for approval to Biogen Inc.'s psoriasis treatment Amevive.

The panel voted 8-2 that Amevive was safe and effective for treating chronic cases of psoriasis in adults.

The FDA, which usually follows its panels' advice, will consider the panel's opinion as it decides whether to clear Amevive for marketing in the United States.

<http://triangle.bizjournals.com/triangle/stories/2002/05/20/daily53.html>

**APPROVED!**

AstraZeneca

Iressa

A panel that advises the Food and Drug Administration recommended approval yesterday of AstraZeneca's cancer drug Iressa, despite concerns by the agency's staff about the drug's effectiveness.

By a vote of 11 to 3, the panel said the drug had met the requirements for approval because it had helped some desperately ill lung-cancer patients, even if the company's data was not as strong as it could be.

The agency, which usually follows the advice of the panels, will now decide whether to approve Iressa.

<http://query.nytimes.com/gst/fullpage.html?res=9C00E7D61239F936A1575AC0A9649C8B63>

**APPROVED!**

Celgene  
Revlimid<sup>1</sup>

An advisory panel of the FDA recommended on Sept. 14 that the agency approve the drug. Although it isn't bound to the decisions of its advisory panels, the FDA generally abides by them.

<http://www.marketwatch.com/News/Story/Story.aspx?guid=%7BF7A3A4A2%2DCD9D%2D468F%2DADCA%2D54F6AC2ADABC%7D&siteid=google>

1) Study design allows adequate characterization of the agent's treatment?  
Yes, 11-4

This was most interesting since the studies were not how Dr. Pazdur liked them. They were single arm and they only got to Phase II.

2) Safety Profile  
Yes, 2-13

The drug was not deemed safe by the Advisory Panel.

3) Does risk-to-benefit analysis warrant approval?  
Yes, 10-5

### **APPROVED!**

#### **FDA APPROVES BLOOD DISORDER TREATMENT REVLIMID**

The FDA has approved Celgene's blood disorder treatment Revlimid, clearing the way for the firm to begin initial shipments of the drug in early 2006.

<http://www.fdanews.com/newsletter/article?articleId=83461&issueId=8859>

Dendreon  
Provenge

THURSDAY, March 29 (PCF) - An FDA Advisory Committee recommended to the FDA that there is substantial evidence of efficacy and safety of Provenge® (sipuleucel-T) for the treatment of patients with asymptomatic, metastatic, androgen-independent (also known as hormone refractory) prostate cancer. The FDA will now review the advisory committee's recommendations and determine whether Provenge should be approved for use. It is expected that the FDA's decision will be made by May 15, 2007.

[http://www.prostatecancerfoundation.org/site/c.itIWK2OSG/b.2692947/k.4FC4/Advisory\\_Panel\\_Recommends\\_FDA\\_Approve\\_Prostate\\_Cancer\\_Vaccine\\_Therapy.htm](http://www.prostatecancerfoundation.org/site/c.itIWK2OSG/b.2692947/k.4FC4/Advisory_Panel_Recommends_FDA_Approve_Prostate_Cancer_Vaccine_Therapy.htm)

If the FDA follows its panel's advice, which it usually does, the vaccine, Provenge, would be the first to directly spur the immune system into attacking prostate cancer.

[http://www.usatoday.com/money/industries/health/2007-03-30-dendreon-stock\\_N.htm](http://www.usatoday.com/money/industries/health/2007-03-30-dendreon-stock_N.htm)

### **NOT APPROVED!**

The way the public has been led to believe the Agency operates is a relevant framework when analyzing a later decision that appears to be an aberration from what the public has been led to expect. While the FDA does not have to follow the advisory committees, when they do not, they must at least answer the questions the public has relative to why they apparently acted capriciously, when they take the unusual action of not following an advisory meeting panels advise, particularly as in this case where they took a *first of its kind action of not following an overwhelming positive recommendation for approval for treatment for a terminal condition (AIPC)*.

The FDA says that before a citizen brings suit on an issue they must file a citizen petition. This petition process has proven to be completely bogus. In practice the agency never responds to these petitions and HAS NEVER granted a petition for reconsideration of denial, approval or non-approval of a drug as is requested in the Plaintiffs citizen petition (Abigail Alliance is still waiting since 2003 for the FDA to answer its petition). The exercise is futile as demonstrated by the full weight of prior FDA actions and *refusals to be responsive to patient rights groups*. The First Amendment provides, in relevant part: "Congress shall make no law ... abridging the freedom of speech ...; or the right of the people ... to petition the Government for a redress of grievances ." U.S.

Const. Amend. I. Even in the case of dying cancer patients the FDA can't answer a citizen petition within 90 days (it asserts that it needs 180) emergency or no emergency. In that 90 days another 70,000 men will have been diagnosed with prostate cancer and another 2,700 will have died without at least the hope that access to Provenge can provide them. As will be further set forth in Plaintiffs memorandum contra Plaintiffs motion to dismiss, not only is the petition requirement a futile act, it is not needed where legal arguments are at issue (as here) and Title 21 section 10 is unconstitutional as applied to dying cancer patients that will not survive to have their concerns addressed by a Court. The FDA is unlikely to admit that their decision was arbitrary and capricious. The confusing, evasive behavior of the FDA, and its utter refusal to respond to Citizen's Petitions on any subject put forth by patients on behalf of patients, including Plaintiffs, makes pursuit futile. From the FDA web site:

"Accordingly, a considerable backlog of pending food standard petitions has accrued. At FDA for example, numerous standing petitions are pending, and many of these have been pending for five or more years."

<http://www.fda.gov/ohrms/dockets/dockets/07p0085/07p-0085-cp00001-02-vol1.pdf>

The FDA's APA procedures are a joke. There is virtually no relief available to anyone under the FDA's Citizen's Process unless the FDA chooses to provide it. There is also no real time constraint placed on FDA to respond to any Citizen's Petition, or for that matter, to even read it, and there is no mechanism at all by which a petitioner can force a supervised process of administrative hearing. The only option for redress that the FDA cannot entirely ignore is a suit filed against the FDA in federal court.

## Public Perception

The public perception created by the actions of the agency have lead to the current public uproar regarding the Provenge decision and demand a reasonable explanation for their apparently capricious decision. What is the reasonable public perception considering the vague explanations and excuses offered by the agency to date:

- I. The public begins with the assumption that the FDA has knowledgeable scientific members who are capable of reading and understanding Biologic License Applications (BLA's) and can interpret clinical trial results.
- II. The public assumes that the agency has only limited funds available and would not indiscriminately waste taxpayer money on worthless activities and not undertake fake proceedings to mollify congress. With that preamble, we are asked to believe the following according to the Defendants Response.
  - a. Having made those basis assumptions they are lead to believe that: The FDA received Dendreon's BLA for a treatment for a terminal condition and no one at the FDA bothered to look at the clinical trial data provided for over a year. Not one person at the FDA questioned the fact that the primary endpoint TTP was missed (no longer a proper endpoint per the FDA itself) or that the survival data was obtained post hoc.
  - b. Having completely failed to observe the (now supposedly) glaring trial deficiencies, the FDA then scheduled an Advisory Committee. FDA employees spent hours preparing briefing documents for the hearing. They spent thousands of dollars arranging travel for the committee members. They had these physicians and scientists take time from their practices and research to review the briefing documents and then travel to and attend the Advisory Committee Hearing.
  - c. That it was only after the Provenge positive Advisory Committee Hearing that the FDA suddenly came to an opposite conclusion of the AC, that the data that had been provided was insufficient and more data was required.

Just what did the FDA see or hear at the meeting other than the nonsensical ranting by the severely conflicted minority of committee members placed on the committee by Richard Pazdur, to cause them to make what seems to have been a capricious decision? The public is left with the fact that either the FDA is inept and wasting taxpayer money on

useless AC hearings and/or trying to fool congress or, they are deliberately using a trumped up excuse for keeping Provenge from the market.

Dr. Grillo-Lopez is the non-voting industry rep on FDA's ODAC panel. Dr. Grilli stated:

*The FDA should refrain from any action that could, even remotely, give the impression that they are manipulating the ODAC. (Dr. Grillo-Lopez has been interrupted on a number of occasions by.....regulator, Dick Pazdur, at ODAC meetings.)*

Dr. Grillo-Lopez also said, though, that

*Presumably the FDA is having a difficult time coming to a decision when it seeks the committee's advice. However I have the distinct impression that at each and every presentation the FDA has already made the decision*

If the AC meetings are a fraud (fake) then the FDA is not following congressional mandate and it is wasting tax payer monies. The Court does not have to buy into *speculative reasons* as to why the FDA took such actions. The FDA should be accountable for the actual reasons that they did. The FDA has yet to present to the Court or the public the procedure they followed to come to the conclusion not to approve Provenge and what the definitive reasons were for not following the Advisory Committee's recommendation. Until such evidence and a complete record are presented, there can be no judicial finding that any potential reasons for the "Complete Response Letter" (CRL) were the actual reasons. The question at this point is whether the actions of the FDA in not following the positive recommendation for conditional approval of a therapy in a life threatening disease of its own Advisory Committee, and then, not clearly explaining the reasons for such rare conduct to the public it is sworn to protect, constitutes arbitrary and capricious conduct and justifies allowing the lawsuit to proceed immediately to an injunctive hearing.

The post hoc survival analysis, the 9901 miss on its primary endpoint of TTP (which was designed per agency instruction and is no longer an appropriate FDA endpoint as survival is now the stipulated gold standard) and even the failure of the Cox models were all included in the Advisory Committee Briefing Materials and were part of the public record that was the basis for the Advisory Committee's positive recommendation. Therefore, absent some extraordinary circumstances, none of those reasons logically should constitute a reasonable basis for overruling the AC when all such reasons were presumptively considered by the AC. A corollary to this situation where the parties refer a complex and difficult case to an arbitrator, and then, when a somewhat unexpected decision is reached, a party not only refuses to respect the decision, but even refuses to explain why. While an Advisory Committee's recommendations are not legally binding on the FDA, *Congress would not have provided for them if their advice was meant to be ignored without justification.* That's why Federal Courts have the power to assure that Federal Agencies do not act arbitrarily and capriciously. The lack of explanation by the FDA is akin to an Appellate Court reversing a lower Court without a decision (even if the lower court action was decided by a jury of 17 experts). The lack of explanation on the part of the FDA renders the decision per se arbitrary and capricious.

Speculative and ever moving reasons espoused by the government counsel's are not sufficient public accountability. Even these hypothetical reasons put forth hold no muster. The requirement for two successful Phase 3 trials was amended by Congress in the mid 1990s so that in a life threatening disease, only one well controlled trial is required, which the FDA has said neither be long or large See: The 11/09/05 FDA Comments on Accelerated Approvals stating (i) that a single well designed clinical trial

neither be large nor long for FDA marketing approval (at page 34), and, (ii) that the FDA always has the power to withdraw Regular Approval should a post approval Phase 4 trial fail (at pages 59 to 65): [http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4191B1\\_01\\_02-21CFR-314-601.pdf](http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4191B1_01_02-21CFR-314-601.pdf). Note that these guidelines were issued about two months after DNDN had its pre-BLA meeting with the FDA in September 2005 at which, DNDN reported that the FDA stated that no additional Provenge efficacy data would be required in spite of a 9902a Kaplan Meier p value in 9902a of 0.331. The pre-BLA meeting was also 6 months after a 3/05/05 ODAC meeting that unanimously recommended that survival be the primary endpoint in all AIPC clinical trials. Finally, in February 2007, the new clinical trial paradigm for cancer vaccines which the FDA jointly developed with the NCI and others was presented at the FDA/NCI Workshop which stated that in trial endpoints such as TTP, time should be allowed for an immune ramp-up, specifically suggesting, as an example, three months before TTP would start to be measured. If that standard had been applied to 9901's TTP it would have easily been statistically significant for TTP.

The FDA had constituted an Advisory Panel per statute to specifically consider the tradeoffs among complex factors. When those factors are part of the record considered by the Advisory Committee in reaching a decision, any AC decision should effectively remove those issues from being factors used by the FDA as reasons for ignoring the AC recommendations absent some extraordinary factors not considered by the AC.

The public has the right to review the full and complete record and to be allowed discovery on a matter effecting vital public interests given the specific unusual

circumstances of this FDA action in issuing a CRL, which could delay a therapy in a life threatening disease from reaching the public, possibly until 2010, without even explaining the vital contrary interests to be protected in overruling the recommendations of its Advisory Committee.

The Defendants response evades this entire issue by going directly to the statute and case law based on the *false premise* that the public has had the same access to an official record, whether it is final and complete or a work in process. Consistently in Complte Response Letters, "CRL's" the FDA gives the recipient (drug manufacturer) a relatively short period of time to file an appeal, obviously not taken here. So that for the Defendants to argue that no appeal can be taken because the record is not final until 9902b results are known is to play games, since Dendreon was undoubtedly given the right to appeal themselves. Most CR letters provide a right to appeal within 10 days to the applicant and it is believed the CR to Dendreon says the same thing. If Dendreon has a right to appeal, then why not the public including the patients that the FDA is sworn to protect. The Defendants assert that the public and even dying patients have lesser rights and cannot contest the agency action in any meaningful way at all.

This was not a management decision made in the ordinary course of business where a principle of executive privilege might have some meaning. This was a life and death decision without specific explanation which was arbitrary and capricious. Cancer patients who believed they were soon to receive Provenge have a right to know why they can't have it now.

Recent history suggests that valid public interests as to safety, availability and other matters may be different from the interests and actions of both the FDA and the sponsors of BLAs and NDAs (drug companies). This Federal District Court does not have to find an expansive right to any public group to second guess FDA decisions to find that, in this case, where the FDA overruled its own Advisory Committee without any accountability to the public, the absence of such accountability, per se, was arbitrary and capricious and thus subject to judicial review. All the other issues can be dealt with when a small amount of discovery provides a complete record.

At a minimum the Court should consider that it will have to have some hearing and conduct some review of this matter so it makes sense to move towards that end.

#### **5 U.S.C.A § 706. Scope of review**

To the extent necessary to decision and when presented, the reviewing court shall decide all relevant questions of law, interpret constitutional and statutory provisions, and *determine the meaning or applicability of the terms of an agency action*. The reviewing court shall--

- (1) compel agency action unlawfully withheld or unreasonably delayed; and
- (2) hold unlawful and set aside agency action, findings, and conclusions found to be--
  - (A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law;
  - (B) contrary to constitutional right, power, privilege, or immunity;
  - (C) in excess of statutory jurisdiction, authority, or limitations, or short of statutory right;
  - (D) without observance of procedure required by law;
  - (E) unsupported by substantial evidence in a case subject to sections 556 and 557 of this title or otherwise reviewed on the record of an agency hearing provided by statute; or
  - (F) unwarranted by the facts to the extent that the facts are subject to trial de novo by the reviewing court.

In making the foregoing determinations, the court shall review the whole record or those parts of it cited by a party, and due account shall be taken of the rule of prejudicial error.

The Plaintiffs citizen petition whether addressed by the Agency or not does not address all the legal issues or factual issues involved in this complex matter so there is *no real petition or time requirement*. Even the granting or denial of the Citizen petition does not necessarily render this case moot (although it's granting might facilitate settlement discussions). Based on history the FDA will never respond to the CTL petition. Even if this Court concludes that a petition must be filed even where legal matters are at issue, that the agency can't provide any sense of urgency to such an important matter and decide it in less than 180 days seems disingenuous, uncaring and insensitive to patients and will lead to a finding that section 10 of Title 21 is unconstitutional as applied to late stage cancer patients. Whether it's to decide a toe fungus cream issue or the capricious nature of a denial of a life saving immunotherapy for cancer patients; that the same non urgent time frame is used to for agency review lacks common sense or compassion. It is a mistaken strategy for the Defendant Agency to push this Court to have to make a determination of the constitutionality of Title 21 USC section 10 (Citizen Petition) when applied to dying AIPC Cancer patients who have a life expectancy of 20 months. This Court need not yet determine the constitutional question and should not have to as the petition was filed as an alternative method of relief and not the sole method. Once the Court finds that the FDA's decision is subject to judicial review the Court need not address the significant constitutional questions Plaintiff has raised regarding Title 21 section 10 (and will further raise in their memo contra Defendants motion to dismiss. It is well-established that judicial restraint requires this Court to refrain from reaching constitutional issues in advance of the necessity of deciding them. *Lyng v. Northwest*

*Indian Cemetery Protective Association*, 485 U.S. 439, 108 S.Ct. 1319, 99 L.Ed.2d 534 (1988); *Ashwander v. Tennessee Valley Authority*, 297 U.S. 288, 346-48, 56 S.Ct. 466, 482-83, 80 L.Ed. 688 (1936) (Brandeis concurring).

This Court should also allow at the hearing some evidence to clarify assist and explain the administrative record that will be before the Court. *Robinette v. Commissioner*, 439 F.3d 455 (8th Cir. 2006); *Murphy v. Commissioner*, 125 T.C. No. 15 (2005). Moreover, the evidence sought is not so much “discovery outside of the administrative record” but, rather, discovery that *clarifies* the administrative record by confirming what evidence was before the unidentified decision makers during the unidentified process at the undisclosed FDA location, when it made its surprising determination not to approve Provenge and by refusing to explain the reasoning process. There is nothing asserted by the parties, therefore, that would appear to prevent the Court from considering this testimony. *Justus v. Roofers' and Waterproofers' Local No. 44* 2007 WL 892997, \*1 (N.D. Ohio) (N.D. Ohio, 2007). Evidence outside the administrative record may also be considered if that evidence is offered in support of a procedural challenge to the administrator's decision, such as an alleged lack of due process afforded by the administrator or alleged bias on its part.

Even if this Court decides it should be deferential despite the lack of definitive explanation for the agency actions, and the unprecedented nature of the decision, the review is never the less required to be still searching. “The arbitrary- and-capricious ... standard does not require us merely to rubber stamp the administrator's decision.” *Jones v. Metro. Life Ins. Co.*, 385 F.3d 654, 661 (6th Cir. 2004) (citing *McDonald v. Western-Southern Life Ins. Co.*, 347 F.3d 161, 172 (6th Cir. 2003)). “Deferential review is not no

review, and deference need not be abject.” *McDonald*, 347 F.3d at 172. The failure of the FDA to follow the independent-review experts and to comply with their recommendations and instructions or to explain why they had disregarded the opinions was arbitrary. *See McDonald*, 347 F.3d at 170-73 (holding a plan administrator's denial of benefits to be arbitrary and capricious where the administrator gave no explanation for ignoring the reports of the treating physicians and two independent file reviewers that the claimant was disabled).

The FDA non explained decision is per se capricious since they refuse to provide the public with objective reasons why they reached a decision to not approve Provenge and the burden should thus be shifted upon Defendants shifting back to Plaintiffs only upon a public and Court disclosure of THE specific reasons and THE specific process it followed to reach the decision and until then the Court cannot make any other determination other then the agency actions are arbitrary and capricious.

WHEREFORE this Court should docket an injunction hearing and allow some brief discovery by Plaintiffs prior to that hearing and thereafter grant the injunctive relief requested.

Respectfully submitted,

S/Kerry M. Donahue

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## CERTIFICATE OF SERVICE

This document was e-filed and it is understood that the United States Clerk will e-mail a copy of this Reply to each counsel of record this 8<sup>th</sup> day of October 2007.

S/Kerry M. Donahue

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Kerry M. Donahue

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<sup>1</sup> The Celgene/Revlimid panel in '05. Arguably the most recent significant oncology drug approval in biotech, a worthwhile benchmark. Martino chaired it, Pazdur delivered opening remarks, it was an ODAC panel. In his remarks Pazdur the stickler highlighted the fact that of the two trials submitted in the filing (neither of which were phase 3 trials, and consisting of one principal plus one supportive trial... sound familiar?) neither were randomized trials. Open label trials without a control arm, placebo or otherwise. Lack of randomized data is not exactly a point of statistical minutiae, goes to the very heart of scientific process. Pazdur said they had asked sponsor to conduct randomized trials and these weren't randomized. But he gave it no teeth... He made mention of it, in sort of duly noted fashion, before explaining how approval could still be merited given such a deficit, anyway, if the context was right. Then moved on. Clarifying a point, that the application would be considered for full approval and not subpart H accelerated approval.

The two trials in the NDA were sized as follows: principal trial 148n, supportive trial 45n. That is not a typo, the supportive trial was just forty five patients. It was a pilot trial (it was accepted as "supportive" and in fact there wasn't much discussion about it as I recall). Revlimid is derived from thalidomide a known dangerous compound. Of course neither trial randomized. A third, larger, randomized phase 3 trial was already underway but had yet to complete enrollment (leaving the door open to awaiting confirmatory data i.e. a plausible approvable letter scenario). ODAC/Pazdur had more than one reason to justifiably deny Revlimid.

The panel voted 10-5 favorably on the approval question, voted no on a different question. Strongly in favor but hardly unanimous again leaving the door open to an approvable. Full approval was granted three months later in Dec 05 after a short extension.

Pages 1 to 99

<http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4174T2-Part1.pdf>

Pages 100 to 199

<http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4174T2-Part2.pdf>

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Pages 200 to 210 - the hearing ends on page 210  
<http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4174T2-Part3.pdf>