

CASE NO. 07-4465

IN THE UNITED STATES COURT OF APPEALS
FOR THE SIXTH CIRCUIT

CareToLive

Plaintiff - Appellant

v.

Andrew von Eschenbach, as commissioner of FDA
Defendant – Appellee

On Appeal from the Southern District of Ohio, Eastern Division

REPLY BRIEF OF APPELLANT

Kerry M. Donahue (0061105)
BELLINGER & DONAHUE
6295 Emerald Parkway
Dublin, Ohio 43016
Telephone: (614) 761-0402
Facsimile: (614) 789-9866

TABLE OF CONTENTS

TABLE OF CONTENTS i

INDEX OF AUTHORITIES ii

LAW AND ARGUMENT..... 1

CONCLUSION 32

CERTIFICATE OF COMPLIANCE 33

CERTIFICATE OF SERVICE..... 34

INDEX OF AUTHORITIES

<i>Abbott Laboratories v. Gardner</i> , 387 U.S. 136, 87 S.Ct. 1507, 18 L.Ed.2d 681 (1967)	4, 5
<i>Air Brake Sys., Inc. v. Mineta</i> , 357 F.3d 632 (6th Cir.2004)	30
<i>Arbaugh v. Y & H Corp.</i> , 546 U.S. 500, 126 S.Ct. 1235, 163 L.Ed.2d 1097 (2006)2	
<i>Atl. States Legal Found. v. Env'tl. Prot. Agency</i> , 325 F.3d 281(D.C.Cir.2003)	31
<i>Bennett v. Spear</i> , 520 U.S. 154, 117 S.Ct. 1154, 137 L.Ed.2d 281 (1997)	30
<i>Center for Auto Safety v. NHTSA</i> , 452 F.3d 798 (D.C.Cir.2006)	3
<i>Center For Biological Diversity v. U.S. Dept. of Housing and Urban Development</i> 241 F.R.D. 495 (D.Ariz.,2006)	2
<i>Cont'l Air Lines, Inc. v. Civil Aeronautics Board</i> , 522 F.2d 107, 125 (D.C.Cir.1974)	30
<i>Gillis v. U.S. Dep't of Health and Human Servs.</i> , 759 F.2d 565 (6th Cir.1985)	30
<i>In re Beck Industries, Inc.</i> , 725 F.2d 880 (2d Cir.1984)	2
<i>Ohio Forestry Ass'n, Inc. v. Sierra Club</i> , 523 U.S. 726, 118 S.Ct. 1665, 140 L.Ed.2d 921 (1998)	4
<i>Presbyterian Church (U.S.A.) v. United States</i> , 870 F.2d 518 (9th Cir.1989)	3
<i>Red Lake Band of Chippewa Indians v. Barlow</i> , 846 F.2d 474 (8th Cir.1988)	3
<i>Reliable Automatic Sprinkler Co. v. Consumer Prod. Safety Comm'n</i> , 324 F.3d 726 (D.C.Cir.2003)	2, 3
<i>Steel Co. v. Citizens for Better Environment</i> , 523 U.S. 83, 118 S.Ct. 1003, 140 L.Ed.2d 210 (1998)	2
<i>Trudeau v. FTC</i> , 456 F.3d 178 (D.C.Cir.2006)	2, 3
<i>United States v. L.A. Tucker Truck Lines, Inc.</i> , 344 U.S. 33, 73 S.Ct. 67, 97 L.Ed. 54 (1952)	2
<i>Wyoming Outdoor Council v. U.S. Forest Service</i> , 165 F.3d 43 (D.C.Cir.1999)	4

Other Authorities

5 U.S.C. § 702	2, 3, 29
5 U.S.C. § 704	30
5 U.S.C.A. § 706	29
21 C.F.R. § 601.2	12, 15
28 U.S.C. § 1331	3
Rule 12(b)(1)	3

LAW AND ARGUMENT IN REPLY

The crux of the argument and issues presented turn on finality. However, when dealing with the Administrative Procedures Act (“APA”), “finality” versus “final agency action” encompass different requirements.

FINAL AGENCY ACTION UNDER ADMINISTRATIVE PROCEDURES ACT

An action under the APA takes final agency action. However final agency action is not a jurisdictional requirement and thus the factual disputes regarding that issue are subject to discovery, which the lower Court disallowed. Under the APA one of the elements is final agency action but the one single document that would go a long way in determining whether the agency action was final is the Complete Response (CR) Letter. While Defendants have had the opportunity to fully review that document, neither the Plaintiff nor the Court has had the privilege of doing so. In addition, we must take Commissioner von Eschenbach at his word when he stated in a private meeting with advocates, “there would be no change” and that the decision not to approve Provenge was final and would not be reconsidered. That’s as final as can be. Other evidence may be available through discovery that would be relevant to support that a determination was made and that there was a sufficiently final agency action that allows Plaintiff to invoke the immunity waiver contained in the APA. The District Court dismissed under

12(b)(1) and the Plaintiff has a right to conduct discovery on the issue of final agency action.

Discovery may be appropriate regarding jurisdictional challenges and the issue of final agency action is a factual question entitling Plaintiffs to discovery. *Center For Biological Diversity v. U.S. Dept. of Housing and Urban Development* 241 F.R.D. 495, 501 (D.Ariz.,2006). See *Trudeau v. FTC*, 456 F.3d 178, 184 (D.C.Cir.2006) (explaining that “the APA's final agency action requirement is not jurisdictional”). See 5 U.S.C. § 702 (authorizing judicial review of “agency action”). While it is true that some opinions have loosely referred to the final agency action requirement as “jurisdictional, that is hardly surprising, as jurisdiction ... is a word of many, too many, meanings.’ ” *Arbaugh v. Y & H Corp.*, 546 U.S. 500, ----, 126 S.Ct. 1235, 1242, 163 L.Ed.2d 1097 (2006) (quoting *Steel Co. v. Citizens for Better Environment*, 523 U.S. 83, 90, 118 S.Ct. 1003, 140 L.Ed.2d 210 (1998)). Or, as Judge Friendly and Justice Frankfurter put it more poetically, the word is “ ‘a verbal coat of too many colors.’ ” *In re Beck Industries, Inc.*, 725 F.2d 880, 881 (2d Cir.1984) (Friendly, J.) (quoting *United States v. L.A. Tucker Truck Lines, Inc.*, 344 U.S. 33, 39, 73 S.Ct. 67, 97 L.Ed. 54 (1952) (Frankfurter, J., dissenting)). In *Reliable Automatic Sprinkler Co. v. Consumer Prod. Safety Comm'n*, the Court made clear that, where “judicial review is sought

under the APA rather than a particular statute prescribing judicial review, the requirement of final agency action is *not* jurisdictional.” 324 F.3d 726, 731 (D.C.Cir.2003). In a case recently decided, the court followed *Reliable*, reaffirming that the APA's final agency action requirement is not jurisdictional. *See Center for Auto Safety v. NHTSA*, 452 F.3d 798, 805 (D.C.Cir.2006) (citing *Reliable*, 324 F.3d. at 731). *Trudeau v. Federal Trade Com'n* 456 F.3d 178, *184, 372 U.S.App.D.C. 335, **341 (C.A.D.C.,2006). The Court in Trudeau:

In sum, we hold that APA § 702's waiver of sovereign immunity permits not only Trudeau's APA cause of action, but his nonstatutory and First Amendment actions as well. We also hold that the waiver applies regardless of whether the FTC's press release constitutes “final agency action.” *Accord Presbyterian Church (U.S.A.) v. United States*, 870 F.2d 518, 525 (9th Cir.1989) (holding that the government's “attempt to restrict the waiver of sovereign immunity to actions challenging ‘agency action’ as technically defined in § 551(13) offends the plain meaning of the amendment”); *Red Lake Band of Chippewa Indians v. Barlow*, 846 F.2d 474, 476 (8th Cir.1988) (rejecting the contention that the waiver in § 702 “exists only to allow review of a final agency decision,” and holding that “[t]he waiver of sovereign immunity contained in section 702 is not dependent on application of the ... review standards of the APA”). The district court therefore had subject-matter jurisdiction to hear Trudeau's suit under 28 U.S.C. § 1331, and its dismissal of the complaint for lack of jurisdiction pursuant to Rule 12(b)(1) was erroneous.

Because the lower Court dismissed this matter on the basis of lack of jurisdiction under 12 (b)(1), and because the Court accepted unsupported factual contentions of the Defendants without having accepted the Plaintiffs factual

contentions, and did this without discovery, the Court essentially without notice to Plaintiffs, turned a motion to dismiss into a motion for summary judgment. Furthermore, since clear factual errors were made by the District Court, this matter must be reversed.

ARTICLE III RIPENESS AND FINALITY

To meet the Article III requirements of ripeness in the context of a challenge to an administrative action, a plaintiff must demonstrate both (1) the fitness of the issues for judicial decision, and (2) the hardship to the parties of withholding court consideration. *See Abbott Laboratories v. Gardner*, 387 U.S. 136, 149, 87 S.Ct. 1507, 18 L.Ed.2d 681 (1967). In evaluating such a challenge, a court must consider whether judicial intervention would *inappropriately* interfere with further administrative action, whether the court would benefit from further factual development of the issues, and whether delayed review would cause hardship to the plaintiffs. *See Wyoming Outdoor Council v. U.S. Forest Service*, 165 F.3d 43, 48-49 (D.C.Cir.1999) (quoting *Ohio Forestry Ass'n, Inc. v. Sierra Club*, 523 U.S. 726, 733, 118 S.Ct. 1665, 140 L.Ed.2d 921 (1998)). The ripeness doctrine prevents the courts through premature adjudication “from entangling themselves in abstract disagreements over administrative policies,” and it “protects agencies from judicial interference until an administrative *decision has been formalized and its effects felt*

*in a concrete way by the challenging parties.” Abbott Laboratories v. Gardner, 387 U.S. at 148-49, 87 S.Ct. 1507. The FDA, with the help of a slew of in house attorneys, has created a labyrinth of regulations, all designed to avoid oversight and minimize due process. One of the latest creations of the FDA is the Complete Response Letter (“CR”), which is a very important, yet still unseen document in this litigation. In the magical world of the FDA they have created a mechanism that Houdini would be proud of. They turned a functionally final decision, into a self declared non-final decision. The issuance of the CR letter, that essentially is believed to say come back and see us in one, two, three or more years, when, or if, you get more data, *is no different in application or in function than an outright denial of the application*, yet the FDA forces people to accept their contrived definition, which is that a “Complete Response” letter is not a “final response” or even a decision, and that there is still an ongoing process, as they could still approve the application, sometime in the nebulous future. In Provenge's case, the CR letter operates to the applicant, the dying patients, the patient's families, and everyone else, as a complete denial. A CR letter is just the latest fiction created to avoid oversight.*

To gain approval after a CR letter, the applicant must go through the same process as if they were submitting a new application. Following either a denial, or

a CR letter, dying cancer patients still can't have access to the treatment. A CR letter and a denial, result in the same outcome in the real world. Certainly there is an ongoing process, but this is a bit of a farce because *there is always an ongoing process between the FDA and every biotech or pharmaceutical company in the country*. If the FDA denied Provenge via a not approvable letter, there would still be an ongoing process and if the FDA approved Provenge, there would still be an ongoing process since the FDA can always revoke the license or demand more data any time it wishes.

The description the FDA puts on an action is not determinative of the reality of the action. Just because the agency says it is not a final decision does not change the fact, that a non approval by CR, and a denial, are in effect the same thing. Apparently the only thing a CR does differently from a not denial, is to diminish both the applicants and the patients due process rights to contest it. Even if the FDA issued a denial letter for Provenge on May 8, 2007 instead of a "complete response letter", the applicant would not have just taken their ball and gone home. They would still be doing the exact same thing: working with the FDA to try to gain approval for Provenge. The same is true for any company that believes it has a medicine that is safe and effective and has cleared all regulatory hurdles to approval. The applicant would be, and will be, doing the same thing, whether the

FDA stated it denied the application, or whether it non approved it. The patients will also be doing the same thing, either way.

Further, there is no appreciable difference in communications between the FDA and the applicant after a Complete Response Letter and a denial. The FDA meets with applicants, offers advice for ongoing trials, and provides guidance for how to get the drug approved, regardless of which letter template they decided to use to frame their response.

Another option that was available for the FDA, was to grant conditional approval. Under a conditional approval, patients would have been allowed access to Provenge, while even further confirmation of efficacy is obtained. If that action had properly been taken, patients would now be benefiting. That it didn't happen is a crime against humanity.

The issue of finality is even clearer if this Court looks at this situation through the eyes of the thousands of men that will have died without the hope that Provenge could provide them. To the thousands of men that have died since the FDA denied approval (issued the CR letter), instead of approving or conditionally approving the license, the action of the FDA is absolutely final. To CareToLive member John Fish who died of late stage prostate cancer on December 18, 2007, the decision was final. To CareToLive member Marilyn Fish, John's wife, and his

children the Provenge decision was final. To all the other AIPC patients, including an Ohio Judge who recently died of AIPC, who had shorter, less quality lives because they could not access Provenge, the Provenge decision was final.

The issues are sufficiently refined for judicial review, and the process is not more or less interrupted by a review, whether the Agency had issued a CR or a denial. A clearer understanding necessitates a consideration of the process by which a Biologics License Application (“BLA”) is submitted and reviewed.

A. BLA PROCESS AND FDA ACTIONS IN RESPONSE TO BLA

In recognition that safe, effective treatments were taking too long to get to patients who have serious life threatening conditions such as cancer, Congress enacted legislation designed to get treatments to the patients in a more timely manner. First, a Biologics License Application (BLA), can receive Fast Track Status. Later in the process, if there are sufficient data, a BLA can be granted “Priority Review Status”. When Priority Review is granted, the Prescription Drug User Fee Act (“PDUFA”) date, which is the date the FDA must *return their decision* on the BLA, is 6 months from the date the completed application was submitted by the applicant.

A drug that receives Fast Track designation is eligible for some or all of the following:

- More frequent meetings with FDA to discuss the drug’s development plan and *ensure collection of appropriate data* needed to support drug approval
- More frequent written correspondence from FDA about such things as the design of the proposed clinical trials

The frequency of communication assures that questions and issues are resolved quickly, theoretically leading to earlier drug approval and access by patients.

Products regulated by CBER are *then* eligible for priority review if they provide a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious or life-threatening disease. Products are not generally granted Priority Review (and presented to an Advisory Committee (“AC”)) if there are *insufficient data*.

Fast Track designation also means that the BLA is eligible for Rolling Review, (ie; portions can be submitted and reviewed while other portions are still being written). This is opposed to the normal process where the entire application must be submitted at once. *Both the clinical and non clinical sections* of the Provenge rolling submission were completed and provided to the FDA as of August 24, 2006

<http://investor.dendreon.com/ReleaseDetail.cfm?ReleaseID=208238>. The chemistry manufacturing and controls sections submitted in November 2006 completed the application process. The Rolling Review allows the FDA clinicians

to review the sections of the data as it comes in and work with the applicant to make sure that they have the proper and required data, rather than waiting to begin their review only after the entire BLA has been submitted. Importantly, *the FDA had all the final clinical data supporting the safety and efficacy of Provenge as of August 24, 2006.*

<http://investor.dendreon.com/ReleaseDetail.cfm?ReleaseID=225661>. Between August 24th, 2006 and the issuance of the Complete Response (CR) Letter on May 8th 2007, the FDA actions were contrary to the later capricious assertion that the data were not sufficient to be able to evaluate the safety or efficacy of Provenge. The FDA does not empanel Advisory Committees if there are insufficient data for the experts to make an evaluation. After years of review of the rolling submission and then clinical review of the final application submitted on or about November 15, 2006, the FDA approved the application for filing and assigned it priority review status on January 16, 2007. The Dendreon press release stated:

SEATTLE, WA, January 16, 2007.. Dendreon Corporation today announced that the U.S. Food and Drug Administration (FDA) has accepted for filing and has assigned priority review status to the Company's Biologics License Application (BLA) for PROVENGE® (sipuleucel-T), its investigational active cellular immunotherapy for the treatment of asymptomatic, metastatic, androgen-independent (also known as hormone refractory) prostate cancer.

Priority Review is granted to products that, if approved, would provide a significant improvement in the safety or effectiveness of the treatment,

diagnosis or prevention of a serious or life-threatening disease. The goal for reviewing a product with Priority Review status is six months from the filing date. The Prescription Drug User Fee Act (PDUFA) date for completion of review by the FDA of the PROVENCE BLA is May 15, 2007.....

The Provenge BLA was submitted on or about November 15, 2006.

Therefore, once Priority Review status was granted, the decision date by which the FDA had to approve, not approve, or to give conditional approval to Provenge, or in other words, the date for which the FDA was required *to act* in the case of Provenge, was May 15, 2007. It was after a full review by clinicians within the FDA, that it was determined by those clinicians that there were *sufficient data* to evaluate Provenge. When the FDA accepted the Provenge application and granted Priority Review status to the application, it did so because FDA clinicians determined that there were in fact *sufficient data*, and because Provenge is a treatment for a life threatening condition for which there are no viable treatment options.

If the application was “incomplete” (lacked sufficient data) the FDA should have, in accordance with regulation, refused to accept it for filing, as it often does. If not for the belief that there were sufficient data to evaluate, the FDA never would have taken the next step, which was to convene an Advisory Committee, who after a full hearing, determined that Provenge was safe and demonstrated substantial evidence of efficacy. If the data in the application were insufficient for

evaluation, the FDA should not have evaluated it and wasted millions of dollars doing so.

Once the application was accepted rather than “refused to file”, the options available to the FDA were to approve, to not approve, or to grant conditional approval. Asking for “more data” after more than 9 months from submission of the entire clinical portion had passed, is essentially stating that the application was incomplete, something more reasonably determined before accepting the BLA, and before wasting millions of dollars. It was at the time application was made, not later, that the FDA had the following choice: FDA may (1) 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, (Appellee brief at p. 7).

Either the Provenge BLA was complete, containing all necessary data, or it wasn't. The data didn't change. If a Biologics License Application (BLA) is incomplete, or in other words, does not contain sufficient data to be evaluated, then it should not be evaluated. Provenge WAS evaluated, including an evaluation by 17 outside experts. The experts, at the time of voting, did not say, I can't vote yes or no because there are insufficient data.

Congress has mandated that the FDA (after it has determined that an application is complete and accepts it), convene a panel of experts to help it

evaluate treatments such as Provenge. This mandate was issued because Congress recognized that which the FDA recently admitted in a self evaluation subcommittee report http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf , that the FDA does not have the resources and the agency experts available to properly evaluate new cutting edge treatments (like Provenge). The report indicated that the main problem areas at the FDA are a weak scientific organizational structure, *major gaps in scientific expertise*, and an inadequate IT infrastructure, which the subcommittee called disturbing. In addition to recruitment challenges, the turnover rate of the science staff is double that of other government agencies.

This is exactly why the expert AC meetings are so important, and why the FDA acted capriciously when it acted contrary to the opinion of the outside experts recommendations in this matter. The FDA does not have the ability to evaluate these novel new treatments on its own. In this case, a very few individuals, some of whom worked for a competitor of Provenge, were able to override the overwhelmingly positive majority of the AC experts, who overwhelmingly recommended to approve Provenge.

After years of clinical review, the FDA followed the Congressional mandate and empanelled the Advisory Committee of 17 outside experts to assist it in evaluating Provenge. If an AC is empanelled in situations where there are not sufficient data for the outside experts to properly review the application, it not only undermines the Congressional mandate to get safe and effective treatments to cancer patients more quickly, it wastes a huge amount of taxpayer resources. The convening of outside AC panels are *extremely* expensive for both the applicant and the FDA. This case is a perfect example of an unmet medical need, Fast-tracked given Priority Review status and approved by the AC, all as per the Congressional mandate, but then delayed for improper reasons, thereby achieving the opposite of the mandate to speed treatments along to patients, and instead stalling and resetting the clock in backwards motion, thereby delaying an effective, safe therapy for countless years on end.

Once an application has been accepted, reviewed by FDA clinicians, granted Fast Track status, granted Priority Review status, given a hearing and discussed and reviewed by 17 experts and otherwise considered for 6 months, then the FDA reasonably and properly has two choices:

21 C.F.R. § 601.4 Issuance and denial of license.

(a) A biologics *license shall be issued* upon a determination by the Director, Center for Biologics Evaluation and Research....a biologics license shall be

valid until suspended or revoked.

(b) If the Commissioner determines that the establishment or product does not meet the requirements established in this chapter, the biologics license *application shall be denied* and the applicant shall be informed of the grounds for, and of an opportunity for a hearing on, the decision....

21 CFR § 601.2 (emphasis added)

The newly created oversight avoiding subsection (3), is the proposed rule regarding issuing CR letters, instead of approving or not approving the application. The FDA, in order to avoid Congressional and Court oversight, has proposed that they be able to issue these CR letters, and that such letters do not constitute final decisions. A decision not to approve is a final decision in all ways that matter. It is not a decision that they are going to change, absent the applicant reapplying with additional “data” which are accumulated whenever a patient in the trials dies (either a Provenge recipient or a placebo recipient). Unless further “data” are submitted, the FDA could later close the file, or they could leave it open for eternity, never ever making a “final” decision and forever avoiding review. The mistake is therefore one that could be repetitive yet one that avoids review. There is no known regulation that says the agency must ever take “final” action. The FDA may *never* take any additional action on Provenge. Any *further* agency action

is contingent on some action (resubmission) by the applicant, which makes the last agency action (CR) sufficiently final for judicial review.

A denial and CR letter functionally act the same way. They both deny access to late stage prostate cancer patients who have been given a death sentence, the ability to access Provenge, and there is no chance for later access, *unless* the applicant chooses and/or has the ability to spend another hundred million dollars or so, to obtain the additional data, which were so capriciously requested by the FDA. In the meantime, the unreasonable, arbitrary and capricious action of the FDA is costing AIPC patients longer, better quality lives, and effectively slowing the advancement of immunotherapies in general, for treatment of all types of cancer.

The Appellee makes much of the applicant being agreeable to continue to work with the FDA, but the applicant is left with no other viable alternative than to try to placate the FDA, no matter how unreasonable the FDA is acting. Dendreon, as most applicants, has other products in development and has to deal with the FDA repeatedly in the future. Most applicants cooperate out of fear of the FDA's power and because they cannot afford to aggravate the FDA, whom they must keep an amiable, working relationship with, no matter what. The applicant, being a public corporation, has little choice but to act in the best interest of its shareholders, even if that might not necessarily be in the best interest of the current

AIPC patients. It's the patients who suffer painful, premature deaths due to the actions of the FDA.

The patients' only recourse is to file a Citizens Petition and/or to commence litigation. Seeing as how the Appellee opened the door in its brief, the Appellant wants to respond to the assertion that the FDA properly responded to the CareToLive Citizens Petition in January 2008 (proper response due by FDA by January 24, 2008). They did not, because they merely stated that they were still reviewing it (the same legal maneuver executed thus far successfully with the CR letter). They did not properly respond. This was the pertinent section of the response:

In your citizen petition you request the Commissioner of Food and Drugs to reconsider FDA's failure to grant a biologics license application for Provenge...We are still considering your request and supporting information stated in your citizen petition....we will respond to your petition as soon as we have reached a decision on your request".

However, 21 CFR(e)(2) states:

(2)... the Commissioner shall furnish a response to each petitioner within 180 days of receipt of the petition. The response will either:

(i) Approve the petition....

(ii) Deny the petition; or

(iii) Provide a tentative response, *indicating why the agency has been unable to reach a decision on the petition, e.g., because of the existence of other agency priorities, or a need for additional information.* The tentative

response may also indicate the likely ultimate agency response, and may specify when a final response may be furnished.

The response did not indicate “why”. Again the FDA merely uses these tactics to avoid any oversight and neither the applicant, nor the Plaintiffs, has received their due process of law. The patients are left without recourse to obtain a benefit they have a constitutional right to access. The FDA strategy should be seen for what it is; to employ a mechanism of “ongoing consideration” to thwart review and the assertion that their actions are arbitrary and capricious.

The record is fully established. We even have had a hearing judged by handpicked outside experts followed by an FDA decision in contravention of the expert panel’s opinion. Rights to access have been decided and denied.

The hardship to the parties is undeniable since there is no greater hardship than death. The lower Court made at least two errors when it determined a lack of hardship to the parties, both factually and as applied to the case law. The Court assumes the hardship to the Plaintiffs has to be different than the hardship to other patients suffering serious life threatening conditions. Appellant does not agree that the hardship must be demonstrated to be a different hardship, considering the extent of the harm. Regardless, in this case it actually is different. The lower court was incorrect in determining that the patients were merely missing out on a

speculative, unproven benefit. This case is unprecedented in that the patients herein are missing out on a treatment that:

1. Has been through a decade of testing,
2. has proceeded through phase one, phase two, and two phase three trials, all under the guidance of the FDA,
3. has been reviewed by FDA clinicians and determined to be worthy of Fast Track Status,
4. has been accepted for final and complete filing
5. was reviewed by FDA clinicians and determined to be worthy of Priority Review Status,
6. has been granted a hearing overseen by a panel of 17 outside experts,
7. has had an expert panel find overwhelmingly that it is safe and that it has demonstrated substantial evidence of efficacy (the Congressionally mandated standard),
8. which is a treatment for a late stage prostate cancer (AIPC) patient class.

This makes the case *unprecedented* and the factual conclusion reached by the District Court clearly erroneous. Further evaluation of the important factual error is best understood, in light of an overview of the science.

THE SCIENCE

Contrary to the Appellee's assertion, the lower Courts finding that the patients have suffered no harm because they have merely been denied a speculative future benefit was clearly erroneous because Provenge was proven beyond a reasonable doubt to be both safe and effective. Never before has the FDA not followed the overwhelming recommendation of its Advisory Committee when

considering a treatment for a serious life threatening condition. It is only because of the clearly capricious conduct by the FDA that these men continue to be denied Provenge.

Appellee attempts to underwhelm the Court by stressing a 4.5 month “average” extension in survival to Provenge patients. That understates the effectiveness. Average is different from median. It’s an important distinction because misuse of the term "median survival" is one of the deceptive arguments used by those who are against Provenge approval (FDA). When anti-Provenge forces use the "average" terminology and attribute it to the median, they are undercutting the total Provenge beneficial effect. At the time of the committee meeting it is estimated that the actual average survival benefit in the 9901 trial was in the 10-12 month range, judging from the likely survival through Feb/Mar 2007 of 20 out of the 28 three-year survivors from 10/04. These 20 Provenge arm survivors would have lived anywhere from 5.5 to 7 years after their randomization between 1/00 and 10/01.

All trials show that Provenge is efficacious by extending survival (D9901 and D9902a). Triple the survival after 3 years. All six clinical studies following PC patients after Provenge treatment have all demonstrated the effectiveness of Provenge. The Provenge arm had a *median* survival advantage of 4.5 months vs.the

control arm. The *median* survival is calculated from each arm by taking the survival time of the person in each arm *at the 50th percentile*. It does not reflect the true long term benefit of a treatment. The Appellee stresses that result because the layman tends to misinterpret it. Numerous patients are doing well on an ongoing basis at 5, 6 and even 7 years since receiving Provenge, whereupon the men who were randomized to placebo in these trials are nearly all dead. For example, say for two treatments, “a” and “b”, the median is a month. After a year all patients in group “a” are dead yet all remain alive in group “b”. The median stays the same in spite of the fact that many patients are still alive in “b”.

The more stunning figure is the 34% survival after three years in the Provenge arm, vs 11% in the control arm. This is a disease stage where the typical survival was 16-19 months, so a 34% three-year survival is very impressive. Also, we knew that in March 2007, only 8 of the 28 three-year survivors in the 9901 trial had died (the calculations for the trial ended in Sept 2004). Therefore, this means that as of 3/07, 20 out of 82 men survived between 5.5 and 7.1 years (the enrollment period for 9901 was 1/00 to 9/01).

The Appellee also stresses that Provenge missed the no longer favored primary endpoint, Time to Progression (TTP). When the trial began nearly 10 years ago the FDA suggested this TTP endpoint, which has since been determined

by the FDA, including Drs. Scher and Hussain, *to be less important than survival*, which is an endpoint that cannot be faked or manipulated. What is meant when the FDA says "it missed its primary endpoint" is that it did not slow selected symptoms of disease progression to an *extremely statistically significant level*. The p value, as calculated by the study investigators, was 0.052, meaning that it barely missed being "stat sig" to the arbitrarily high level of 0.05. It is not as if the results show that the treatment "failed to slow progression." The results do show that the treatment slowed progression of symptoms of the disease. *Most biostatisticians* would call a p=0.052 level of significance "nominally statistically significant." Why the FDA did not think so in this case is unknown.

Unfortunately the FDA forced clerical errors to be counted in the final analysis, which meant that the FDA-calculated p value was 0.085. This still means that the slower progression seen in the Provenge arm was 91.5%-94.8% due to the Provenge, and not due to random chance. Therefore, combined with the 0.01 survival p value (99% due to the Provenge), you have a pretty strong correlation. So, should a correlation of 91.5% (low end of ttp) and 99% be thrown completely out, as the Appellee suggests by omission? Not when, in the real world, you are talking about people's lives. Not when the FDA hasn't believed since at least 2005 that TTP is not an appropriate endpoint.

Fundamentally, the FDA denied Provenge because it did not meet an endpoint the FDA has already said is unacceptable. Provenge met the survival endpoint, *the only endpoint the FDA has accepted for approval since 2005*, at the $p=0.01$ threshold of significance. There is no defensible, real-world reason (as opposed to biostatistical mathematical abstractions) why the data on survival is less accurate simply because it was not listed as a “primary” endpoint. People die when they die, and whether that death is counted first or second on a piece of paper makes no difference as to whether the person is dead or alive.

Importantly the FDA knew full well that Provenge had missed on the inappropriate FDA advised endpoint of TTP *when it accepted the BLA submission*. The later proclamation that more data were needed because Provenge missed on TTP was therefore post ad hoc contrived. This was completely understood and accepted by the FDA and was not supposed to be a barrier to approval. The scientific community has changed its thinking on TTP and determined along with the FDA that TTP is a chemotherapy evaluation technique that does not translate to evaluation of the efficacy of an immunotherapy like Provenge. The FDA’s Oncologic Drugs Advisory Committee (ODAC) determined in 2005 that *survival was the only acceptable endpoint for prostate cancer*. Every pivotal trial for AIPC since then has been advised by the FDA to make survival as a primary endpoint.

The FDA has, to the Appellant's knowledge, never agreed to a Special Protocol Assessment for an AIPC trial with any primary endpoint but survival.

Now, take Provenge's negligible side effects when compared to the only currently approved treatment for late stage prostate cancer, a Chemotherapy treatment called Taxotere. Taxotere kills 2% of its advanced PC patients outright according to published data, not to mention its other severe and debilitating side. Despite the severe side effects, Taxotere extends life on average by only 2.5 months. Compared to Provenge, which has occasional side effects of mild flu like symptoms for a few days after treatment (6-9 days total for the entire course of treatment), the current approved treatment is *less* safe and *less* effective. What the antiquated FDA has done is to evaluate new therapies, like Provenge, the same way it has evaluated chemotherapy treatments through the years. The FDA, by virtue of its own revised trial design guidance, has demoted the importance of traditional markers such as TTP, subordinating them to overall survival. Nonetheless, Appellees continue to trot out TTP like a champion mare when it suits them in this case, while telling anyone else designing a trial that it is an unacceptable endpoint for making an approval decision.. The 9902a study was terminated early because the applicant, prior to the FDA arriving at the same

conclusion, determined that survival *should* be the endpoint rather than TTP, and *not* because TTP would be missed as suggested by Appellee.

This begs the question to Appellees: “Which is it?” Your guidance since 2005 has been that TTP is not a suitable endpoint for an approval decision in AIPC, only survival. Yet in the situation with Provenge, TTP was *supposedly* the driver for the decision and the FDA said the survival benefit was insufficient for approval.

The safety profile of Provenge was never really an issue, until Howard Scher (the FDA special employee, who according to newly established guidelines implemented right after the Provenge AC, would not have been eligible to participate in the process, *even* if just only his disclosed conflicts were considered) *after voting with all other AC members that Provenge was safe*, improperly implied in a post AC letter that there may be a safety issues. Appellees seek to use it again now as a second red herring to try to justify the non-approval decision. Appellees talk of concern of cerebral vascular accident (“CVA”) events (strokes) but the CVA’s were not statistically significant as, in this older patient population, small numbers of CVA events are normal. The risk of CVA’s of U.S. men older than 65 is anecdotally estimated to be 2-3% per year. For the 147 patients in the 9901/9902A treated group, there were 8 CVA’s. If one estimates that the average

survival of this group for the three-year study period was ~26 months, this data would be consistent with the expected risk of CVAs. The Provenge AC voted *unanimously positive on the safety question*, a vote which occurred after the AC discussion of the issue, and members were informed that the FDA and Dendreon have planned to subsequently monitor 3000 Provenge patients for CVAs and any other identified safety issues, in a post approval follow up study. Provenge is considered to have very minimal side effects, in stark contrast to chemotherapy treatments.

Importantly, the FDA statistician himself said that the chance that the survival data were in error was 1 in 40. Yet the FDA, at the urging of a few employees with their own agenda, delayed approval, with a request that rings hollow; “for more data”. At the three year measuring point, 27% of high grade Gleason grade patients (the sickest to begin with) were alive vs 0% for placebo.

Plaintiff is not asking the FDA for any special treatment regarding the rigorous scientific license requirements. Provenge has met each and every Congressional statutory requirement as the submitted BLA data proves. It has also met the endpoint guidance the FDA put in place beginning in 2005. Only the FDA appears to be ignoring its own licensing requirements and guidance. Plaintiff merely seeks review of the Agency actions that appear to have been capricious.

EXTENT OF HARM

The clear error of the Court in accepting Defendants statement that, in not having access to Provenge the patients suffer a harm no different than when they wait for approval of other innovative treatments, misses the point that the FDA acted capriciously in making the decision not to approve (CR). It's the capriciousness of the action that has caused the harm. A factual determination that the patients are only missing out on a merely speculative benefit is difficult to comprehend in the face of the scientific facts coupled with the overwhelming opinion of the 17 member expert committee, hand selected by the FDA to provide their opinions. The Court has made a factual determination from the record that is contrary to the weight of the evidence and contrary to the conclusions of the experts. The FDA's refusal to accept the decision of the experts in this matter is akin to this Court having the luxury of selecting a jury of 17 experts of its choice, from throughout the country, then having those experts review and listen to the evidence, and then ignore their verdict.

Approximately 27,000 men a year are dying from late stage prostate cancer. There are no good treatment options. Unlike other medications evaluated by the Courts, for the first time ever in any Court of Law, this discussion concerns a treatment for an absolutely terminal disease (AIPC) that has no chance of

remission, and involves a treatment that was voted overwhelmingly to be safe and to have demonstrated substantial evidence of efficacy by the expert committee. AIPC is different from earlier stage prostate cancer, where 70% of men die of something other than their prostate cancer, or any other cancer that is in earlier stages. In those situations the patient could be treated by other medicines and could have their cancer go into remission. Dendreon sought access to Provenge ONLY for late stage prostate cancer patients who are AIPC (androgen independent prostate cancer that has later returned after failure of hormone therapy, surgery, and radiation therapy). This is not a class of patients that has other reasonable treatments available or that has hope for remission. This is a first ever, absolutely unprecedented case whereby such circumstances exist, yet the patients are being denied access. The result (harm) is not some minor malady, it is death. Provenge is undeniably safe, so what possible harm could have resulted from conditional approval, enabling men to access it now while additional “data” are accumulated.

The harm done to persons who are already very sick, as late stage prostate cancer patients are, and who are allowed to get sicker by the day awaiting treatment, is irreparable. Sickness and chance of wellness in the case of late stage prostate cancer patients is compounded by an already weakened immune system, which becomes more damaged as the illness progresses and makes the chance of

recovery more and more remote as the compromised immune system has less and less chance to repair itself to attack the cancer. Delay, non approval, and denial, all add up to the same thing, a rapidly approaching, painful death with no viable treatments.. Unlike the patient class in *Rutherford*, unless something else kills them first AIPC patients will die from the cancer

THE ADMINISTRATIVE PROCEDURES ACT

Immunity is really a non issue since a waiver is provided under the APA.

5 U.S.C.A. § 702

A person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action... is entitled to judicial review thereof. An action in a court of the United States seeking relief other than money damages and stating a claim that an agency or an officer or employee thereof acted or failed to act in an official capacity.....

The lower courts authority and scope of review is set forth in section 706.

5 U.S.C.A. § 706

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..

(E) unsupported by substantial evidence...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.

To state a claim for relief under the APA, a plaintiff must allege that his or her injury stems from a final agency action for which there is no other adequate remedy in court. 5 U.S.C. § 704; *Gillis v. U.S. Dep't of Health and Human Servs.*, 759 F.2d 565, 575 (6th Cir.1985.). An action is final where it: (1) marks the “consummation of the agency's decision-making process;” and (2) determines rights and obligations or occasions legal consequences. *Bennett v. Spear*, 520 U.S. 154, 177-78, 117 S.Ct. 1154, 137 L.Ed.2d 281 (1997); *Air Brake Sys., Inc. v. Mineta*, 357 F.3d 632, 639 (6th Cir.2004). For hardship, the court looks to see whether the party can show that it will suffer *injury in the interim*. *Id.* Importantly, “[c]ourts confronted with close questions of ripeness are appropriately guided by the presumption of reviewability.” *Ciba-Geigy*, 801 F.2d at 434 (citing *Cont'l Air Lines, Inc. v. Civil Aeronautics Board*, 522 F.2d 107, 125 (D.C.Cir.1974)).

THE CONSTITUTION

The lower Court also did not consider the Constitutional argument. A Court must examine whether a dispute is fit for judicial review and whether withholding court consideration would cause hardship to the parties. *OhioForestry*, 523 U.S. at 733; *Wyoming Outdoor Council*, 165 F.3d at 48. To measure fitness, the court looks to “*whether the issue is purely legal*, whether consideration of the issue would benefit from a more *concrete setting*, and whether the agency's action is *sufficiently final*.” *Atl. States Legal Found. v. Env'tl. Prot. Agency*, 325 F.3d 281, 284(D.C.Cir.2003).

The District Court stated that the issue was not purely legal since only the Plaintiffs Constitutional argument was a legal one. That fails to recognize that the Plaintiff has a right to plead in the alternative. All issues do not have to be purely legal, one is enough to justify an APA review of that issue. To rule otherwise would render the result that the Plaintiff could go back and file an entirely new complaint just setting forth the Constitutional argument alone.

It was error for the Court to not accept jurisdiction of the purely legal Constitutional issue of whether dying patients have a right to access treatments that have gone through ten years of clinical testing, been granted fast track status, been accepted for filing, been granted priority review, and then been overwhelmingly

found to be safe and effective by a handpicked panel of outside experts after a hearing.

CONCLUSION

WHEREFORE, this Court should reverse and remand and/or provide other legal or equitable relief.

Kerry M. Donahue

CERTIFICATE OF SERVICE

It is hereby certified that a copy of the Appellant's reply brief was sent by regular US mail, postage prepaid to Andrew E. Clark, U.S. Department of Justice, PO Box 386, Washington DC 20044 this 5th day of March 2008.

Kerry M. Donahue

CERTIFICATE OF COMPLIANCE

Pursuant to Sixth Cir. R. 32(a)(7)(c), the undersigned certifies this brief complies with the type-volume limitations of Sixth Cir. R. 32(a)(7)(B).

1. EXCLUSIVE OF THE EXEMPTED PORTIONS IN SIXTH CIR. R. 32(a)(7)(B)(iii), THE BRIEF CONTAINS:

_____ 7372 _____ words, or
A. _____ lines of text in monospaced typeface.

2. THE BRIEF HAS BEEN PREPARED:

in proportionately spaced typeface using:
Software Name and Version: Microsoft Word 2000
In Times New Roman, 14-point font

3. IF THE COURT SO REQUESTS, THE UNDERSIGNED WILL PROVIDE AN ELECTRONIC VERSION OF THE BRIEF AND/OR A COPY OF THE WORK OR LINE PRINTOUT.
4. THE UNDERSIGNED UNDERSTANDS A MATERIAL MISREPRESENTATION IN COMPLETING THIS CERTIFICATE, OR CIRCUMVENTION OF THE TYPE-VOLUME LIMITS IN SIXTH CIR. R. 32(a)(7), MAY RESULT IN THE COURT'S STRIKING THE BRIEF AND IMPOSING SANCTIONS AGAINST THE PERSON SIGNING THE BRIEF.

Kerry M. Donahue