June 30, 2004

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

The undersigned submits this petition on behalf of Computerized Thermal Imaging, Inc. ("CTI") seeking leave, pursuant to 21 C.F.R. § 10.25(a), to initiate proceedings to permit CTI to supplement the administrative record in connection with CTI's premarket approval application ("PMA") in P010035.

A. Action Requested

CTI contends that consideration of its PMA was severely and improperly prejudiced because of pervasive bias against the company by the Food and Drug Administration ("FDA") staff reviewers who improperly undermined the Advisory Panel's review of CTI's application and ultimately caused the FDA to reject that application. Because proof of subjective bad faith renders agency action arbitrary and capricious, and because review of agency action is limited to the administrative record, CTI seeks leave under the citizen petition provisions, *see* 21 C.F.R. § 10.30(h), to investigate and supplement the record concerning this bias. *See* 21 C.F.R. § 12.1, *et seq.* CTI further requests that the Commissioner grant the relief requested in this petition on an expedited basis.

B. Statement of Grounds

This citizen petition to supplement the record is necessitated by the flagrant bias, procedural irregularities, improprieties and bad faith that pervaded the FDA's handling and

disposition of CTI's application for premarket approval for a medical device that would spare countless women unnecessary biopsies. For over seven years, CTI consulted and worked extensively with FDA officials to design and conduct clinical studies to assess the safety and effectiveness of CTI's device. CTI responded to all of the agency's requests for additional information and, most significantly, sought and obtained agency approval before modifying study protocols to address and resolve any and all concerns the agency raised. Indeed, as of July 2002, when the FDA announced that the PMA application for the device would go to panel in October 2002, FDA staff had approved all of CTI's protocols and had expressed satisfaction with the statistical reliability of CTI's clinical studies.

All of that changed, however, after September 2002, when the FDA initiated an audit of CTI's clinical studies. Although the agency later admitted that the audit uncovered no flaws in the integrity of CTI's studies, the initiation of the audit coincided with a sudden, unexplained, and wholly improper sea change in the attitude and behavior of FDA staff towards CTI and its application. Thereafter, FDA staff deemed unreliable the very same protocols that they had previously blessed; disseminated highly critical and unbalanced evaluations of these same FDA-blessed protocols and study results to panel members; breached confidentiality agreements and understandings with CTI; failed to disclose potential conflicts of interests of several panel members until the actual panel meeting, when CTI could not evaluate the conflicts or object to the participation of financially interested panel members; violated agency procedures and requirements by refusing to permit discussion or consideration of even a conditional approval of the device; attempted to cover-up that violation; and failed to abide by representations concerning the nature of the presentation they would present to the Advisory Panel. Indeed, the evidence demonstrates that several FDA staff reviewers were unalterably

opposed to approval of CTI's PMA before the panel was convened, and that they sought to ensure that the panel effectively adopted—and thereby legitimated—their views.

Unable to consider conditional approval, the panel in fact deadlocked on approval of the device, and the tie was broken by the panel chair, who voted against approval. Thereafter, the Office of Device Evaluation ("ODE") promised to consider CTI's proposals for re-analysis of the existing data before acting on the application, and agreed to meet with the company the following month. On the eve of that meeting, however, and with no prior notice, ODE sent CTI a letter denying approval of the application.

Because proof of subjective bad faith renders agency action arbitrary and capricious, and because any administrative or judicial challenge CTI might mount to the FDA's non-approval decision will be limited to the administrative record, *see* 21 U.S.C. § 10.33(d); 5 U.S.C. § 706, CTI is entitled to conduct discovery into the staff's bias in order to supplement the administrative record. Indeed, courts have long recognized that, upon "a strong showing of bad faith or improper behavior . . . inquiry may be made" into the conduct and "mental processes of administrative decisionmakers." *Citizens to Preserve Overton Park v. Volpe*, 401 U.S. 402, 420 (1971). As CTI explains in detail below, there is more than sufficient evidence of bias to justify the relief sought in this petition.

1. BCS 2100

In 1996, CTI, through its subsidiary Thermal Medical Imaging, Inc. ("TMI"), began consulting with the FDA about a new clinical device called BCS 2100. BCS 2100 is designed to be used as an adjunct to a mammography x-ray to determine whether a mammographically identified breast lesion may be monitored rather than biopsied. *See* Panel

Review Materials Submitted by CTI on September 6, 2002 ("CTI's Panel Presentation") at 6-7 (attached as Exhibit 1). The benefit of this procedure would be to reduce the number of unnecessary biopsies performed each year. *See id.* at 7. Over 4.5 million breast biopsies are performed each year and over 1.3 million are performed in the United States alone. About 80 percent of these biopsies result in benign findings. *See* Computerized Thermal Imaging, Inc. BCS 2100, at 2, *available at* http://www.fda.gov/ohrms/dockets/ac/02/briefing/ 3918b1_sponsor-Final.htm (attached as Exhibit 2). This means that every year over one million patients in this country must experience unnecessary trauma, discomfort and risk associated with biopsies. *See* CTI's Panel Presentation at 6-7. The BCS 2100 would reduce the number of unnecessary breast biopsies by more accurately differentiating between malignant and benign tissue because of the relatively lower thermal temperature of benign tissue. After three years of consulting and working with the FDA about the proper clinical protocols and after starting the clinical trial, on April 12, 1999, the FDA granted CTI's request to begin submitting the Modular PMA for BCS 2100. *See* April 12, 1999 Letter from Daniel G. Schultz, FDA, to TMI's Director of Marketing & Regulatory Affairs at 1 (attached as Exhibit 3).

2. The PMA Process

The Modular PMA was divided into five parts. The first four submissions, or modules, provided information such as the clinical protocols, the description of the device, the device characteristics, manufacturing information and non-clinical testing. *See* Attachment to Exhibit 3 at 1-4. CTI submitted Module 5, the final part of the application, on June 15, 2001, and in this submission provided the FDA with the clinical data demonstrating the safety and effectiveness of the BCS 2100. The objective of the clinical study was to show that BCS 2100 could lower the number of breast biopsies performed each year on benign lesions by more

accurately differentiating between malignant and benign tissue, thus providing an important new tool in the fight against breast cancer. *See* CTI's Panel Presentation at 7. With the FDA's acceptance and approval, the clinical study was designed to collect data for three subsets of lesions: (1) masses, (2) microcalcifications, and (3) distortions.

3. Amendment 4 and Amendment 5

After CTI submitted Module 5, the FDA, as is typical in the PMA process, sent deficiency letters to CTI requesting additional information that the FDA staff members needed to evaluate the application. On September 5, 2001, the FDA sent a deficiency letter outlining several areas where CTI needed to provide additional information. *See* September 5, 2001 Letter from Nancy C. Brogdon, FDA, to CTI's President at 1-2 (attached as Exhibit 4). Among other things, the FDA requested a data set of patients for whom no malignancies were missed, in other words, 100 percent sensitivity. *See id.* at 2. On February 28, 2002, CTI submitted a response in the form of Amendment 4. Amendment 4 revised the indications for use ("IFU") of the BCS 2100 by narrowing its scope to look at only those patients whose lesion descriptors were masses and, by analyzing the pathology reports, compared the performance of the BCS 2100 against the decision to perform a biopsy on these patients based on the mammography x-ray. *See* CTI's Panel Presentation at 18 (summarizing the results of Amendment 4). The data in Amendment 4 showed that the BCS 2100 correctly identified 90 out of 90 malignant masses that were biopsied for 100 percent sensitivity. The BCS 2100 correctly identified 58 out of 322 benign masses for 18 percent specificity, or in other words, the BCS 2100 would have prevented 58 unnecessary breast biopsies. *See* CTI's Panel Presentation at 18.

The FDA responded to Amendment 4 on April 10, 2002 with another deficiency letter indicating that, based on the changed IFU, CTI needed to confirm the results for the mass subset. *See* April 10, 2002 Letter from Nancy C. Brogdon, FDA, to CTI's President at 1-2 (attached as Exhibit 5). Soon thereafter, CTI's Vice President of Engineering had a telephone conference call with Dr. Harry Bushar and Dr. William Sacks of the FDA to discuss ways to confirm the data in Amendment 4. *See* May 4, 2002 Email from CTI's Vice President of Engineering to John C. Monahan, Lead Reviewer at 1-2 (attached as Exhibit 6). CTI proposed taking the set of 275 patients enrolled after the original clinical trial's cut-off date, unblinding it, and analyzing the data for the confirmatory study. *See id.* At the time, the results were vaulted and blinded at Quintiles, CTI's contract research organization responsible for monitoring the clinical trial. At this meeting, the parties agreed that the data would be evaluated against the decision to perform a biopsy. *See id.* Because the biopsy decision was chosen as the baseline comparison, CTI had to degenerate part of the ROC curve making ROC curve comparisons inapplicable. *See id.* At Dr. Sacks's suggestion, on May 4, 2002, CTI's Vice President of Engineering sent an email to John Monahan outlining the proposal for the confirmatory study so that the FDA could consider it before CTI unvaulted the data. *See id.* John Monahan, after conferring with Dr. Bushar, Dr. Sacks and Robert Phillips, wrote back stating that CTI's proposal was acceptable and that the company could begin its analysis of the data. *See* May 13, 2002 Email from John Monahan, Lead Reviewer, to CTI's Vice President of Engineering at 1 (attached as Exhibit 7).

After receiving the FDA's approval, CTI unvaulted the data and began to analyze the data for the 275 patients in the confirmatory study by comparing the BCS 2100 results against the biopsy decision on patients exhibiting breast masses. As expected, the BCS 2100

proved its efficacy. In the confirmatory study, the BCS 2100 evaluated 63 benign masses and 15 malignant masses. The device correctly identified 14 out of 15 malignant masses for a sensitivity of 93.3 percent and 12 out of 63 benign masses for a specificity of 19.2 percent. *See* CTI's Panel Presentation at 18-19. Aggregating the data from Amendment 4 with the data from Amendment 5—as the FDA staff had agreed CTI could do—the BCS 2100 correctly identified 104 of 105 malignant masses for 99 percent sensitivity and 74 out of 385 benign masses for 19.2 percent specificity. *See id.* at 19.

Thus, when CTI submitted Amendment 5 on May 24, 2002, the FDA staff had agreed that CTI's proposed methodology was valid. Specifically, the FDA staff, including Drs. Sacks and Bushar, had agreed that the biopsy decision was an appropriate baseline for evaluating the BCS 2100's performance with respect to the mass subset, that it was acceptable to combine the data from Amendment 4 with the data in Amendment 5, the confirmatory study, and that the combined data would properly be considered a prospective, not a retrospective, study.

4. The Decision to Go to Panel

On July 17, 2002, CTI's Vice President of Engineering had a meeting with many of the same FDA staffers who approved Amendment 4 and Amendment 5, namely, Jack Monahan, Bob Phillips and Bill Sacks. At this meeting, CTI's Vice President of Engineering was informed that the FDA would send the PMA to panel on October 16, 2002. The decision to go to panel is significant because at that point, the FDA has some evidence to support the device's clinical efficacy, safety, and statistical performance. In effect, this decision is *prima facie* evidence that the PMA is ultimately approvable. Moreover, the decision to send the application to panel provided further confirmation that Amendment 4 and Amendment 5

resolved the issues raised in prior FDA deficiency letters. Indeed, at no point during this meeting did any FDA staff person suggest that there were any remaining or unresolved problems with CTI's study or data. To the contrary, they stated that "the data speak for themselves"—*i.e.*, that the PMA was on track for approval. Thus, the July 17th meeting confirmed, if any further confirmation were needed, that the FDA staff agreed with CTI (1) that it was appropriate to evaluate BCS 2100 efficacy against the biopsy decision and not to do a ROC curve comparison; (2) that the results of Amendment 4 and Amendment 5 could be combined; and (3) that the selection of the mass subset was prospective. Indeed, the clinical study protocols from the very beginning specified that there should be data for three subsets of lesions, one of which was masses, which account for approximately half of all breast disease.

The parties also agreed at the July 17th meeting to meet prior to the panel to exchange presentation materials. On July 23, 2002, CTI received an email from John Monahan at the FDA confirming the meeting of the Radiological Devices Panel for October 16, 2002. *See* July 23, 2002 Email from John C. Monahan, Lead Reviewer, to CTI's Vice President of Engineering at 1 (attached as Exhibit 8). A publicly accessible meeting announcement also was placed on the FDA's website. CTI submitted its information package on September 6, 2002.

5. The Weeks Leading to the October Panel Meeting

On September 9, 2002, to CTI's surprise, Linda Cherry of the FDA Denver office announced that she would be performing an audit of CTI beginning on September 16, 2002. Ms. Cherry informed CTI that she was conducting the audit to find out what happened to 275 missing patients, the same patients whose results were analyzed for the confirmatory study. As CTI explained when it submitted Module 5, these patients were not "missing" but rather their data

was collected after the cut-off date for the clinical trial and thus were not used. The results, however, remained blinded at Quintiles. Shortly into her audit, Ms. Cherry concluded that the 275 patients were not missing and even suggested that based on her investigation, the reason for the audit was unclear. After finishing the audit on September 24, 2002, she made only two observations regarding the clinical study: (1) CTI lacked written standard operating procedures for monitoring the investigation and (2) for one of the clinical subjects, CTI did not have a signed informed consent. CTI implemented corrective actions, and the FDA responded by letter dated February 27, 2003 that these corrective actions were sufficient. *See* February 27, 2003 Letter from David R. Kalins, FDA, to CTI's Vice President of Engineering at 1 (attached as Exhibit 9).

On October 1, 2002, about a week after the audit concluded, CTI representatives met to review the panel presentation materials with the FDA staffers who had been working on the PMA, namely, John Monahan, Bill Sacks, Bob Phillips, Robert Doyle, Nancy Brogdon and David Segerson. At this meeting, the FDA officials announced for the first time that they had serious problems with CTI's data. Ms. Brogdon claimed that, as a result of a supposedly more detailed review, the FDA staff had come to believe that the data they had previously deemed acceptable was now unreliable, and that they would share these newly discovered concerns with the panel on October 16. Equally shocking, these staffers discouraged CTI from exercising its right to present new data in response to these last-minute concerns. Dr. Sacks added that even if the panel recommended approval, he did not believe that the FDA would or even could approve the PMA. In detailing their problems with CTI's data, the staff members identified issues that they themselves had previously agreed were resolved by Amendments 4 and 5. Ms. Brogdon

then gave CTI until October 10 to decide whether to go forward as planned or to postpone the meeting; she assured CTI that the reasons for the delay would not be discussed publicly.

Such a sudden change of course, and the revival of previously resolved issues on the eve of panel, was, to petitioner's knowledge, unprecedented agency action, reflective of bad faith on the part of the relevant FDA staffers and undertaken by them with knowledge that their actions would have a devastating adverse impact on the value of CTI itself. Unfortunately, in the weeks that followed, CTI's suspicions of bias and hostility were confirmed through numerous other extraordinary and improper actions. On October 3, 2002, the FDA sent a package of material to the panel members which included a memorandum from Dr. Sacks. Incredibly, Dr. Sacks claimed in his memorandum that CTI's confirmatory study was impermissibly retrospective. *See* October 3, 2002, Memorandum from William Sacks, FDA, to John C. Monahan at 1 (attached as Exhibit 10). This was precisely the issue CTI had addressed and resolved through Amendments 4 and 5 about five months earlier, *and Dr. Sacks himself was one of the staffers who had approved the confirmatory study and failed to identify any problem with it prior to or at the July 17th meeting.* Now, in an inexplicable and unjustified about-face, Dr. Sacks had suddenly discovered problems so serious that the PMA could not be approved.

Not only was the substance of Dr. Sacks's criticism profoundly unfair and inaccurate, the tone of the memorandum, which was the first document in the packet of materials sent to the panel members, was extraordinarily harsh and negative. Indeed, the FDA itself tacitly acknowledged the unfairness of this memorandum on November 19, 2002, when it took the highly unusual step of requesting that the panel members return the Sacks memorandum. *See* November 19, 2002 Letter from Robert J. Doyle, FDA, to Panel Members at 1 (attached as Exhibit 11). The FDA, however, waited for over a month before acting, and when it finally

recalled the memorandum, it did nothing to ameliorate its highly prejudicial effect by selecting new panel members whose minds had not already been unfairly prejudiced by exposure to Dr. Sacks's suddenly hostile views.

On October 8, 2002, CTI and the FDA had another meeting to discuss some of the problems that the FDA staff had with the data. At the meeting, Dr. Schultz acknowledged that the FDA must be careful not to cause undue harm to CTI because of the postponement and therefore all parties agreed that there would be no public discussion until Dr. Schultz sent a letter regarding the postponement. Shortly after the October 8 meeting, FDA staffer Robert Doyle, who was present at the meeting and was fully aware of the importance of controlled disclosure, improperly notified a CTI shareholder by email that the panel meeting was postponed. Although Mr. Doyle's actions plainly violated the FDA's confidentiality rules, he was later selected to serve as the Executive Secretary at CTI's panel.

As Dr. Schultz had understood at the meeting, the disclosure of this information to the general public would cause the company's stock prices to fall, which is exactly what happened. These last minute criticisms alone put the company in a difficult position. Now, the company had to contend with falling stock prices and a shrinking pool of money to fund additional studies.

In an effort to address or otherwise respond to the FDA's new-found concerns, CTI agreed to postpone the panel until December 10, 2002. After the panel meeting was postponed, the FDA sent two emails to CTI officials on October 18 and October 31, 2002, asking over 40 questions (including sub-parts) that primarily concerned CTI's clinical data and statistical analysis. *See* Computerized Thermal Imaging, Inc. Breast Cancer System 2100, PMA

P010035, Amendment 6, November 8, 2002, at 3 (attached as Exhibit 12). In particular, Question 1 concerned the FDA's newly-minted belief that Amendment 4 retrospectively redefined the clinical study's hypothesis. In response, CTI submitted Amendment 6 (referred to as Amendment 7 in the FDA presentation) on November 8, 2002, which systematically addressed these concerns. *See id.* With respect to Question 1, CTI explained that Amendment 4 did not redefine the hypothesis at all because the original protocols called for the analysis of the data by various lesion types, including masses. *See id.* at 9-10. By focusing on masses, Amendment 4 did not introduce a new (or re-defined) hypothesis but merely refined the original hypothesis, which is entirely permissible. *See id.* at 9-10. CTI explained how and why its statistical analysis was therefore appropriate.

On December 6, 2002, FDA staff reviewers assured CTI in a telephone conversation that CTI's responses to their detailed questions had resolved virtually all open issues, and that the FDA's only remaining concern with the clinical data related to CTI's response in Amendment 6 to FDA's Question 1, namely the purported use of retrospective data. Later that same day, however, CTI received draft copies of the FDA's panel presentation and discovered that, contrary to the assurances CTI had just received, the staffers' criticisms would be far more extensive than they had represented. With only a few days before the panel meeting, CTI attempted to prepare a response to the FDA's expanded criticism.

The conduct of FDA review staff at the Radiological Devices Panel held on December 10th confirmed their continuing bias and hostility towards CTI's application. At that meeting, the FDA provided three of the panel members with conflict of interest waivers based on the fact that each of these panel members had financial interests that could be adversely effected by a favorable decision for CTI. *See* Transcript of the December 10, 2001 Meeting of the Center

for Devices and Radiological Health, Radiological Device Panel ("Tr.") at 12-14, *available at* http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3918T1.htm (relevant excerpts attached as Exhibit 13). Remarkably, and improperly, the FDA staff had given CTI no prior notice of these conflicts. This action precluded CTI from investigating the nature of the conflicts or seeking recusals in a timely manner.

Once the substantive proceedings got underway, the FDA staffers offered a highly critical presentation of CTI's application. Contradicting prior assurances they had given, the FDA reviewers failed to tell the panel that they had had a positive view of CTI's study as recently as July 2002. In addition, the FDA staffers breached the assurances they had given during the December 6th telephone call by offering criticisms well beyond the supposed retrospectivity of CTI's data.

In addition, the FDA permitted Robert Doyle, who had improperly leaked information about the postponement of the panel meeting, to serve as the panel's Executive Secretary. Towards the end of the meeting, Mr. Doyle explained the procedures that would be followed when voting on the PMA. *See* Tr. at 269-71. One of the options available to the panel was to approve with conditions, which could encompass "physician or patient education, labeling changes, or further analysis of the existing data." *Id.* at 270 The voting rules specifically provided that, "[p]rior to voting, all of the conditions *should be discussed* by the Panel." *Id.* at 270-71 (emphasis added). These ground rules were consistent with a flowchart sent by the FDA to CTI depicting the process of allowing discussion of and votes on all proposed conditions before voting on the main motion. *See* Panel PMA Recommendation Flowchart (attached as Exhibit 14). After the company and the FDA review staff made their presentations at the hearing, one of the panel members, Dr. Toledano, the panel statistician, made a motion for

approval subject to specified conditions. *See* Tr. at 271. While there was some preliminary discussion, Dr. Toledano was not permitted to propose specific conditions. *See id.* at 271-72. The Chairman, a non-FDA panel member, cut short discussion and proceeded to a vote on the main motion, which resulted in a three to three tie. When another panel member asked whether there could be another vote after discussing specific conditions, Mr. Doyle inexplicably—and improperly—said "no." *Id.* at 273. The panel Chair then broke the tie by voting against the motion for approval with conditions and the PMA was disapproved.

The FDA staff reviewers subsequently sought to disguise the agency's improper refusal to permit consideration of conditional approval. In response to an email from a member of the general public, Nancy Brogdon, Deputy Director, inaccurately represented that the comment "no" which ended the debate on the motion for approval with conditions actually was made by the panel Chair, a non-FDA scientist, rather than Mr. Doyle, and that the transcript would be changed accordingly. *See* February 14, 2003 Email from Nancy C. Brogdon at 2 (attached as Exhibit 15). The videotape of the panel proceedings, however, clearly shows that it was Mr. Doyle who ended the debate. While the purported "correction" was never made, primarily because of the objection voiced by CTI in a March 6, 2003 letter sent from CTI's President to Commissioner McClellan, the FDA staff's willingness to misrepresent transcript proceedings so that responsibility for cutting short debate was shifted from an FDA staffer to a panel member is further persuasive evidence of bias.

6. Bias After the Panel Meeting

After the panel disapproved CTI's application, several FDA staffers, including Dr. Schultz, Ms. Brogdon and Mr. Segerson, approached CTI's President to compliment him on

the strength of CTI's panel presentation. More important, Dr. Schultz gave CTI's President assurances that the ODE would approach CTI's application with an open mind and would consider everything presented to the panel before taking action on the application. Encouraged by Dr. Schultz's representations, CTI set up a meeting for January 13, 2003, between CTI and FDA representatives at the FDA headquarters in Rockville, Maryland. The meeting eventually was postponed until January 24, but in telephone conversations between CTI's President and Dr. Schultz, Dr. Schultz indicated that the meeting would go forward as planned. CTI understood that it would have the opportunity to discuss its PMA with Dr. Schultz before the FDA took action on the application. Specifically, CTI hoped to convince the FDA that, through discussion or re-analysis of the existing data, it would demonstrate the device's efficacy and also would assuage the FDA's concerns about the data. Because CTI faxed a meeting agenda to Dr. Schultz, the FDA staff reviewers knew this to be the purpose of the meeting.

On Thursday, January 23, 2003, CTI representatives and consultants retained by CTI traveled to Maryland from Utah for the meeting. When they arrived at their hotel, however, they received a rude shock. Dr. Schultz's office faxed a letter, dated January 23, 2003, disapproving the BCS 2100 application. *See* January 23, 2003 Letter from Daniel G. Schultz, FDA, to CTI's President at 1 (attached as Exhibit 16). The letter completely contradicted Dr. Schultz's prior assurances that he would listen to CTI before acting on the PMA. The manner in which the disapproval letter was transmitted to CTI also made clear that Dr. Schultz never intended to discuss CTI's options and further demonstrates the bad faith of the agency staffers.

Following the aborted January 24th meeting, CTI's President sent three letters, dated January 27, March 6 and March 25, 2003, to Commissioner McClellan explaining the problems with the PMA process including the scientific issues and asking the Commissioner to

look into the matter further. *See* January 27, 2003 Letter from CTI's President to Mark B. McClellan, FDA (attached as Exhibit 17); March 6, 2003 Letter from CTI's President to Mark B. McClellan (attached as Exhibit 18); March 25, 2003 Letter from CTI's President to Mark B. McClellan (attached as Exhibit 19). The initial response to these letters came in the form of a letter dated March 21, 2003, from Linda Kahan, Deputy Director for the Center for Devices and Radiological Health ("CDRH"). This letter summarily dismissed CTI's allegations of bias. *See* March 21, 2003 Letter from Linda Kahan, FDA, to CTI's President at 3-4 (attached as Exhibit 20).

CTI also discussed possible routes of administrative appeal with the FDA's Ombudsman, Les Weinstein. Mr. Weinstein acknowledged that it could take up to 9 months to a full year as it did with one other company and could cost a substantial amount of money for CTI to appeal to an independent review board. Given its shortage of funds, CTI realized that this option was impractical. Indeed, Weinstein himself acknowledged that CTI's less formal efforts to negotiate with the agency was the better route.

In fact, this approach initially seemed promising. A telephone conference call was arranged for April 7, 2003 between Dr. Schultz, Les Weinstein, and CTI, and the FDA Commissioner's office indicated that Dr. Schultz would be prepared to discuss on this call CTI's proposal to re-analyze the existing data. Unfortunately, it became clear early on in the conversation that Dr. Schultz was unprepared to engage in a substantive discussion of the issues. Nevertheless, CTI explained its view that re-analysis of the data could support PMA approval and the next day, April 8, 2003, sent a letter to Dr. Schultz memorializing the proposed re-analysis. *See* April 8, 2003 Letter from CTI's President to Daniel G. Schultz, FDA, at 1-2 (attached as Exhibit 21).

While the telephone conference call of April 7 was not as productive as CTI had hoped, it appeared at the time that CTI had succeeded in reopening consideration of the PMA. On April 15, 2003, CTI met with the FDA staffers, including Dr. Schultz, in which the specifics of CTI's proposed re-analysis were discussed in greater detail. On May 9, 2003, CTI's President wrote a letter to Dr. Schultz in which he explained at length why the re-analysis of the data was proper and supported approval of the PMA. *See* May 9, 2003 Letter from CTI's President to Daniel G. Schultz, FDA at 3-6 (attached as Exhibit 22). Furthermore, the data supported approval of the device based on the criteria established by the FDA staffers in the April 15, 2003 meeting. *See id.* at 2-4. Unfortunately, despite the fact that CTI satisfied the statistical criteria suggested by the FDA staffers, in a conference call with Dr. Schultz on May 30, 2003, the rules suddenly changed again. Dr. Schultz now concluded that the re-analysis of the data did not support approval and that a new study was needed.

Unable to make any headway with Dr. Schultz and his staff, CTI arranged a meeting on July 9, 2003, with FDA Deputy Commissioner Dr. Lester Crawford and FDA General Counsel Daniel Troy to discuss how to gain approval for the BCS 2100. At the meeting, Dr. Crawford and Mr. Troy instructed CTI to draft a document outlining the relevant scientific issues in order to obtain independent review from the Commission staff. Shortly thereafter, on July 29, CTI submitted this document. The agency, however, never responded to this document. In fact, it took nearly a full year until then Commissioner McClellan finally concluded that although no medical device is perfect, the CTI demonstrated performance of efficacy of 93% to 99.05% was simply not good enough. This position is unreasonable and has been rebutted in writing by Dr. Yuri Parisky, Chief mammographer, University of Southern California, Norris Cancer Center, Los Angeles. CTI has continued to work diligently with the FDA and has

engaged in a series of correspondence with the agency, but as reflected in CTI's May 13, 2004 letter to Dr. Crawford, the parties are no closer to resolving the PMA for BCS 2100. *See* May 13, 2004 Letter from Thomas C. Green, Sidley Austin Brown & Wood LLP, to Dr. Lester Crawford, Acting Commissioner, FDA, at 1-3 (attached as Exhibit 22).

Argument

CTI is plainly entitled to supplement the record and investigate the agency bias that infected consideration of its application. 21 C.F.R. § 10.25(a) (citizen petition can ask the Commissioner "to take . . . any . . . form of administrative action"). Although CTI intends to seek appropriate administrative and judicial review of the disapproval of its PMA, any such review would be limited, by regulation and statute, to the administrative record currently in existence. *See* 21 U.S.C. § 10.33(d); 5 U.S.C. § 706; *see also John D. Copanos & Sons, Inc. v. FDA*, 854 F.2d 510, 527 (D.C. Cir. 1988) (petitions based on information outside the administrative record should be rejected). Because "proof of subjective bad faith by [agency] officials . . . constitutes arbitrary and capricious action," *Latecoere International, Inc. v. United States Dep't of the Navy*, 19 F.3d 1342, 1358 (11th Cir. 1994), CTI is entitled to information currently outside the administrative record concerning the bias and bad faith of key FDA staffers and the extent to which they sought to ensure that the panel adopted and thereby legitimated their hostility towards CTI's application. *See Sokaogon Chippewa Community v. Babbitt*, 961 F. Supp. 1276, 1281 (W.D. Wisc. 1997) (noting that direct evidence of agency bias cannot typically be found in administrative record).

Courts have long recognized that a party can seek to develop extra-record evidence of agency bias and misconduct based upon "a strong showing of bad faith or improper

behavior." *Citizens to Preserve Overton Park v. Volpe*, 401 U.S. 402, 420 (1971); *see also Sokaogon*, 961 F. Supp. at 1279-80 (courts permit "extra-record discovery and examination of agency personnel" after a strong showing of bias or improper motivation of the agency). Indeed, some courts have allowed discovery on less than the strong showing required by *Overton Park* where the party would otherwise not have access to the crucial information. *See Public Power Council v. Johnson*, 674 F.2d 791, 795 (9th Cir. 1982); *Pension Benefit Guaranty Corp. v. LTV Steel Corp.*, 119 F.R.D. 339, 343-44 (S.D.N.Y. 1988). Because CTI has more than satisfied its burden of making a strong showing of bias, it is clearly entitled to an order permitting it to supplement the record through an investigation into the bias of the FDA staffers involved in the disposition of CTI's PMA.

1. CTI Has Made Out A Strong Showing Of Improper Bias And Bad Faith

There can be no doubt that the extraordinary misconduct of key FDA personnel is more than sufficient to make out the strong showing of bad faith and improper behavior necessary to justify extra-record discovery and examination of those personnel. Indeed, this case is replete with evidence of the bad faith and bias of the agency staffers in the ODE who were responsible with evaluating CTI's PMA. Those staffers became unalterably opposed to approval of CTI's application, and sought to legitimate their improper hostility by prejudicing the advisory panel's review of CTI's application.

The unprecedented decision of the staff members to disclose, just two weeks prior to the panel meeting, that they objected to protocols *that they themselves had previously deemed acceptable* is clear evidence of bias. Indeed, there is no credible, legitimate reason for the highly prejudicial timing of this disclosure. *See Latecoere International, Inc.*, 19 F.3d at 1358 (lack of

alternate explanation supports allegation of bias). Drs. Sacks and Bushar and John Monahan had agreed in advance to CTI's proposed modifications of its protocols based on Nancy Brogdon's letter of September 5, 2001, requiring a lesion group performance at 100% sensitivity and had concurred in the validity of the resulting performance data. After receiving the data in May 2002, these same staffers raised no objections or concerns at a meeting two months later, when the FDA formally announced that CTI's application was ready to go to panel. Because the step of going to panel is such a significant event—both for the agency itself, which devotes significant time and resources to convening and conducting panel review, and for the applicant—it is simply inconceivable that the FDA staffers would have recommended taking CTI's application to panel without having carefully considered the propriety of the protocols identified in Amendments 4 and 5 and the resulting data.

Any suggestion, therefore, that these staffers somehow failed to focus on the validity of studies and the resulting data until *after* the decision to go to panel had been made is simply not credible. Rather, the inference of bad faith and impropriety is both inescapable and powerful where, as here, FDA staffers announce a complete about-face on crucial issues on the eve of panel. *See Sokaogon*, 961 F. Supp. at 1284 (despite facial reasonableness of agency's decision, the fact that it represented a "complete turnabout" from views the agency expressed only weeks earlier supported inference of bad faith and "pretext"). This is particularly true where the issues are not newly discovered ones, but rather are ones that the staffers and applicant have discussed at length and about which they had previously reached agreement.

The detrimental effect on CTI's financial health of this last minute disclosure is also highly indicative of bad faith. Because the decision to go to panel is reasonably viewed, by applicants and their investors, as a *prima facie* finding of approvability, postponing a previously

scheduled panel has a devastating impact on the value of a medical device company such as CTI and its ability to raise capital. Thus, by waiting until the eve of panel to raise serious questions about data and protocols that the staffers had discussed with CTI months (and indeed, years) earlier—and had in fact previously deemed proper and acceptable—the staffers essentially precluded CTI from being able to address their purported new concerns about the data and protocols which CTI believed had been resolved long ago. *See Sokaogon*, 961 F. Supp. at 1282 (agency delay in notifying plaintiffs of opposition to their application "suggests that the [agency] . . . was not interested in allowing plaintiffs to remedy the problems").

The injury to CTI was compounded by Robert Doyle's wholly improper disclosure to a CTI shareholder of news that the panel would be postponed. That disclosure was made within hours of a meeting at which FDA personnel, including Mr. Doyle himself, agreed *not* to disclose the fact of the postponement precisely because of the devastating impact the news would have on CTI's stock price. Doyle's disclosure also violated the agency's own regulations. *See* 21 C.F.R. § 814.9(g). The fact that the agency's own improper actions caused CTI significant harm underscores the bad faith nature of the staffers' last-minute objections to CTI's application. As a result of the decision to postpone and Doyle's improper disclosure, previously available sources of capital became unavailable, precluding CTI from raising the funds needed to perform additional clinical trials and the approval of the BCS 2100 was placed in jeopardy.

Nor is this the only evidence that buttresses the powerful inference of bad faith and impropriety. Indeed, following the decision to postpone and the improper disclosure of that decision, many of the same FDA employees engaged in a variety of other improper, and otherwise inexplicable, actions. The agency itself, in turn, consistently failed to take appropriate

corrective actions, and instead in at least one instance initially sought to cover-up the impropriety.

Chief among these subsequent improprieties was the circulation of Dr. Sacks's memorandum to the panel members. At the October 1st meeting at which FDA staffers first disclosed their 11th hour problems with CTI's data, Dr. Sacks had expressed the view that, even if the panel approved CTI's PMA, the FDA itself would not or could not approve it. Having thus made plain his open hostility towards, and improper prejudgment of, CTI's application, he then sought to ensure that the panel reached his pre-ordained conclusion by drafting and circulating a memorandum in which he castigated CTI for protocols and data that he himself (among others at the FDA) had previously blessed. After CTI complained vociferously to Dr. Schultz about the Sacks memorandum, the agency effectively acknowledged both the fundamental lack of balance and fairness in Dr. Sacks's memorandum and its highly prejudicial impact on panel members by agreeing to ask panel members to return it. The agency, however, waited for over a month to take this corrective action, and when it finally asked the panel members to return the memorandum, it did nothing to eliminate its harmful taint. It did not seek new panel members, or, to CTI's knowledge, even interview the exposed members to see if the memorandum had influenced their views.

Nor did the FDA remove Dr. Sacks from further involvement with CTI's application, despite his blatant bias and hostility towards that application. Because of Dr. Sacks's actions, CTI strongly objected to his further participation in the process and asked Dr. Schultz to ensure that Dr. Sacks would not be involved in the panel meeting. Dr. Schultz denied this request and instead allowed Dr. Sacks to continue to play a central role. Indeed, Dr. Sacks apparently played a central role in the agency's lengthy follow-up questions to CTI, despite his

awareness that CTI had previously addressed these same issues with him. He also participated in the December 6th conference call during which the agency misled CTI about the nature of the presentation it would make to the panel and the scope of its concerns about the application. And Dr. Sacks was allowed to present his views on the application to the panel itself. *See* Tr. at 127-38; 153-65.

Dr. Schultz also allowed Mr. Doyle to serve as the Executive Secretary to the Panel, despite his prior improper leak of the news of the panel postponement. In that capacity, Mr. Doyle once again acted improperly by cutting off any discussion by the panel of the types of conditions the panel could attach to approval of the device, after a motion was made for approval with conditions. That violation of the panel ground rules and FDA standard practice may well have been a decisive factor in the panel's negative recommendation on approval of the PMA, given the closeness of the vote and the otherwise favorable views expressed by several panel members who voted against the application. *Cf. Latecoere International, Inc.*, 19 F.3d at 1359 (agencies do not have discretion to change previously announced ground rules for decision). In fact, the two non-voting members indicated that if they had been allowed to vote, they would have voted for approval with conditions. Tr. at 278-79; 285-86. Once again, the agency did nothing to correct this improper conduct.

Indeed, the agency compounded this violation of agency procedures when Ms. Brogdon suggested in an email that the transcript of the panel proceedings was inaccurate and should be altered. By inaccurately representing that the panel Chair, a non-FDA independent reviewer, had refused to allow a re-vote after discussion of conditions, the agency sought to shift responsibility for this violation from its biased employee to an independent reviewer. As CTI's President pointed out in a March 6, 2003 letter to Commissioner McClellan, Ms. Brogdon's

proposal to alter the transcript conflicted with the videotape of the proceedings and the recollections of those present at the panel meeting.

The actions of Dr. Schultz after the panel meeting demonstrate the continued bias against CTI. Based on Dr. Schultz's representations, CTI invested additional time and money to consider ways to re-analyze the data so that the PMA could be approved immediately rather than after a new clinical trial which CTI could not afford to conduct. The issuance of the January 23, 2003 letter before the promised consultation between CTI and the FDA could take place shows that neither Dr. Schultz nor any of the other FDA reviewers intended to consider the PMA with an open mind.

Moreover, the manner in which the FDA broke the news to CTI reeks of bad faith. Before a disapproval letter can be finalized, it must go through several layers of review, and this process usually takes a week or two. Thus, when CTI called Dr. Schultz a few days before to confirm the meeting, Dr. Schultz knew must have known that the decision to disapprove the PMA already had been made. Rather than tell CTI representatives this fact on the phone, Dr. Schultz allowed CTI to incur substantial travel expenses for a meeting that he knew had been rendered moot by his action. Dr. Schultz's conduct was not merely inconsiderate; considering the dire financial health of CTI at this time, it was vindictive. By ambushing CTI with the January 23, 2003 letter, the agency once again made it abundantly clear that it had no intention of reviewing CTI's PMA in a fair and equitable manner. And after CTI succeeded in reopening the PMA for reconsideration in April 2003, Dr. Schultz engaged in yet another form of statistical manipulation at the end of May when he changed changing the statistical criteria used to evaluate the device, leaving CTI with little hope of getting the PMA approved.

In short, based on the incomplete record that currently exists, CTI has identified strong—indeed, compelling—evidence of bias and bad faith on the part of key FDA staffers. Beginning with their sudden and inexplicable "complete turn-about" on the propriety of CTI's protocols and analyses, *cf. Sokaogon*, 961 F. Supp at 1384, these staffers consistently acted in bad faith by breaching assurances made to CTI, violating standard procedures and rules in a manner that consistently harmed CTI's application, *see Latecoere International, Inc.*, 19 F.3d at 1359, failing to correct those violations, and, in one instance, seeking to disguise a violation. *See United States v. Shaffer Equipment Co.*, 11 F.3d 450, 460 (4th Cir. 1993) (fraud committed by EPA official responsible for conducting environmental clean-up called into question the administrative record). This strong evidence of bad faith is more than sufficient to establish CTI's right to conduct further investigation to uncover direct evidence of bias and vindicate its right to fair and unbiased review of its application. *See Sokaogon*, 961 F. Supp. at 1281.

2. Public Policy Strongly Favors Further Investigation

There are also compelling public policy reasons that support CTI's petition. First, the FDA itself has a strong interest in discovering the source and nature of the bias and misconduct of the FDA staff members. *Cf. Singer Sewing Machine Co. v. NLRB*, 329 F.2d 200, 208 (4th Cir. 1964) (concluding that the "search for truth is more important" than the deliberative process privilege). The existence of FDA staffers who are guided by bias or other improper motives instead of sound scientific principles undermine the legitimacy and integrity of the PMA process because these staffers play an important role in the process. While their recommendations are not necessarily adopted by the panel members, as a practical matter, "[t]he tenor of FDA staff's preliminary evaluation of a PMA application often influences a panel's deliberations." Robert B. Leflar, *Public Accountability and Medical Device Regulation*, 2 HARV.

J.L. & TECH. 1, 59 (1989). In turn, while the panel's recommendation is not binding, the FDA tends to follow that recommendation. *See id.*; *see also* Theresa J. Pulley Radwan, *Meeting the Objectives of the MDA: Implied Preemption of State Tort Claims by the Medical Device Amendments*, 10 J.L. & HEALTH 343, 347 (1995/1996).

Second, in this case, it appears likely that the bias of FDA staffers may ultimately have harmed the public health. The BCS 2100 has the potential to reduce substantially the number of unnecessary breast biopsies performed each year, and there was no dispute in clinical trials or among the panelists that the BCS 2100 is safe. Indeed, Canada recently gave CTI a license to market BCS 2100, and CTI's understanding is that BCS 2100 is proving to be a very effective adjunct technology. *See* May 13, 2004 Letter from Tom Green to Lester Crawford at 3. Furthermore, the clinical trials demonstrated that the device would be able to eliminate about 20 percent of the biopsies performed on benign masses. Of course, by a narrow margin, the panel concluded that the clinical data did not support the efficacy of the device. It is worth noting, however, that even those panelists who voted to disapprove the application, seemed convinced that a future clinical study would demonstrate the BCS 2100's efficacy. Tr. at 280-83. Thus, even among the panel members voting against the device, there seemed to be agreement that the device will prove to be effective at reducing biopsies but that the data and the clinical study was not as clean as they would like.

Because the panel was so closely divided in its review of CTI's PMA, the bias of staff members in their presentation of the data to the panel likely influenced the outcome. In fact, several of the panel members voting against BCS 2100 suggested that they believed that the technology ultimately would be proved to be effective. *See* Tr. at 280-83; 285. As the advisory panel's statistician who moved to approve subject to conditions explained, if the new data,

collected in the optimal way, supports the same answer, "that does not mean sending someone back to the drawing board" rather it means "approval subject to conditions." Tr. at 284. The panel rejected the application because of seemingly minor flaws with the clinical data, but not because the panel believed the device to be ultimately ineffective. Thus, the bias of the staffers likely tipped the balance against the company. The harsh evaluation in the Sacks memorandum, the FDA's unfair presentation at panel and the decision of Mr. Doyle to cut short discussion of the motion to approve with conditions may well have made the difference. Given the potential utility of this device, the closeness of the vote, the strong showing of bias, and what should be FDA's policy of insuring that decisions are made based on scientific merit, public policy weighs heavily in CTI's favor.

Because of the bias of agency staffers responsible for reviewing CTI's application, CTI's PMA did not receive fair consideration and was subsequently disapproved. CTI's has made a strong showing that bias infected the PMA process and has provided persuasive policy justifications for permitting CTI to supplement the record through an investigation into its allegations of pervasive bias. Accordingly, CTI requests that the Commissioner grant this citizen petition to permit CTI to supplement the administrative record.

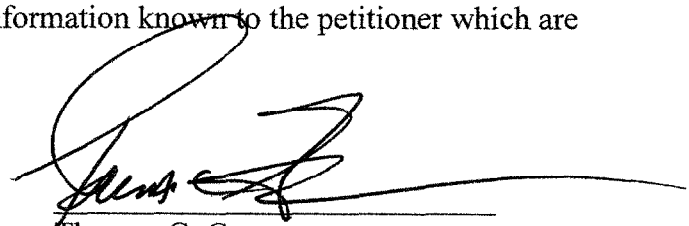
3. CTI Is Entitled To Expedited Review Of Its Petition

The Commissioner should grant CTI's petition on an expedited basis. As detailed above, the agency's decision to announce significant concerns with CTI's application on the eve of panel had a predictably devastating impact on CTI's stock, which in turn precluded CTI from conducting the additional clinical trials that the staff erroneously insisted were necessary. As a result of the denial of CTI's PMA, the company has been pushed into financial *extremis*.

To be meaningful, judicial review must be prompt in light of CTI's precarious financial condition. Accordingly, CTI must obtain the relief sought in this petition promptly as well. Because the misconduct of the FDA staffers caused the very financial harms that CTI seeks to remedy through judicial review, the Commissioner should grant the petition on an expedited basis and authorize CTI to begin conducting extra-record discovery at once.

C. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



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June 30, 2004

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CITIZEN PETITION

In connection with the citizen petition filed on June 30, 2004 on behalf of Computerized Thermal Imaging, Inc. ("CTI") pursuant to 21 C.F.R. § 10.25(a), CTI submits the following:

Environmental Impact

CTI claims that its petition is covered by the categorical exclusions outlined in 21 C.F.R. §§ 25.30 and 25.34 and thus does not need to prepare an environmental impact statement.