PMA MEMORANDUM

From: William Sacks, Ph.D., M.D.

To: John C. Monahan
Lead reviewer

Subject: Background information for amended Panel Pack, P010035
CTI Breast Cancer System (BCS 2100), Dynamic thermal imaging system

Sponsor: Computerized Thermal Imaging, Inc.

Date: October 3, 2002

Historical overview and context for Panel package

The company made several changes in their selection of the data that they chose to subject to analysis between their submission of the PMA (Clinical Trial Module) on June 15, 2001, and their submissions of Amendment 4 on February 28, 2002, and Amendment 5 on May 24, 2002, (see accompanying package). The company, each time, made these changes for subsequent submissions after viewing the results of their analysis, which raises a question of generalizability of the results.

Indeed, Amendment 5 was requested by the FDA as a result of some of these retrospective selections of data for Amendment 4. In particular, the device results for cancers indicated mammographically as either microcalcifications or architectural distortion were not as sensitive as they were for those cancers indicated mammographically as masses. So in Amendment 4 the company asked to reduce their Indications for Use from all mammographic lesions to only those represented mammographically as masses. Since such a retrospective change in lesion mix would not give confidence that the results for masses would be generalizable in larger target populations, the FDA asked the company to submit data on a new group of subjects.

Amendment 5 was the response to that request. This amendment involved an additional group of 275 subjects whose data had been collected prior to submission of the PMA, but had never been previously analyzed. Of these 275 additional subjects, 69 met the new criteria for inclusion, the others having either microcalcifications or architectural distortion, or one of the older criteria for exclusion applied in the original PMA, such as inadequate BCS image, unobtainable or nonexistent mammogram, or failure of the subject to get the recommended biopsy. (See accompanying data flow chart.)

Before proceeding, a brief explanation of the attached flow chart may be in order. The company collected data on a total of 2407 subjects, who were divided into three groups--700 for training the algorithm and determining a threshold for IOS, 1432 for analysis in the PMA, and the last 275, who were submitted in Amendment 5. At each stage, significant numbers of subjects were excluded based on a variety of considerations, described both in the preceding paragraph and at the bottom of the flow chart.

Other retrospective changes made by the company include the following:

In the original PMA the analysis, in addition to sensitivity/specificity data, was also given in the form of comparisons of areas under the ROC curves (AUCs) for mammographic level of suspicion (LOS) alone and for a combination of LOS and index of suspicion (IOS) from the BCS results--LOS versus IOS/LOS. Some of the ROC curves included all subjects from LOS 1 to 5 and others only LOS 1 to 4, and included all mammographic signs (masses, microcalcifications, architectural distortion). Furthermore two sets of comparisons were made, one for LOS using an equivalent of the BIRADS system and the other for LOS using an expanded scale for LOS (or BIRADS) 4 consisting of 5 sublevels. The company found that there was a statistically significant gain in AUC from LOS alone to IOS/LOS for the unexpanded LOS 4, but this statistical significance for gain in AUC disappeared when the comparison was made for the expanded LOS 4. This suggested that the statistical significance of the first comparison was an artifact of the paucity of points in ROC space, i.e., insufficient number of levels of suspicion. As a result, the company omitted ROC analysis in Amendment 4 and thereafter, and instead relied only on the sensitivity/specificity data at an IOS threshold of 20.59, a threshold, albeit, which had been appropriately preselected from a training set of 700 subjects.

One peculiarity in the data consists of the high number of subjects with multiple lesions said to be recommended for biopsy. In particular, 90 out of 769 subjects (11.7%) in the PMA, 23 out of 388 subjects (5.9%) in Amendment 4, and 7 out of 69 subjects (10.1%) in the PPMA (Amendment 5) had more than one lesion to which the BCS was applied. All these lesions were included in the analysis. However, in actual clinical practice it is extremely rare (<<1%) to recommend biopsy on more than one lesion in a single patient. This raises the question as to how many of the second, third, and even fourth lesions that were analyzed were, in fact, not recommended for biopsy by the clinical radiologist caring for the patient. It was, after all, on the basis of this radiologist's recommendation that the subject and lesion became eligible for enrollment in the study. This, in turn, raises the question of how many of the 490 (412+78) masses included in the analysis in Amendment 6 were part of the intended target population of lesions. Without that knowledge it is difficult to know what proportion of masses recommended for biopsy, but that turn out to be benign, would be saved a biopsy by the BCS. In particular, it could be substantially lower than the 19.2% found in Amendment 5, since of those 19.2% an unknown number may not have been recommended for biopsy by the clinical radiologist.

Another issue is a discrepancy between the inclusion criteria for subjects in the trial and the target population for the device in the company's proposed Indications for Use. The Indications for Use underwent change during the various submissions. At first it called for the device to be used on all women who are being considered for biopsy, excluding those with "clear indications for biopsy," and this was later amended to include only those women with mammographically suspicious masses. Yet the clinical trial failed to exclude women who had "clear indications for biopsy," i.e., BIRADS 5. Furthermore the trial included women with BIRADS 1, 2, and 3 assignments, so long as they were biopsied on the basis of either a palpable mass (whether or not it was mammographically suspicious) or simply the patient's desire to be biopsied rather than wait for follow-up imaging. In other words, the clinical trial included a broader category of women going to biopsy than simply the category of women in the proposed Indications for Use, namely those with mammographically suspicious masses. It is also unclear what the source was of those subjects with BIRADS 1 or 2 designations, since BIRADS 1 women would, by definition, not have had a mammographically localizable

lesion (which the company states was a necessary criterion for localization on the BCS image) and since BIRADS 2 women would no longer have been recommended for biopsy, even if they had a palpable mass, since the BIRADS 2 designation signifies pathognomonic benignity of even a palpable mass.

One additional point: The company was asked about the exclusion of those subjects who had inadequate BCS images. They stated that these were due to the need in the early stages for the technologist to begin the imaging at the same time as the cold air began blowing on the subject's breast, but that, subsequent to collection of all the trial data, a newer version of the device has been developed for which this procedure has been automated. It is this latter version that the company hopes to market if the PMA is approved. The company felt that, given this automation, they were warranted in excluding from the analysis those subjects for whom the imaging began late, and that an "Intent-to-Treat" analysis, that included all such subjects, would not be representative of the device's current capabilities. This leaves open the possibility of any clinical secondary effects of changes from the older, non-automated to the newer, automated version, since the newer version has not been part of any clinical trial. We need the panel to deal with the clinical aspects of this issue, while the engineering issues will be dealt with by the FDA in-house.

In summary:

a) By the time Amendment 4 was submitted, three changes had been made based on retrospective viewing of the data, namely 1) masses only (versus masses/microcalcifications/architectural distortion), 2) sensitivity and specificity at a particular IOS threshold only (versus entire ROC curves), and 3) masses recommended for biopsy excluding those of highest suspicion (versus all masses recommended for biopsy). This reduced to a total of only 388 subjects (with 412 masses) out of those 1432 subjects who were not used for training the algorithm and choosing the IOS threshold (see flow chart).

b) Amendment 5--for which the company unvaulted the results from previously unanalyzed, though already imaged, subjects--added only 69 new subjects (with 78 new LOS 1-4 masses) to the original 388 subjects (with 412 LOS 1-4 masses), all to be analyzed by sensitivity and specificity of IOS alone, and not by ROC analysis comparing LOS alone to IOS/LOS combined. And finally,

c) It is unknown what percentage of analyzed masses were actually recommended for biopsy by the original clinical radiologist, and are actually part of the intended target population for the BCS.

d) The target population(s) in the Indications for Use do(es) not correspond to the inclusion/exclusion criteria used in the clinical trial, so that using the trial data renders problematic a judgment of the safety and effectiveness of the device for the intended target population.

e) The latest version of the device, which is the one intended for marketing, was not the one used in the clinical trial.