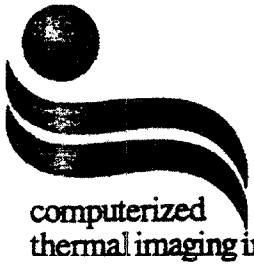
Exhibit 22




Daniel G. Schultz, M.D.
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Center for Devices and Radiological Health
U.S. Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

May 9, 2003

RE: PMA P010035
Breast Cancer System 2100 (BCS2100)
Computerized Thermal Imaging, Inc.

Dear Dr. Schultz:

I would like to thank you and your staff for taking the time to meet with CTI on April 15, 2003. CTI found the meeting to be particularly helpful in understanding the FDA's perspective on PMA P010035, and the company's participants gleaned much useful information from the meeting. We have reviewed our previous submissions in the light of the new information, and have determined that, with your assistance, there are steps that we can take that we believe will immediately place the PMA into approvable form. The purpose of this letter is to present two options for your review to assist CTI in preparing the formal amendment to PMA P010035.

As you will recall from the meeting on April 15, FDA's focus was primarily on statistical demonstration of BCS2100 efficacy. Two main topics arose. The first related to the appropriate target population for the BCS2100; the second to the criteria used by the FDA to determine device efficacy.

The first topic related to the question of whether or not the BCS2100 must show efficacy in the overall study population of all lesion types, as opposed to only the masses subset. The FDA indicated that efficacy must be demonstrated in an overall population in order to demonstrate efficacy in a subset of that population. CTI stated that it is statistically valid to claim efficacy in a subset without demonstrating efficacy in an overall population, as long as the correct statistical adjustments are made. The FDA and CTI did not reach an agreement on this issue. Despite the difference of opinion, however, CTI understands that the FDA would approve the device if it were to show "overall treatment effect" (a term used by the FDA to explain this concept, but which, as Dr. Sachs pointed

out during the meeting, is not exactly correct, as the BCS2100 is a diagnostic device, not a therapeutic device.)

CTI came into the meeting believing that the need to show "overall treatment effect" was a statistical issue, that is, that the validity of the subset analysis required a concurrent demonstration that the device performed statistically better than random chance in the overall population. The submitted data as presented in Module 5 dated June 15, 2001 meets this requirement. The FDA explained during the recent meeting that this approach would result in the device being labeled for use in all lesion types, with the disclosure that it performed best in masses appearing under the "Precautions" section of the labeling.

Prior to the meeting, CTI had not been told that the device must be labeled for all lesion types. CTI and FDA discussed focusing on masses prior to performing the confirmatory PPMA study which the FDA approved on May 13, 2002. The realization that the FDA was now stating that the BCS2100 must show efficacy and utility in the overall lesion population led to the second main topic, a discussion of the criterion that the FDA would use to determine device effectiveness in the overall population.

Prior to the meeting, the FDA's criteria for judging the efficacy of the BCS2100 were unclear, as CTI could not discern a clear basis for the FDA's review of efficacy data in PMA P010035. One clearly beneficial outcome of our meeting was that the FDA finally articulated its criterion for evaluating efficacy, and the basis for that criterion. The criterion for establishing efficacy that the FDA set at the meeting was that the rate of malignant lesions assigned to short-term follow-up by the BCS2100 should be the same as the rate of malignant lesions assigned to short-term follow-up by mammography, that is, the rate of malignant lesions assigned to a mammographic BIRAD category 3. The FDA stated their position that, because the proposed recommendation for care was the same (short-term follow-up), the negative predictive value (NPV) for the two populations should be the same. Thus, the BCS2100 should demonstrate a NPV of approximately 98%, the value commonly associated with the mammographic BIRAD category 3.

After careful review of the literature and interviews with experienced mammographers, CTI has found overwhelming evidence that many non-clinical factors contribute to a physician's assignment of a lesion to BIRAD category 3. This can be seen, for example, in a study that the Centers for Disease Control and Prevention (CDC) conducted, in conjunction with Battelle Memorial Institute, for the purpose of understanding the factors affecting the use of BIRAD category 3 by physicians participating in the National Breast and Cervical Cancer Early Detection Program (NBCCEDP). Researchers found that the following non-clinical factors contribute to the assignment of a lesion to a mammographic BIRAD category 3 – malpractice concerns, relatively low level of physician mammographic experience, and lack of confidence in diagnostic ability. (Battelle Centers for Public Health Research and Evaluation. November 1998. *Evaluation of the Use of the Code "Probably Benign – Short-term Follow-up Suggested" to Classify Mammograms.* Final Report for Contract No. 200-96-0599 Task 9, Centers for Disease Control and Prevention, Atlanta Georgia.) Radiologists interviewed by CTI reported the

same factors. One mammographer stated that she had moved from a state with a relatively low litigation rate associated with breast cancer to a state with a much higher breast cancer associated litigation rate. She observed that physicians in the litigious state were much more likely to recommend that benign appearing lesions undergo short-term rather than routine follow-up, that is, they assigned them to a mammographic BIRAD category 3 instead of a BIRAD category 2.

Consideration of these non-clinical factors suggests that a physician may assign a BIRAD 3 to a lesion in order "to be safe," that is, to a lesion that a more experienced or confident physician, or one less worried about lawsuits, would assign to a BIRAD 2 category. This "loading" of the BIRAD 3 category with lesions that are essentially BIRAD 2 lesions that have been upgraded for non-clinical reasons inevitably leads to an artificially low incidence of cancer in this population. Consequently, the NPV of the "true" BIRAD category 3 lesion population is most likely lower than what is currently reported.

The medical community has studied the BIRAD category 3 and found its NPV to be approximately 98%, that is, to have a malignancy rate of approximately 2%. This has been accepted as a reasonable level of risk for this population of patients recommended to short term follow-up. This forms the basis for the FDA's requirement that the BCS2100 should display an NPV at or near 98%, as the recommendation for care for a BIRAD category 3 lesion is the same as the currently proposed recommendation for care for a lesion assigned a negative IR test result (short term follow-up). It appears that this "acceptable" NPV value for mammography was not based on a prospectively stated objective that mammography was expected to meet and consequently met, but was a standard derived from existing data. (Orel, SG et al. BI-RADS Categorization as a Predictor of Malignancy. *Radiology* [1999] 211:845-850)

When BCS2100 usage is restricted to lesions described as masses, which was the pathway that CTI had followed previous to our meeting per the April 2002 discussions, the device exhibits a NPV of 98.7%, and thereby fully meets the FDA's criterion of a NPV of 98%, with an accompanying sensitivity of 99.0% and a specificity of 19.2%. However, the FDA's new requirement that the overall population must also demonstrate an NPV of 98% is not met by the overall lesion population data as currently submitted in Module 5 on June 15, 2001, which shows a NPV of 94.1%, with a corresponding sensitivity of 96.4% and a specificity of 15.3%. Because the BCS2100 was tested only in women who were scheduled for biopsy, this presents a more challenging patient population for the BCS2100 than those patients who are categorized as a clinical BIRAD 3. To meet the NPV threshold required by the FDA, CTI envisions two viable options. The first option is to modify the IR threshold to achieve approximately 98% NPV in the overall lesion population. The second option is to modify the recommendation for care following IR imaging so that it is not the same as the BIRAD category 3 recommendation for care, thereby removing the basis for the premise that the NPVs of the two populations should be the same.

CTI believes that either of these two options is reasonable, that these options meet FDA's approval criteria. In the interest of advancing this process, CTI presents the following information.

**OPTION 1:** Modify the IR imaging threshold so that the NPV for all lesions is the same as that generally accepted for all lesions assigned to a mammographic BIRAD category 3, that is, approximately 98%.

- Favorable aspects of this option:
  - The BCS2100 will meet the FDA's stated efficacy criterion, that is, it will show a NPV at or near 98% for the overall population. This still provides the benefit of reducing the need for biopsies of benign lesions.
  - Because the IR test results and the threshold are numerical scores, the threshold may be chosen to precisely meet any given performance criterion.
- Concerns related to this option:
  - Increasing the NPV means that the specificity will decrease. Nevertheless, if the FDA accepts this option, CTI agrees to work with the FDA to modify its claim regarding overall device specificity as presented in Module 5 submitted June 15, 2001. The extent of the trade-off between NPV and specificity in the trial population can be seen in the following table.

**ALL LESION TYPES: Threshold performance levels**

| IOS Threshold | Negative Predictive Value | Sensitivity | 95% Lower Confidence Bound on Sensitivity | Specificity | 95% Lower Confidence Bound on Specificity | Ratio of Unnecessary Biopsies Prevented to Cancers with Delayed Diagnosis |
|---|---|---|---|---|---|---|
| 5 | 99.3 | 99.9 | 98.4 | 5.3 | 4.1 | 135.0 |
| 6.4 | 98.2 (target NPV) | 99.6 | 98.0 | 6.4 | 5.0 | 53.8 |
| 10 | 97.0 | 99.0 | 97.1 | 9.0 | 7.4 | 32.6 |
| 15 | 96.6 | 98.4 | 96.3 | 12.2 | 10.4 | 28.1 |
| 20.59 (current) | 94.1 | 96.4 | 93.7 | 15.4 | 13.4 | 16.0 |

**OPTION 2**: Modify the recommendation for care for lesions assigned a negative IR test result so that it is different than the recommendation for care for lesions assigned to the mammographic BIRAD category 3. The modified recommendation would be more prescriptive, and recognize and accommodate the lower NPV of the IR-negative overall lesion population. For example, the differences between the NPVs of the BIRAD 3 and the IR negative populations can be prominently displayed in the labeling. Additionally, the time interval for lesion follow-up can be shortened for all

lesions, or, alternatively, for only those lesions that are not masses. Another labeling option would include a precaution that biopsies should be delayed only in patients who are highly likely to return for lesion follow-up at a prescribed time.

- Favorable aspects of this option:
  - Modifying the recommendations for care for IR-negative lesions to be more prescriptive than for BIRAD 3 lesions would mitigate the clinical consequences of a small decrease in NPV of the IR-negative lesion population when compared to the NPV of the BIRAD category 3 lesion population.
- Concerns related to this option:
  - The BCS2100 would not meet the FDA's single stated criterion for demonstrating BCS2100 efficacy of a 98% NPV in the overall lesion population.

We would like to state that CTI favors the first option, in spite of the fact that it would require that we reduce our overall device specificity. CTI believes this approach to be more straightforward and consistent with medical practice.

When the BCS2100 is used in a target population of masses, it results in a rate of delayed malignant biopsies that the FDA has stated to be acceptable, that is, equivalent to the rate of malignancy in the BIRAD category 3 population. To clarify, the following table shows the NPV associated with the performance results for all masses that were submitted to the FDA on May 24, 2002 in PMA P010035 Amendment 5.

**Masses: Performance at current threshold**

| IOS Threshold | Negative Predictive Value | Sensitivity | 95% Lower Confidence Bound on Sensitivity | Specificity | 95% Lower Confidence Bound on Specificity | Ratio of Unnecessary Biopsies Prevented to Cancers with Delayed Diagnosis |
|---|---|---|---|---|---|---|
| 20.59 | 98.7 | 99.0 | 95.6 | 19.2 | 16.0 | 74.0 |

CTI notes that at the time it submitted these data, CTI fully believed that the FDA had agreed that demonstration of device efficacy in this population would be sufficient to gain PMA approval, as long as the device indication was restricted to masses. CTI also notes that the NPV of this population met the FDA's target for acceptability that the FDA has now articulated.

However, CTI recognizes that the FDA's newly stated requirement – that the device must be indicated for use in all lesion types – would result in slightly more delayed malignant biopsies than would be true if use of the device were restricted to masses. As noted in Option 1, the rate of delayed malignant lesion biopsies would be reduced to the FDA's stated acceptable level (while still providing the benefit of reduced unnecessary biopsies) if the IR test threshold were modified. This threshold would result, however, in a

decrease in device specificity. Should the FDA determine that Option 1 is preferable, that is, to modify the IR threshold to reduce the percentage of delayed malignant biopsies in a lesion population that is not restricted to masses, CTI agrees to work with the FDA to revise its efficacy claims accordingly.

CTI would also like to make it very clear that we plan to target future studies of the BCS2100 to lesion populations that are confined to masses. Accordingly, CTI anticipates that future supplements to PMA P010035 will include data from post-approval studies of the BCS2100 that show that it can contribute even more significantly to the evaluation of suspicious masses than shown in the data supporting its use in all lesion types. We believe that additional studies will provide the necessary information to maturate the product and improve performance. IR imaging is a very safe technology – it is noninvasive and does not expose a patient to ionizing radiation. IR imaging accommodates situations where there is a concern about patient modesty, as it does not involve any breast contact other than that of the associated mammographic procedure. IR imaging also holds tremendous potential to contribute significantly to the scientific community's understanding of the physiological processes associated with disease. It is CTI's intention to exclusively market the BCS2100 to MQSA certified facilities under the control of board certified radiologists. CTI looks forward to working with the FDA to introduce these benefits to the radiological/medical community by bringing the BCS2100 to market, and developing its full clinical capabilities through scientifically rigorous post-approval studies that will satisfy the most intense scrutiny regarding study design, conduct and conclusions.

In closing, CTI believes that it has adequately demonstrated that the BCS2100 is safe and effective, and that the FDA's concerns regarding the device's approvability can be addressed through threshold modification or by revisions to the proposed labeling or both.

We would like to discuss with you as soon as possible these options and have the opportunity to design, with you, an appropriate post-approval clinical study that targets masses.

Sincerely,

John M. Brenna
President
Computerized Thermal Imaging Inc.