Exhibit 12

Computerized Thermal Imaging, Inc.

Breast Cancer System 2100

PMA P010035

Amendment 6

November 8, 2002

CTI Proprietary

Computerized Thermal Imaging, Inc.
1719 W. 2800 S.
Ogden, Utah 84401

November 8, 2002

John Monahan
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Re: P010035
CTI BCS2100
Filed: June15, 2001
Amended: August 21, 2001
Amended: September 7, 2001
Amended: September 11, 2001
Amended: February 28, 2002
Amended: May 24, 2002
Amended: November 8, 2002 (current)

To Whom It May Concern:

This letter is to inform you that CTI is submitting Amendment 6 to the PMA cited above. The amendment contains responses to e-mail messages sent to CTI on October 18, 2002 and October 31, 2002. Twenty copies of this amendment are being submitted, per FDA's request. We do not believe this constitutes a major amendment. However, even if it is deemed a major amendment, it should not affect the timing of the advisory panel meeting scheduled for December 10, 2002.

CTI believes that this amendment constitutes a complete and adequate response to FDA questions as they have been communicated to CTI, and that the BCS2100 has been shown to be a safe and effective device. If there are any questions regarding this amendment, please contact Lynn Satterthwaite at (801) 776-4700.

Thank you,

John M. Brenna
President, Computerized Thermal Imaging, Inc.
1719 W. 2800 S.
Ogden, Utah 84401

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I. INTRODUCTION

This amendment contains material not previously submitted to the FDA that demonstrates that the CTI BCS2100 is a safe and effective device when used adjunctively to mammography to avoid biopsies of benign masses that would otherwise have undergone biopsy.

This amendment includes revised product labeling, including a revised indication statement, device description, and warning statement section. This revised material replaces the indication statement, device description and warning statement section in the previously submitted proposed labeling. Following the sections containing revised labeling is a section containing responses to questions that the FDA forwarded to CTI on October 18, 2002.

It is noted that this amendment breaks with the previous amendments' format in which CTI addressed questions from the FDA by presenting full discussions and detailed analyses of the issues as the body of the amendment, with the answers to the FDA's specific questions included as appendices to the amendments. It was not possible to complete such a comprehensive treatment of the FDA's concerns for this amendment due to the severe time limitations imposed on CTI, as discussed below.

The BCS2100 was originally scheduled for Panel review on October 16, 2002. CTI was completely unaware that the FDA had any outstanding concerns about the approvability of the BCS2100 until October 1, 2002, two weeks before the scheduled Panel meeting. On that date, CTI representatives met with FDA personnel in Washington DC for the stated purpose of discussing the Panel meeting agenda and presentations. At that time, the FDA presented a large set of issues, many of which concerned material that CTI believed had been previously reviewed and accepted by the FDA.

The FDA and CTI subsequently agreed to postpone the Panel meeting until December 10, 2002. The FDA instructed CTI to address its (the FDA's) issues in a formal amendment to be received by the FDA prior to the December Panel meeting. The FDA agreed to put its issues into a set of questions that it would forward by e-mail to CTI. CTI received thirteen questions by e-mail from the FDA on October 18, 2002. Each of these questions had several subparts, with the result that the FDA had actually posed 37 separate questions. CTI met with the FDA on October 24, 2002 to clarify the questions. Because of material discussed at this meeting, the FDA requested additional time to reword two of its original questions. CTI received these two revised questions on October 31, 2002, along with two additional questions that had not been previously posed. One of these two questions included five subparts, bringing the total number of FDA questions to 43.

Although many of the questions covered material that CTI had already submitted, the FDA's phrasing of many of its questions required that CTI perform substantive data review and analyses in order to answer the specific questions posed. Because the questions were so comprehensive and presented to CTI at such late dates, it was difficult for CTI to generate a comprehensive response to each of the FDA's concerns within the allotted time frame. However, CTI endeavored to assure that each FDA question was adequately answered and that supporting information was offered wherever possible. CTI believes each of these responses is adequate to address the FDA's specific concern as stated in the question posed. For clarity, in the parts of the amendment dealing with this material, the FDA question is presented in italics, followed by CTI's response in plain text.

II. REVISED LABELING

CTI has revised the proposed BCS2100 labeling. Revised material includes the BCS2100 Indication for Use Statement and Device Description. CTI also reviewed the warnings section in order to respond to a query from the FDA. The changes and response to the FDA's query are specified below. The complete version of the revised device description appears in Appendix II. CTI will forward to the FDA all labeling documentation affected by these changes as soon as the changes are reviewed and accepted.

A. Revised Indication for Use Statement

CTI has revised the BCS2100 Indication for Use statement. The proposed Indication for Use statement appears below. All prior Indication for Use statements should be disregarded.

> The CTI BCS2100 is a dynamic computerized infrared (IR) based image acquisition and analysis system intended for use as an adjunct to mammography to safely avoid biopsy of benign breast masses that would otherwise have undergone biopsy. A physician should not base a decision for patient care solely on the results of testing with this device, but rather on the results of this test in combination with all other findings and risk factors associated with a specific patient. The CTI BCS2100 provides additional information to guide a breast biopsy recommendation.
>
> Because demonstration of device effectiveness was limited to breast lesions that included "mass" as a lesion descriptor, use of the CTI BCS2100 should be limited to the evaluation of breast lesions that include "mass" as a lesion descriptor. Presence of another lesion descriptor does not contraindicate use of the CTI BCS2100, if the lesion is also described as a mass.
>
> It is recommended that the appropriate recommendation for care for all patients receiving a negative IR test result be similar to the recommendation for care of a mass that is assigned to mammographic category 3. That is, a short interval follow-up is recommended in order to establish the stability of the finding.

B. Revised Device Description

CTI has revised the BCS2100 Device Description that appears in device labeling to enhance component descriptions and to better elucidate the physical and functional relationship between BCS2100 components. The revised proposed Device Description appears in Appendix II of this PMA amendment (PMA P010035 Amendment 6). All prior versions of Device Description labeling should be disregarded.

C. Warnings Section

In an email sent to CTI on October 24, 2002, the FDA asked CTI to explain one of the warnings in the device labeling. Specifically, the FDA found CTI's claim that the BCS2100 complies with IEC 601-1 to conflict with the following warning statement.

> "Electric shock will result if the operator touches the signal input or signal output ports on the computer, UPS, monitor, printer, or similar type device and the patient simultaneously."

CTI confirms that CSA has certified that the BCS 2100 is IEC 601-1 compliant. CTI also confirms that it was a CSA requirement that this statement be included in the BCS2100 labeling.

III. RESPONSES TO FDA QUESTIONS OF OCTOBER 18, 2002 (1-3, 6-13) and OCTOBER 31, 2002 (4, 5, 14, 15)

A. Question 1

FDA question(s):

a) Amendment 5 combined the results of the Amendment 4 (388 subjects) and PPMA studies. Given that the results in Amendment 4 were used to redefine the hypothesis of the study, please explain how the same data from Amendment 4 together with the PPMA data can be used to validate the new hypothesis presented in Amendment 4.

b) If the data cannot be combined to validate the new hypothesis, please justify the use of the PPMA alone to validate the new hypothesis, in terms of size and results.

c) Do you believe, given the concerns raised above regarding the current dataset, that a new trial is required -- either premarket or postmarket?

CTI response:

a) In the meeting between CTI and the FDA on October 24, 2002, the FDA clarified that the issue raised by this question is CTI's selection of masses as a lesion subset in which to demonstrate primary device efficacy when the clinical study did not limit enrollment to only masses. In that same meeting, CTI pointed out that the clinical trial protocol prospectively planned for analysis of device efficacy by lesion type. Thus, CTI asserts that the results of Amendment 4 were not used to retrospectively redefine the hypothesis, but rather to refine the hypothesis as prospectively planned for in the clinical trial protocol. If the hypothesis of efficacy in masses had been selected retrospectively from an unrestricted set of potential hypotheses, then "redefine" would be a proper verb to employ. However, the original protocol specifically called for analysis of the clinical trial data by lesion type, size and depth. Therefore, the hypothesis of efficacy in masses constituted one of a very restricted set of possible hypotheses that were prospectively planned for in the clinical trial protocol.

   CTI does believe that the FDA would be correct to expect some adjustment to the statistical procedures used to demonstrate efficacy because the hypothesis was refined based on results from the PMA data set. The appropriate adjustment should be based on the number of possible target populations that could have emerged from the original hypothesis/analysis plan and the adjustment can be accomplished conservatively by applying a Bonferoni correction, as is commonly applied for multiple comparisons within a single experiment.

   There were three lesion types defined for analysis in the original protocol – masses, calcifications and architectural distortions. Analysis of these lesion types could have resulted in demonstrating efficacy in the following seven target populations.

   * Calcifications
   * Masses
   * Distortions
   * Calcifications and Masses
   * Calcifications and Distortions
   * Masses and Distortions
   * Calcifications, Masses, and Distortions

An extremely conservative point of view would be to consider subsets that included both lesion size and lesion depth as criteria that constrain the target population. Based on the lesion size subsets that were prospectively defined in the protocol, three possible lesion size criteria could have been selected for the target population:

* No size limit
* Greater than 0.5 cm
* Greater than 1 cm.

Similarly, three possible lesion depth limits could have been selected for the target population:

* No depth limit
* Intermediate and superficial lesions only
* Superficial lesions only.

Taking the possibility of size and depth limits into account, as many as 63 (7 x 3 x 3) target populations could have emerged.

Confidence intervals for sensitivity and specificity for the combined PMA/PPMA dataset were reported as (95.6, 100.0) and (16.0, 22.8), respectively, in Amendment 5. If these intervals are adjusted using a Bonferoni correction based on the seven target populations defined by lesion type, these intervals become (93.5, 100.0) and (14.5, 24.6), respectively. If lesion size and depth are used as refining variables to define a total of 63 target populations, these intervals become (91.3, 100.0) and (13.4, 26.2), respectively. The assumed biopsy performance in the dataset is 100% sensitivity and 0% specificity. While CTI believes that seven is the appropriate number of potential target populations to use to adjust the confidence intervals to account for planned hypothesis refinement, the results for 63 potential target populations are presented as an extremely conservative bound.

In conclusion, because CTI did not retrospectively "redefine the hypothesis" as suggested by this question, the PPMA data was appropriately combined with PMA data to establish device efficacy in "masses with no size or depth limits". It is appropriate, however, to apply a Bonferoni correction when calculating the confidence intervals for device sensitivity and specificity, to account for the planned hypothesis refinement that resulted in the selection of masses as the target population for the device. CTI believes that 7 is the appropriate number of potential target populations to use in making the correction, which results in confidence intervals of (93.5, 100.0) and (14.5, 24.6) for sensitivity and specificity, respectively.

b) As stated in the response to Question 1a, CTI believes that the PMA and PPMA data can be combined to demonstrate the efficacy of the BCS2100. Therefore, there is no need to justify the use of the PPMA data alone.

c) CTI does not believe that a new trial is required. The initial clinical trial protocol prospectively called for examination of device efficacy by lesion type. If statistical significance levels are adjusted for the number of target populations that could have been considered as proposed in the response to Question 1a, CTI believes that there is no need for a new clinical trial – either pre-market or post-market.

B. Question 2

FDA question(s):

A total of 2407 subjects were enrolled in the clinical trial. A subset of 700 subjects was used for algorithm development, leaving 1707 subjects eligible for inclusion in the effectiveness analyses. Of these a total of 457 [388 (Amendment 4) + 69 (Amendment 5)] subjects (with mammographic masses) were used in the effectiveness analyses in Amendments 4 and 5.

a) Please account in detail for each of the 1250 eligible subjects that were eliminated from the effectiveness analyses in Amendments 4 and 5. That is, categorize them as to operator error, no mammogram, etc.

b) In addition to verbal description, please also present this information in the form of a flow chart, with the numbers of i) subjects and ii) lesions following each pathway in the chart and a categorization of each of the pathways.

c) Please explain why this very high level of exclusions does not introduce bias into the database that you used to draw conclusions about safety and effectiveness.

CTI response:

a) Most of the following information was submitted to the FDA in June 2001 as part of Module 5. A spreadsheet containing each subject and lesion (Appendix III), and the three flowcharts provided in the response below (Response 2b) account for the 1250 subjects that were not included in the final effectiveness analysis. The flowcharts are constructed to be consistent with the manner in which the eliminations occurred during the analysis phase of the investigation.

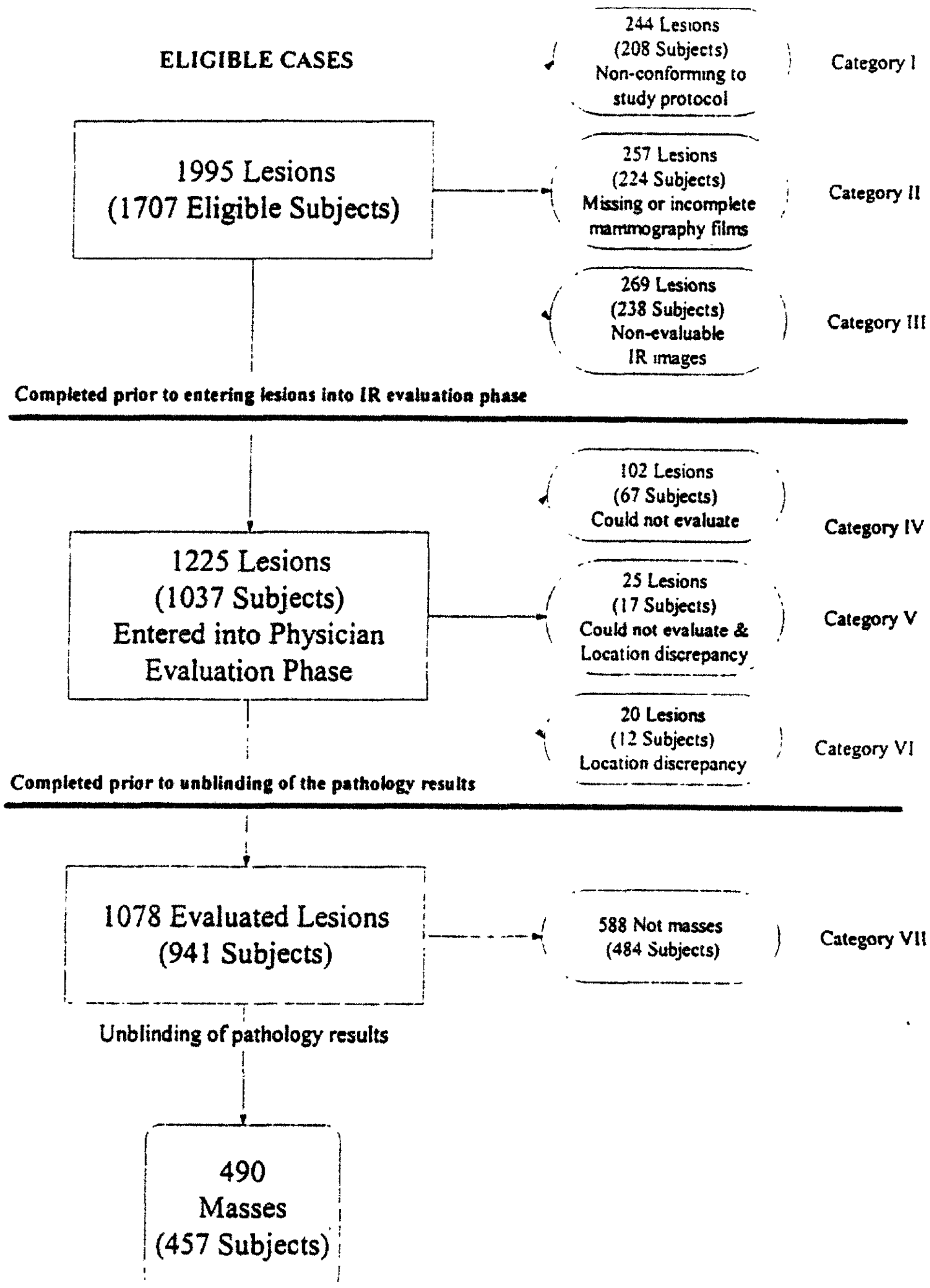
Category I exclusions are those cases that were not consistent with the study protocol and include those where no biopsy was performed, where a significant protocol deviation occurred, where the subject did not complete the study, or where the pathology result was inadvertently sent to CTI. This category involves 244 lesions in 208 subjects. Category II exclusions were those where there were missing or incomplete sets of mammography films supplied to CTI to use for the physician evaluation phase. This exclusion is described in detail in the original Module 5 submission on page 476. This group includes 257 lesions in 224 subjects. Category III exclusions were those cases where the IR images were determined to be unevaluable during CTI's internal review as extensively detailed in the Module 5 submission on pages 475-476. This group includes 269 lesions in 238 subjects. It is important to note that all of these exclusions were determined prior to unblinding, and the great majority was determined prior to proceeding towards the infrared physician evaluation phase. A small number of exceptions occurred after IR evaluation, when it was discovered that the biopsy had been cancelled or the pathology results had been sent to CTI in error (5 cases). All of these determinations were made prior to unblinding of the pathology results.

The next three categories of exclusions occurred in cases that entered the IR evaluation phase. A total of 1225 lesions in 1037 subjects were available for IR evaluation. Category IV exclusions were those cases wherein the reviewer did not localize the lesion due to a variety of reasons, such as no visible lesion (i.e. palpable cases with no mammographic evidence), poor mammographic quality or failure to find an identifiable lesion that was consistent with the case description. In this category, there were 102 lesions in 67 subjects. Category V lesions were those with mixed results among evaluators, e.g., one evaluator of a specific lesion could not localize whereas another evaluator placed an ROI but there was a localization discrepancy. This group included 25 lesions in 17 subjects. Category VI exclusions were a small number of cases where the evaluator completed an IR assessment, but the location was inconsistent with the case information. This issue is discussed in detail under Question 4 in this Amendment. As shown on the flowcharts in Response 2b, this exclusion applied to 38 lesions in 27 subjects. All determinations for exclusion under Categories I through VI were made prior to unblinding of the pathology data.

Category VII was established after unblinding to separate lesions into typological categories. That is, CTI wished to establish device efficacy in lesions that were described as masses, and therefore excluded from final efficacy analyses all lesions that did not include the descriptor "mass. Category VI exclusions involved 588 non-mass lesions in 484 subjects.

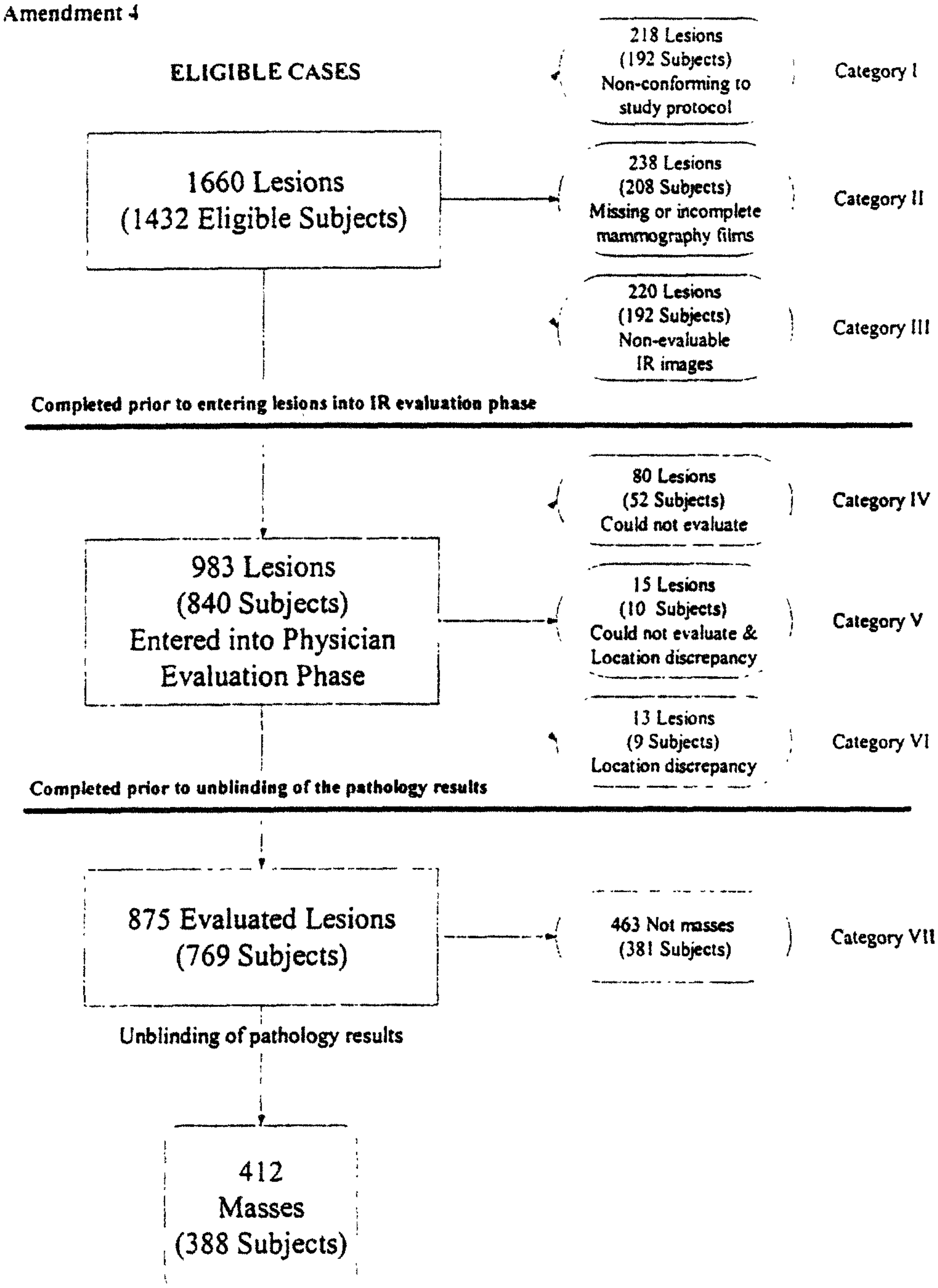
b) Flowcharts are presented on the following pages for the three sets of subjects used in primary efficacy analyses – PMA and PPMA subjects combined, and PMA (Amendment 4) subjects and PPMA (Amendment 5) subjects presented separately.

Combined PMA and PPMA subjects



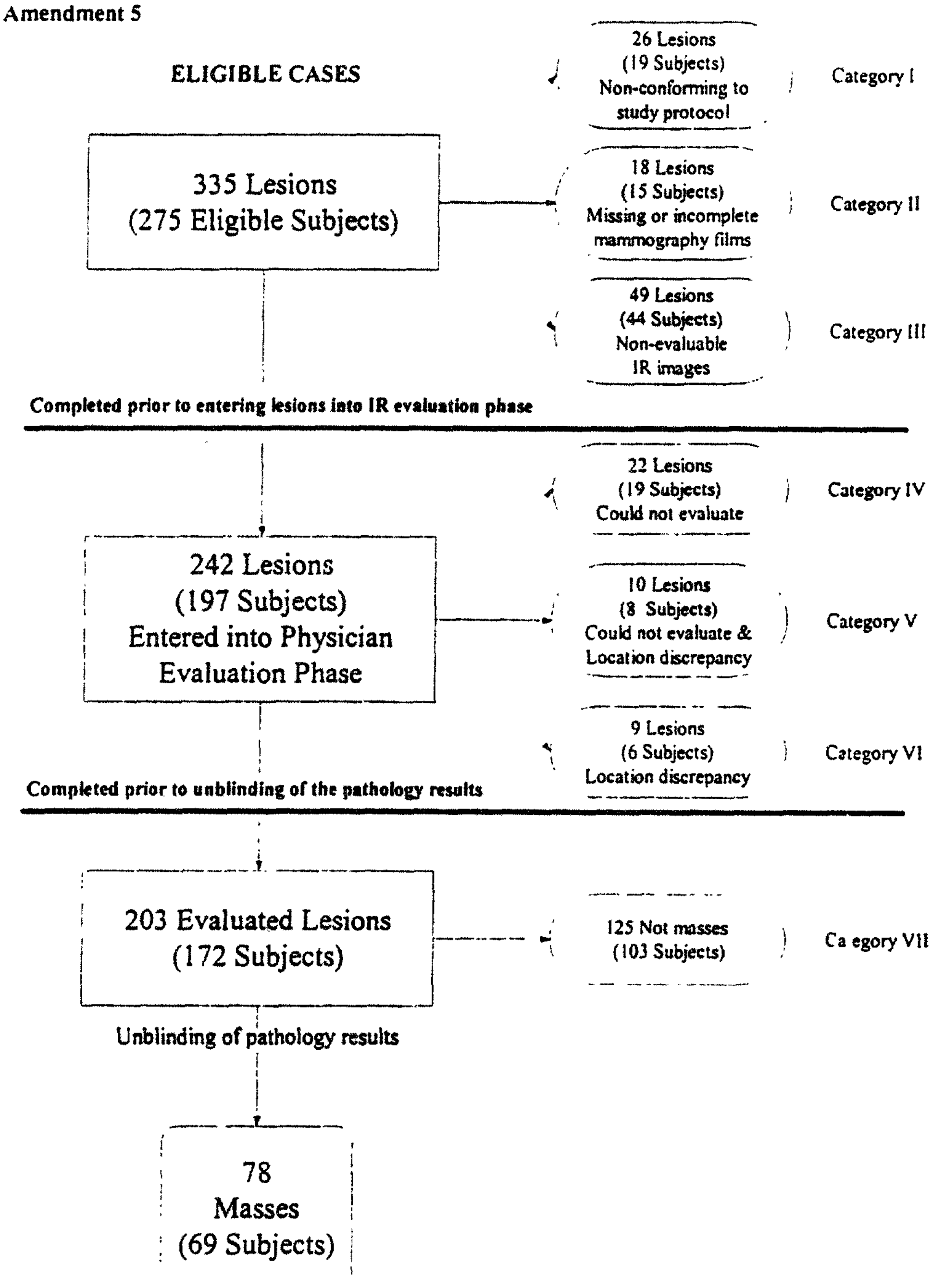
PMA subjects

Amendment 4



PPMA subjects

Amendment 5



c) The included and excluded evaluations of masses for the PMA and the combined PMA and PPMA datasets were compared by lesion location, presence of microcalcification, presence of architectural distortion, presence of spiculation, presence of asymmetric density, presence of irregular border, biopsy method, LOS and IOS. For both the PMA and combined PMA/PPMA datasets, the only variable that showed evidence of a difference between included and excluded lesions was the presence of spiculation.

For the PMA set, the percentage of spiculations associated with a mass in the included lesions was 12.1%, versus 3.5% for the excluded lesions. For the combined dataset, the percentage of spiculation in the included lesions was 11.6%, versus 2.8% for the excluded lesions. That is, more spiculated lesions were present in the included lesions than the excluded lesions in both the PMA and combined datasets.

Observing spiculations associated with a mass required adequate mammographic films and a prominently visible lesion. These conditions naturally led to fewer exclusions in Categories II, IV, V and VI (please see response to 2a for category definitions). Therefore, the inclusion of more spiculated masses is an unavoidable outcome of the exclusion process.

C. **Question 3**

FDA question(s):

The inclusion criteria for the subject set used in the safety and efficacy analyses are broader than the criteria used to describe the target population in the proposed Indications for Use. Please explain how these differences can permit application of the clinical trial results to this target population, or propose modifications to the intended target population that would eliminate both

a) these differences and

b) any retrospective subject selection effects.

CTI response:

The FDA clarified in its meeting with CTI on October 24, 2002 that its concerns involved the following statements in CTI's proposed BCS2100 Indications for Use.

> It is not recommended that results from the CTI BCS2100 be used to delay biopsy of any mass if the physician feels that a clear indication exists for biopsy. The decision to proceed with, or delay, biopsy must ultimately be based on the physician's clinical judgment. Factors that may contribute to this decision include the mammographic assessment, the patient's involvement in the health care decision, family history of breast cancer, other known risk factors, physical findings or findings from other diagnostic testing. (PMA P010035, Amendment 5, Appendix II)

Specifically, the FDA indicated that the phrase "clear indication exists for biopsy" was similar to that of previously approved devices in which this term was understood to refer specifically to lesions assigned to a mammographic BI-RADS category 5. However, CTI meant only to indicate that physicians should not base their decision regarding lesion biopsy solely on the IR test outcome. CTI did not intend to suggest that use of the BCS2100 should be restricted on the basis of mammographically assigned BI-RADS scores. In fact, CTI has no evidence to suggest that there is a direct connection between mammographic features per se and IR values, and no reason, therefore, to predicate use of the device upon mammographic features alone.

Furthermore, CTI believes that patients with masses assigned a high mammographic level of suspicion should not be denied the benefit of the device if their physicians feel information from the exam might be useful to the patients' clinical care. It is relevant to note that not all masses that are assigned to BI-RADS category 5 turn out to be malignant. For example, a study cited in *American Journal of Roentgenology* in 1998 found that only 81% of its BI-RADS category 5 cases turned out to be malignant (Liberman et al. 1998). In CTI's PMA dataset, 79% of the masses assigned a pre-device level of suspicion category 5 turned out to be malignant (33 of 42).

In order to remove any possible implication that patients should be selected for IR examination solely on the basis of mammographic features, while retaining the important information that the IR procedure is not meant to be a "stand-alone" test, CTI proposes to replace the statements above with the following statement.

> A physician should not base a decision for patient care solely on the results of testing with this device, but rather on the results of this test in combination with all other findings and risk factors associated with a specific patient.

The FDA's interpretation of the previous statement to refer specifically to BI-RADS category 5 masses led the FDA to question whether it was appropriate to apply the study's efficacy results that included BI-RADS category 5 lesions to the proposed target population if that population did not also include BI-RADS category 5 lesions. The FDA agreed in the October 24, 2002 meeting that eliminating the statement would eliminate the FDA's concern regarding the applicability of study results to the target population.

CTI's responses to the FDA's specific questions are as follows.

a) The removal of the phrase "clear indication exists for biopsy" eliminates the concern that physicians might interpret this phrase in the BCS2100 labeling to have a similar meaning to the same phrase in the labeling of other devices, namely that the device should not be used in the assessment of any lesion with a mammographic BI-RADS category 5.

b) By removing the suggestion that the target population should be selected on the basis of mammographic BI-RADS category, CTI has eliminated any retrospective subject selection effect based upon BI-RADS categories.

D. Question 4 (revision – original question withdrawn by FDA; revised question forwarded to CTI on October 31, 2002)

FDA question(s):

Some subjects were excluded from the effectiveness analyses because of a sufficiently large discrepancy between the ROI location selected by the doctor and the lesion location recorded on the case report form. We recognize that you have verbally given us answers to some of the following issues, but please provide us the answers in writing.

a) Please describe the precise criteria used to identify such discrepancies.

b) Please describe the procedure used to identify such discrepancies. Include in your answer who it was who made the judgment as to whether the i) subject and ii) lesion met the discrepancy criteria for exclusion.

c) What happened to subjects with multiple lesions in whom not all of the lesions met the discrepancy criteria for exclusion? In particular, were the subject, and those of her lesions that did not meet the criteria for exclusion, included in the analysis?

d) Please characterize the lesions for which such discrepancies occurred, in terms of their mammographic signs (i.e., masses, calcifications, etc.), their locations in the breast, their method of biopsy (i.e., open surgery, stereotactic core biopsy, etc.), their mammographic LOS, their IOS, and any other relevant characteristics.

e) Please show how the exclusions made on this basis do not bias your results.

CTI response:

a) The criteria to identify localization discrepancies were applied to each individual evaluation of a lesion. Lesion locations were described in one of three ways on the case report forms (CRF): (1) central location, (2) quadrant location, or (3) clock position. The "Central" designation was used for retro-areolar lesions. The four quadrant designations employed were upper outer (UO), upper inner (UI), lower outer (LO), and lower inner (LI). Clock positions were used for lesions that were not retro-areolar and were located on quadrant boundaries. The four clock position designations were 3:00, 6:00, 9:00, and 12:00. The following criteria were applied to the placements of the ROI circle on the IR image by the physician evaluators.

   1. For lesions designated as "Central" on the CRF, the center of the ROI circle placed by the physician was required to lie within 40 pixels of the center of the nipple on the IR image.

   2. For lesions designated by a quadrant location on the CRF, the center of the ROI circle placed by the physician was required to lie within one hour of the quadrant boundaries on the IR image. The quadrant designations by side (right or left breast) and the corresponding acceptable locations for the center of the ROI circle (in parentheses) were:

      A. Right breast, UO (8:00-1:00)
      B. Right breast, UI (11:00-4:00)
      C. Right breast, LO (5:00-10:00)
      D. Right breast, LI (2:00-7:00)
      E. Left breast, UO (11:00-4:00)
      F. Left breast, UI (8:00-1:00)

G. Left breast, LO (2:00-7:00)
H. Left breast, LI (5:00-10:00)

3. For lesions designated by a clock position on the CRF, the center of the ROI circle placed by the physician was required to lie within one hour of the designated clock position on the IR image. The clock positions and the corresponding acceptable locations for the center of the ROI circle (in parentheses) are:

A. 3:00 (2:00-4:00)
B. 6:00 (5:00-7:00)
C. 9:00 (8:00-10:00)
D. 12:00 (11:00-1:00)

If the pertinent criterion was violated, then the corresponding evaluation was excluded from the efficacy analysis.

b) The procedure for identifying localization discrepancies was automated. Therefore, no person was involved in the decision as to whether an evaluation met the discrepancy criteria for exclusion and no "judgment" was exercised. The automated procedure used to identify localization discrepancies was as follows.

In order to identify breast tissue for IR analysis, the breast was outlined and its nipple located on the IR image, as discussed elsewhere in this amendment (PMA P010035 Amendment 6). The physician's designated nipple location was associated with a single pixel on the IR image that was identified as the center of the nipple. The distance from this pixel to the pixel at the center of the ROI targeted by the physician was calculated for each evaluation according to the following formula.

$$\text{DISTANCE} = [(X\_RC - X\_NL)^2 + (Y\_RC - Y\_NL)^2]^{1/2}$$

where (X_RC,Y_RC) and (X_NL,Y_NL) are the locations of the center of the ROI circle and the nipple, respectively, on the thermal image.

A clock position, designated HOUR, was calculated for each evaluation according to the following formulas.

DX = X_RC - X_NL
DY = Y_RC - Y_NL

If DY=0 and DX=0 then HOUR=missing
If DY=0 and DX<0 then HOUR=3
If DY=0 and DX>0 then HOUR=9
If DY<0 then HOUR=arctan(DX/DY)/30
If DY>0 then HOUR=(180+arctan(DX/DY))/30

where the arctan() result is in degrees.

For a lesion location designated as "Central" on the CRF, DISTANCE was required to be less than or equal to 40 pixels. For a lesion location designated by either quadrant or clock position on the CRF, HOUR was required to lie within the pertinent clock position interval identified in the response to Question 4a, endpoints included.

c) The criteria to identify localization discrepancies were applied to each individual evaluation of a lesion. If an evaluation was found to meet the discrepancy criteria for exclusion, that evaluation, and only that evaluation, was excluded from the efficacy analysis. The exclusion of an individual evaluation from the efficacy analysis had no effect on the inclusion or exclusion of other evaluations of the same lesion or evaluations of other lesions within the same subject.

d) Since the localization discrepancies were eliminated on a per evaluation basis, the discrepancies were accounted for as follows: Each evaluation was assigned a weight based on the number of usable evaluations for the lesion before localization discrepancies were eliminated, so that each lesion received a total weight of one. The total number of discrepancies eliminated is based on the sum of the weights of these evaluations. For example, if only one out of three evaluations was eliminated, it was given a weight of 1/3. For this reason, the number of lesions for each type is fractional.

IOS was not calculated for the eliminated evaluations.

Characterization of Mammographic Signs for Eliminated Evaluations

Lesion Type	All Lesions	Masses Only
Mass	30.83	30.83
Microcalcification	33.33	5.17
Architectural Distortion	2.33	0
Spiculation	1.5	1.17
Irregular Border	3.67	2.33
Asymmetric Density	3.17	0.33

Note: Since each lesion could exhibit more than one mammographic sign, the totals are greater than the number of lesions for each dataset.

Characterization of Lesion Locations for Eliminated Evaluations

Lesion Locations	All Lesions		Masses Only	
	Left	Right	Left	Right
Upper	5.17	6	3.5	4
Lower	1.67	4.33	0	2
Outer	7.83	2.83	2.67	0.67
Inner	3.33	3.5	0.33	0.83
Upper/Inner	4	2.33	2.33	0.33
Upper/Outer	5	4.33	0.67	4.33
Lower/Inner	5	2.67	3.67	0.33
Lower/Outer	2.5	3	2.5	2.67
Total	63.5		30.8	

Characterization of Biopsy Method for Eliminated Evaluations

Biopsy Method	All Lesions	Masses Only
Core Needle	44.67	18.33
Surgical	18.83	12.5
Total	63.5	30.8

Characterization of LOS Score for Eliminated Evaluations

LOS	All Lesions	Masses Only
0	7.17	4.83
1	0.33	0.33
2	4.17	1.83
3	7.5	5.17
4	37	14.67
5	2	1
Missing	25.33	10.33
Total	83.5	38.2

e) Statistical tests comparing the included evaluations and the evaluations excluded for localization problems showed no evidence of a difference in biopsy method or LOS score. Due to the low number of lesions with various mammographic signs, there were insufficient data to perform reliable statistical tests for the presence of architectural distortion or spiculation for either dataset, nor was it possible to test for differences in the presence of irregular border or asymmetric density for the masses only dataset. In all other cases there was no evidence of a difference in mammographic signs between the included and excluded evaluations. There is evidence of a difference in lesion location, with a much greater proportion of lesions in the Upper/Outer quadrant for included (45%) versus excluded (16%) lesions.

E. **Question 5 (revision – original question withdrawn by FDA; revised question forwarded to CTI on October 31, 2002)**

FDA question(s):

A closely related question was asked of you in our 9/18/02 communication, and answered in your 9/30/02 responses. It also concerned the robustness of the IOS value of any particular lesion to inaccuracies in the user's placement of the ROI on the IR image. Your response was that the standard deviation for 3 mammographers reading all cases was "only 4 IOS units." This is a remarkably low SD for interreader variability. Indeed it raises the question of whether the low SD resulted from a frequent overriding of the radiologist's ROI placement by the search algorithm. Please explain in detail how many times, among the cases retained for analysis, the search algorithm located the highest contrast 5-pixel-radius circle (the one used to calculate the IOS value) completely outside the initial ROI chosen by the radiologist (i e., so that the initial ROI and the 5-pixel-radius circle failed to intersect). Include in this explanation a listing of the nearest distances (in terms of pixels) between the initial ROI and the 5-pixel-radius circle, for those pairs that failed to intersect.

CTI response:

For 602 (48%) of the 1254 evaluations upon which the efficacy analysis was based, the ROI center was not changed from the center of the ROI circle placed by the physician. For all 1254 evaluations, a circle of radius 5 pixels centered at the location selected by the physician intersected with the final ROI. Since there were no evaluations that failed to intersect, no listing is provided.

F. Question 6

FDA question(s):

Approximately 6.6% of the subjects used in the effectiveness analyses had multiple lesions that were biopsied. This percentage appears to be much larger than would be expected in clinical practice.

a) Please explain why this percentage is so high.

b) Please explain why you believe that this high percentage is representative of the proposed target population for the device.

c) Please provide the relevant portions of the clinical (original) mammographic report recommending biopsy, or, if biopsy was not recommended in the clinical (original) mammographic report, the reason why the subject was going to biopsy in spite of this, or why the particular lesion was, in fact, biopsied.

d) Please explain how correlation among multiple (up to 4) lesions within subjects was handled during your statistical analyses.

CTI response:

a) This question asks CTI to justify the percentage of subjects in the efficacy analysis who presented with multiple lesions. In order to respond, CTI has reviewed the literature to determine factors that affect the number of breast lesions that undergo biopsy. Given the increasing use of breast-conserving therapy, preoperative delineation of the extent of breast disease is necessary to facilitate appropriate surgical planning and treatment. Studies have shown that residual tumor foci present at the time of radiation after local resection of a primary malignant tumor are largely responsible for local malignant recurrences if the residual tumor(s) is (are) macroscopically recognizable (Sentis et al., 1997). One risk factor for breast conservation treatment failure that ranges from 3% to 19% is the presence of multifocal or multicentric malignant breast lesions (Berg and Gilbreath, 2000). Ipsilateral breast lesion recurrence after lumpectomy is associated with an increased risk of distant relapse and mortality (Sentis et al., 1997). Thus, it is important to identify and evaluate all breast lesions in the ipsilateral and contralateral breasts that are suspicious using the accepted practice guidelines for early diagnosis (Anderson and Cherry, 2000). In conclusion, biopsy of multiple lesions within a patient is often warranted and appropriate.

   There is an extensive body of literature describing the occurrence of multiple concurrent malignant lesions within patients. The prevalences of multifocal and multicentric breast cancers, estimated conservatively to be between thirteen and seventeen percent, appear dependent upon a number of factors including the varying definitions of multi-focus and multi-centricity, biopsy sample characteristics, type of breast disease, location of breast carcinoma, lesion characteristics, and the methodology used to identify and sample the lesions (mammography, ultrasound, magnetic resonance imaging, histopathologic analysis of resected specimens, amount of breast tissue examined) [Fisher et al., 1975; Schwartz et al., 1980; Westman-Naeser et al., 1981; Lesser, Rosen, and Kinne, 1982; Egan, 1982; Ringberg et al., 1991]. Examining 282 mastectomy specimens of invasive cancer in the 1980s, Holland and colleagues (1985) found that 20% of the specimens had additional unsuspected tumor foci within 2 cm of the index cancerous lesion. In 43% of the specimens, additional cancer was found more than 2 cm away from the index cancer lesion, with 27% being in situ and 16% invasive.

There is increasing evidence that the extent of malignant disease is often underestimated with mammography and clinical examination. Imaging devices other than mammography are identifying hidden lesions in many women that impact the treatment plan. Recently, Berg and Gilbeath (2000a) reported on a study of forty women who had known breast cancer or were highly suspected of having breast cancer mammographically, (i.e., BI-RADS category 5 lesion). They found that 55% of these women had unifocal disease, 22% had multifocal disease, and 22% had multicentric disease. Of the twenty women who were mammographically suspected of having unifocal disease, three had additional multicentric foci depicted during ultrasound and, as a result, a wider surgical excision was performed. In fact, this investigation revealed that 17% of the cancers found on by ultrasound were mammographically occult cancers. Using magnetic resonance imaging of 176 patients with biopsy-proven or presumed breast cancer, Orel et al (1995) reported that magnetic resonance imaging depicted additional foci that were not visible mammographically in 34% of the patients. In 20% of these women, the magnetic resonance detected lesions were mammographically and clinically unsuspected multifocal or diffuse cancer. Based on magnetic resonance results, treatment was altered for seven of these patients. Fisher et al. (1999) conducted preoperative contrast-enhanced magnetic resonance breast imaging in a sample of 463 women with probably benign lesions, suspicious lesions, and lesions highly suggestive of malignancy to determine if magnetic resonance imaging could detect the presence of multifocal or multicentric lesions that could or would impact therapeutic decisions. Based on results of a clinical exam, and mammography and/or ultrasound, 63 patients were classified as having a "probably benign" abnormality. These women underwent open biopsy based on patient preference, cosmetic considerations, or a recommendation from the referring outside radiologist. Of the remaining patients undergoing biopsy, 230 had suspicious findings and 170 had findings highly suggestive of malignancy. In total, there were 548 biopsied lesions in the 463 patients with 405 malignant and 143 benign outcomes. Slightly more than 10% of the 405 malignant tumors showed multifocal tumor growth at histopathologic analysis with an additional 12% being multicentric. The therapeutic plan was changed from lumpectomy to quadrantectomy or mastectomy in 14% of the patients as magnetic resonance imaging depicted more extensive disease than was appreciated with mammography, ultrasound, or clinical evaluation.

In summary, the current clinical practice among expert radiologists and surgeons who perform breast biopsies is to perform multiple biopsies in order to rule out the possibility of multi-focal disease and to devise the appropriate follow-up therapy should a malignancy be found.

CTI's responses to the FDA's specific questions are as follows.

a) The percentage is representative of the normal clinical practice that is common among dedicated breast imaging practices.

b) The target population for this device is women scheduled for breast biopsy where adjunctive diagnostic information is desired. Whether the patient has a single lesion or multiple lesions requiring assessment is not a factor in deciding whether this adjunctive procedure is appropriate.

c) It is not possible at this time to reconstruct the clinical scenario that led to the biopsy decision for each individual lesion.

d) It was assumed that lesions within subjects were independent. It was assumed that multiple evaluations of the same lesion were totally dependent. Thus, the effective sample size for the purpose of statistical inference was the number of lesions.

G. Question 7

FDA question(s):

You initially assigned 220 subjects to algorithm development and IOS threshold selection. Subsequently, with FDA concurrence, an additional 480 subjects were randomly selected for algorithm development and IOS threshold selection.

a) Please describe how you determined that an additional 480 subjects were required for algorithm development and IOS threshold selection.

b) Please describe in detail the randomization procedure for selecting the additional 480 subjects.

c) Were any of the 700 subjects in the training set excluded for any of the criteria used for exclusion of subjects among the 1707 in the test sets of Module 5, Amendment 4, and Amendment 5?

d) If so, how many for each category of exclusion?

e) If not, please explain why these same exclusion criteria did not apply to any of the 700 in the training set.

CTI response:

a) During July of 1999, CTI completed an assessment of the effect of training set size on the uncertainty in algorithm performance. At that time, the training set contained 25 malignant lesions and 92 benign lesions. This assessment was performed via a bootstrap program that simulated 1000 replications of training and evaluating an algorithm. The bootstrap simulation results were then used to characterize the uncertainty in assessing true algorithm performance in the target population and the effect of training set size on this uncertainty.

   As a result of this assessment, CTI concluded that the initial training set of 25 malignant lesions and 92 benign lesions was insufficient not only for adequately characterizing true algorithm performance, but also for adequately finalizing the form of the algorithm and the methodology for estimating algorithm parameters. As a result of this conclusion, CTI decided to increase the size of the training set four-fold. Since CTI was considering changes in the form of the algorithm and the methodology for estimating algorithm parameters, a four-fold increase was selected as a sufficiently large increase to represent a logical next step in the algorithm development process. Any larger increase would have relied too heavily on the specific form of the algorithm and the very small amount of training data available at that time.

   A four-fold increase in training set sample size represented an increase of 75 malignant lesions. It was anticipated that as many as 25% of the new algorithm development lesions would be unusable because of incomplete case files. Thus, a target of 100 new malignant lesions was set. The unblinding procedure was expressly defined to continue randomly unblinding subject pathology until at least 100 malignant lesions had been unblinded. This process yielded a total unblinding of 480 subjects.

b) The detailed description of the randomization procedure for selecting additional subjects for algorithm development is as follows.

1. A unique sequence number in the range of 1 through 2500 was assigned to all subjects who were currently enrolled in the clinical trial.
2. Battelle used a random number generator that was available in Microsoft Excel to randomly order the integers 1-2500. The ordered list of integers was attached to an email memo generated by Battelle and addressed to CTI and Ken Palmer at Quintiles that certified that the list was generated randomly and was the order in which images should be extracted for algorithm development.
3. CTI instructed Quintiles to unblind subjects according to the randomly assigned order until at least 100 malignancies had been unblinded.
4. Quintiles identified subjects for addition to algorithm development according to the list of random integers from Step 2 until the number of malignant images required by CTI had been identified. When working through the list of random integers, if no patient corresponded to an integer on the list, that random number was skipped. Quintiles provided CTI the subject numbers of the specific subjects patients to be added to algorithm development. Quintiles then copied and provided to CTI the pathology case report form data that was associated with these subjects.

c) Yes. A total of 471 of the 700 algorithm subjects were excluded because of the application of criteria similar to those used for the PMA and PPMA subjects, except that non-masses were never excluded as a group from the algorithm subject set.

d) In the response to Question 2a, seven exclusion categories were defined for PMA and PPMA patients. During algorithm development, CTI did not separately track exclusions for Categories I and II, nor were exclusions for categories IV, V, and VI separately tracked. Of the 700 algorithm subjects, 213 subjects were Category I/II exclusions, 170 subjects were Category III exclusions, and 88 subjects were Category IV/V/VI exclusions. No Category VII exclusions were made from the algorithm patient set. The resulting final algorithm patient set contained 229 subjects.

e) Since similar exclusion criteria did apply, no response is required.

H. Question 8

<u>FDA question:</u>

Please describe in detail how the IOS threshold of 20.59 was determined.

<u>CTI response:</u>

The threshold for IOS was selected to attempt to achieve the objective of maintaining a sensitivity of at least 99% with 75% confidence. First, a logistic distribution was fitted to the IOS data for malignant lesions in the training data set. The two smallest IOS values appeared to be outliers and were removed from the training dataset in order to diminish their influence on the logistic distribution parameter estimates. Using the fitted logistic distribution, 10000 simulated samples of size 140 were generated for IOS. Samples of size 140 were generated, as it was anticipated that the final evaluation dataset would contain 140 malignant lesions. The second smallest IOS value (IOS_2, an estimate of the 1^{st} percentile of the IOS distribution) was selected from each of the 10000 simulated samples. The classifier threshold was set equal to the 25^{th} percentile (the average of the 2500th and 2501st values of IOS_2) among the 10000 simulated IOS_2 values in order to have 75% confidence that the threshold value selected would result in a sensitivity of 99%.

I. Question 9

FDA question(s):

Please provide a breakdown of lesions used in the safety and effectiveness analyses in Module 5, Amendment 4, and Amendment 5 by biopsy type (surgical, core needle, other), mammographic sign, mass location, LOS, and IOS.

CTI response:

Breakdowns of lesions used in the safety and effectiveness analyses in Module 5, Module 5 Amendment 4 and Module 5 Amendment 5 are shown in the following tables.

Breakdown by Biopsy Type

Biopsy Type	Module 5	Amendment 4	Amendment 5
Core Needle	650	272	340
Surgical	224	139	149
Tru-Cut	1	1	1
Total	875	412	490

Breakdown by Mammographic Sign

Lesion Type	Module 5	Amendment 4	Amendment 5
Mass	412	412	490
Microcalcification	473	58	65
Architectural Distortion	31	10	12
Spiculation	53	46	52
Irregular Border	56	46	53
Asymmetric Density	63	16	18

Note: Since each lesion could exhibit more than one mammographic sign, the totals are greater than the number of lesions for each dataset.

Breakdown by Lesion Location

Lesion Locations	Module 5		Amendment 4		Amendment 5	
	Left	Right	Left	Right	Left	Right
Upper	44	32	21	19	24	22
Lower	16	13	10	7	12	10
Outer	19	25	8	13	11	16
Inner	11	10	6	7	6	8
Central	16	21	3	8	4	10
Upper/Inner	60	56	26	24	33	26
Upper/Outer	183	197	77	87	94	105
Lower/Inner	59	61	33	35	37	39
Lower/Outer	23	29	11	17	12	21
Total	875		412		490	

Breakdown by LOS Score

LOS	Module 5	Amendment 4	Amendment 5
0	178	128	128
1	9	9	9
2	27	19	19
3	65	37	37
4	517	168	168
5	51	42	42
Missing	28	9	87
Total	875	412	490

Note: The only difference in the breakdown between Amendment 4 and Amendment 5 is the number of missing LOS values because LOS scores were not obtained for the PPMA dataset.

Breakdown by IOS Result

IOS Result	Module 5	Amendment 4	Amendment 5
Negative	103.67	58	75
Positive	771.33	354	415
Total	875	412	490

Note: The counts may be fractional because the IOS result may differ across the evaluations. Each evaluation was assigned a weight based on the number of usable evaluations for the lesion so that each lesion received a total weight of one.

J. Question 10

FDA question(s):

There are lesions used in the safety and effectiveness analysis that were assigned LOS scores of 0, 1, 2, or 3. Given that all lesions examined in the clinical trial were headed for biopsy,

a) please explain how each LOS (or BIRADS) 0, 1, 2, or 3 came to be in this group.

b) In particular, given that it was necessary that the doctor be able to localize a mass on the IR image based on its mammographic location, explain how each mass with an LOS score of 1 (which means that no mammographic abnormality was visible) was retained for effectiveness analysis.

CTI response:

The American College of Radiology (ACR) devised the Breast Imaging Reporting and Data System (BI-RADS) to standardize mammographic reporting, and to facilitate consistency between mammographic assessments and clinical management. According to the ACR BI-RADS category definitions, only lesions assigned to BI-RADS categories 4 and 5 are recommended for biopsy. Therefore, it might be assumed that lesions assigned to BI-RADS categories 0 (additional imaging information recommended), 1 (negative finding – normal interval mammography recommended), 2 (benign finding – normal interval mammography recommended) and 3 (probably benign finding – short-term follow-up recommended) would not undergo biopsy. However, various studies have reported that BI-RADS category assignments are not always consistent with the associated treatment recommendations. This is consistent with CTI's findings in its BCS2100 clinical study that lesions in all BI-RADS categories were recommended for biopsy. The following discussion refers to representative current studies reported in the literature that have examined the issue of discrepancy between assigned BI-RADS categories and recommendations for treatment.

Screening Mammography

Taplin et al. (2002) examined the frequency with which BI-RADS mammographic screening assessments were associated with expected clinical management recommendations. This study detailed results in more than 292,000 women screened in 1997 at multiple facilities in seven states using mammographic registries of the Breast Cancer Surveillance Consortium (BCSC). Lesions in almost 92% of the women were assigned to BI-RADS category 1 or 2. For 99.3% of these women, the clinical management recommendations were as expected, that is, that patients should undergo normal interval mammography. However, it was recommended that the remainder of the patients undergo short interval follow-up, additional imaging, clinical examination or surgical consult for biopsy or fine needle aspiration. Of the 10,000 women who presented with lesions assigned BI-RADS category 0, 95.5% received the expected recommendation, while 4.5% did not. Normal interval follow-up was recommended for 2% of the patients, short interval follow-up for 1%, and 1.5% were referred for clinical examination, surgical consult, biopsy or fine needle aspiration. Of the nearly 12,000 women assigned to BI-RADS category 3, only 40.3% were recommended for short interval follow-up, the expected recommendation. Additional imaging was recommended for 36.9%, and normal interval follow-up was recommended for 18.8%. Of note, 4% were recommended for clinical examination, surgical consult, biopsy or fine needle aspiration. In summary, the studies show that biopsies do occur in lesions assigned BI-RADS categories 0 through 3.

Diagnostic Mammography

In a study of 1996-97 data that was supplied by the Breast Cancer Surveillance Consortium from eight mammographic registries, Geller et al. (2002) examined more than 51,000 diagnostic mammograms to determine if BI-RADS mammographic assessments were consistent with the expected patient management recommendations. In BI-RADS categories 1, 2, 4 and 5, the expected management recommendation occurred in 85 – 90% of the cases, with BI-RADS category 3 having the most variability. Biopsy or fine-needle aspiration was recommended for 0.8% of BI-RADS category 1, 1.1% of BI-RAD category 2, and 9% of BI-RADS category 3 assessments. BI-RADS category 3 cases revealed that only 40% received the expected recommendation for short interval follow-up. Other recommendations for BI-RADS category 3 assessments included 13% assigned to normal interval follow-up, 27% to additional imaging, 11% to clinical examination or surgical consultation, and 9% directly to biopsy or fine-needle aspiration. Of the cases assigned to BI-RADS category 0, 64% received recommendation for additional imaging, while another 20% were recommended for either a consultation or biopsy. The rest were advised to regular interval or short interval follow-up.

Other data is provided by Orel et al (1999), who reported data from 1312 biopsies that included 1% BI-RADS category 0 lesions, 4% category 2 lesions, and 11% category 3 lesions, for a total of 15% of the biopsies that were not in Categories 4 and 5. Of the 206 lesions that were biopsied from Categories 0, 2, and 3, malignancies were found in five lesions. Barlow et al (2002) described results in over 32,000 women followed for one year, and reported the occurrence of breast cancer in women with lesions assigned to BI-RADS 0, 1, and 2. They also note that although category 0 lesions should be resolved and re-assigned to another category, many in fact are not resolved before the patient is recommended and undergoes biopsy. They also comment, "that assessments of 0 have a high probability of cancer".

Thus, the literature provides substantial data that, although BI-RADS recommendations are generally followed, compliance is not 100%. Categories 0 and 3 lesions show the highest deviation from the model and a number of lesions in these categories are referred to biopsy. Perhaps as significant, biopsies in all BI-RADS categories result in malignant outcomes.

In summary, the CTI data is consistent with that reported in numerous published investigations involving large numbers of patients. In fact, it would have been inconsistent with the usual clinical practice, had such subjects NOT been enrolled in this research investigation.

The BCS2100 study protocol required that any lesion to be assessed in the study must have been recommended for biopsy prior to study entry. A portion of these biopsied lesions fell into BI-RADS categories 0, 1, 2, and 3, according to information in the radiology reports. In summary, the CTI data, by including lesions in these categories, are consistent with what has been found and reported by numerous investigators at multiple centers and with large numbers of patients.

CTI's responses to the FDA's specific questions are as follows.

a) The BCS2100 protocol required that the recommendation for biopsy be based on mammographic and / or physical examination findings. The case report form recorded this information as a single answer to the following question.

    The subject:

        Has had mammogram, results are interpretable and surgical or core biopsy has been recommended

        OR

        Has had clinical examination, results are available and surgical or core biopsy has been recommended.

CTI did not require that investigators justify biopsy recommendations, and did not gather detailed information that would allow CTI to reconstruct the clinical scenario for each individual lesion that ultimately resulted in the decision for biopsy. As enrollment into the study began more than five years ago, it is doubtful that this information is currently available. Therefore, it is not possible to provide this information. CTI notes, however, that its inclusion of BI-RADS category 0, 1, 2 and 3 lesions in its dataset is consistent with current medical practice, as discussed above.

b) A review of mammographic films of masses assigned a BI-RADS category 1 revealed that markers were placed on the breasts that allowed evaluators to localize suspicious lesions on the IR images. It is assumed that these markers denote palpable masses that were not found to be mammographically apparent.

K. Question 11

FDA question:

A number of lesions used in the effectiveness analyses are described as masses with a pathology result of DCIS. Explain how a mass can have a pathology result of DCIS.

CTI response:

There is substantial literature documenting that DCIS can present as a mass, although this is not the most common mammographic finding. An early study by Ikeda et al (1989) analyzed the mammograms of 190 women with biopsy-proven DCIS and demonstrated unusual radiographic manifestations associated with the disease, including circumscribed or sub-areolar masses in a substantial number (18) of patients. Several more recent investigations support this finding. For example, Lee et al (1999) conducted a study correlating mammographic manifestations and average nuclear grade in 37 cases of DCIS. They found that mass alone was seen in 21.6% of the cases, microcalcifications with associated mass in 19%, and microcalcifications alone in 59.4% of the cases. Slanetz and colleagues (2001) in their report of the mammographic appearance of DCIS found that the mammogram showed only a mass in 10 of 75 cases, a mass and calcifications in three of 75 cases, and calcifications alone in 62 of 75 cases. Finally, a recent study by Jackman et al (2001) involving over 13,000 biopsies reported that for DCIS lesions (1326), 11% presented as masses and 89% as microcalcifications. Thus, the percentage of DCIS cases that presented as a mass in CTI's investigation (10.5%) are consistent with the experience of other studies.

L. Question 12

FDA question(s):

In Module 4 you describe two versions of your device, a prototype that you call "revision 0" and a new configuration that you call "revision 1" or the "production" version. You state therein that revision 0 was the version that was used at the clinical test sites to collect the data presented in the PMA and the subsequent amendments. We assume that you mean to market the "production" version (revision 1). You describe the differences between the two devices in terms of manual and automated functions, respectively.

a) Please describe how the automation of the various functions listed in Module 4 affect the images and/or the IOS determinations of the various parts of the images.

b) If the automation does not affect the images or the IOS determinations of the various parts of the images, please demonstrate this fact.

c) Given that a significant number of IR images were excluded from the analyses due to operator error caused by manual operation, please explain why you are justified in excluding these from analysis rather than performing an intent-to-treat analysis that would include all such subjects.

d) Please explain why you believe that automating those features can be done without obtaining clinical validation.

CTI response:

The automations to which this question refers will be present in the production version of the BCS2100. However, in order to address concerns that the FDA has expressed regarding the device output, it will be necessary to revise the design of the BCS2100. CTI would like to clarify, therefore, that it does not plan to market the Revision 1 device. CTI plans to amend the BCS2100 PMA with a description of the device that it plans to market as soon as all decisions are made that will impact the production version of the BCS2100. CTI will take that opportunity to make other minor changes to the device that will not affect its proven safety and efficacy. Because the Revision 1 device never became a production device, all comparisons in the amendment will be made between the Revision 0 device that was proven in the clinical trials and the proposed production device.

Because CTI does not plan to change the automation in the production model from that described for the Revision 1 device, it is expected that the FDA will have the same questions regarding automation in the planned production device that it had regarding the Revision 1 device. Therefore, CTI's responses to the FDA questions follow on the next page.

a) The functions that will be automated in the production version of the BCS2100 are detailed in the following table, including determination of the effect of automation on IR images and/or IOS scores.

Clinical Version	Production Version	Effect on images and/or IOS determination
Manual control of the A/C, boost fan, and diverter devices associated with the IR challenge	Software control, using an Opto22 interface unit, in order to provide automatic operation of the IR challenge	Assures each patient receives the thermal challenge at the required time. In the clinical trial, images that didn't receive cooling at the specified time were eliminated based on a post- imaging cooling check. Therefore, there is no affect on the images or IOS determination except to assure at imaging session time that the timing and degree of cooling meets specification.
Manual inspection of the images for quality	Automatic image quality check AND Software-prompted manual image quality check	No effect on the images or the IOS determination. This check will insure that the BCS2100 has a quality image before the patient leaves the imaging room. With the clinical version, this check was done at CTI after the images had been transferred from the clinic.
Manual control of electrical distribution	Computer system interface unit control of electrical distribution	No effect on the images or the IOS determination.
Lynx operating system	Windows NT operating system	None. The IR camera takes the same image with the same timing while running under either operating system.
Environmental and device temperatures read by technologist from a control panel and logged manually.	Computer system interface unit connected to temperature probes to read, record, save and print temperatures to a printer.	None. These temperatures are used in determining operating parameters for the device, but do not affect the image or the IOS determination.
Rev 0 patient evaluation software	Rev 1 patient evaluation software	None. Rev 1 software implements the same algorithm as Rev 0.

b) The automation upgrade from Revision 0 to Revision 1 was validated according to CTI's standard operating procedures as documented in the BCS2100 design history file (DHF). All design changes were identified, documented, validated, reviewed and approved as design changes prior to their implementation. Validation was performed under simulated clinical use conditions, and was found to meet all design input requirements.

c) Piantadosi, in his 1997 text entitled *Clinical Trials: A Methodological Perspective*, defined "intention to treat" as "the idea that patients assigned to treatments in randomized clinical trials should be analyzed according to the assigned treatment group rather than the treatment actually received" (Piantadosi 1997). That is, an intent-to-treat analysis is performed after randomization to determine if a randomly assigned treatment (which may be placebo) has affected the ability of subjects assigned to that treatment to successfully complete the study. If the treatment has affected the ability of subjects to complete the study, then an analysis of only the subjects who completed the trial will be biased. An intent-to-treat analysis attempts to quantify this bias.

The BCS2100 study did not randomly assign subjects to treatment groups. Therefore, it is unclear to CTI how an "intent-to-treat" analysis would be performed, and CTI is unaware of any precedent for this type of analysis in clinical trials such as that performed for the BCS2100.

d) The automation upgrade from Revision 0 to Revision 1 was validated according to CTI's standard operating procedures as documented in the BCS2100 design history file (DHF). All design changes were identified, documented, validated, reviewed and approved as design changes prior to their implementation. Validation was performed under simulated clinical use conditions, and was found to meet all design input requirements.

M. Question 13

FDA question(s):

A question concerning the device output of both "positive/negative" as well as the "IOS value" was asked of you in our 9/18/02 communication, and you responded in your 9/30/02 reply. You say, "The mammographer will be instructed to use this information (i.e., the IOS value) as additional information from which to make a decision for patient care." And later on you say, "...we do not recommend any scheme for combining mammographic LOS with IOS."

a) How do you propose, in the labeling, to write instructions for use of the IOS value?

b) On what data from your clinical trial can you base such instructions to the user?

CTI response:

The FDA agreed in the October 24, 2002 meeting with CTI that removing the IOS value from the device output would remove the FDA's concerns. CTI agreed, therefore, to consider removing the IOS from the device output.

However, after the aforementioned meeting, CTI discussed the FDA's concerns regarding IOS display with CTI's consulting physicians. These physicians expressed the strong belief that the IOS should be provided to physicians, in addition to the positive / negative IR test result. They explained that radiologists are accustomed to being presented with visual information that is not accompanied by instructions for its use, and are capable of understanding that the IOS represents a numerical analogue to this same sort of information.

CTI would welcome the Panel's input on this issue. However, in order to expedite the review and approval of the BCS2100, CTI agrees to remove the IOS from the BCS2100 display if no other alternative is found. Therefore, the answers to the FDA's specific questions are as follows.

a) Removal of the IOS value removes the need to write instructions for its use.

b) Removal of the IOS value removes the necessity to provide data upon which to base its use.

N. Question 14

FDA question:

The Operator's Manual (June 13, 2001) tells the physician to "Place the ROI circle over the suspected bulls eye lesion location previously defined through examination or mammography" (p. 68).

a) How is the ROI circle called up by the physician in the first place, or is it already present on the image when the image is called up by the physician?

b) Is the physician able to resize the ROI circle, or is the physician able only to move it from place to place?

c) Is the physician able to reshape the ROI to more closely match the shape of an irregularly shaped mammographic mass, or does the ROI maintain a circular shape regardless of what the physician does?

d) How does the physician move the ROI circle to a different location on the breast image-- with the mouse, or is there some other way?

e) What is the size of the ROI compared to the search region circle that is designed to cover 1/12th of the area of the breast?

f) The physician is permitted to adjust the outline of the breast that is drawn by the technologist. If the breast outline is adjusted by the physician, and the area of the breast outline changes as a result, does the search region change its size automatically to maintain itself as 1/12th the area of the breast?

CTI response:

In this response, "ROI circle" refers to the circle that initially appears when the physician begins his or her evaluation of the breast of interest. The abbreviation "ROI" alone indicates the area that is ultimately designated as the region of interest for algorithm calculations.

The Operator's Manual (June 13, 2001) instructs the physician to "Place the ROI circle over the suspected bulls eye lesion location previously defined through examination or mammography" (p. 68 of the previously submitted manual).

a) The ROI circle is present when the image is called up by the physician.

b) The physician is able to select from three sizes of ROI circles and is able to move the ROI.

c) The ROI circle and ROI are always circular in shape.

d) The ROI circle is moved using the mouse.

e) The ROI used in the algorithm always has a five-pixel radius. The search region size is dependent upon the size of the breast tissue region enclosed by the outlines placed by the technologist and verified by the physician. For the combined PMA/PPMA dataset, the average search region radius was 7.85 pixels and the standard deviation of the radius values was 1.66 pixels.

f) Yes.

O. Question 15

FDA question:

In the meeting between FDA and the company on 10/24/02 Dr. Rust stated that there was some comparison performed by the computer when the physician places the ROI, and that if this comparison surpasses some criterion then one thing occurs, but if the comparison fails to surpass that criterion then another thing occurs. He stated that he would have to look this up to refresh his memory. Please explain this comparison, the criterion, and what it is that either occurs or does not occur based on the criterion.

CTI response:

The comparison Dr. Rust mentioned involves a set of index values calculated for the pixels within an automated search region. The index combines two criteria: higher temperature and local contrast. The standard deviation of the index values within the automated search region is compared to 25th percentile of the standard deviations calculated for the algorithm training set. If the standard deviation of the index values is less than or equal to this 25th percentile, the center of the ROI is placed at the center of the ROI circle placed by the physician. If the standard deviation of the index values is greater than this 25th percentile, the center of the ROI is placed at the pixel within the search region that has the largest index value. A more detailed description of this process appears below.

The center of the ROI circle placed by the physician is taken as the center of the circular automated search region. The radius of the circular automated search region is determined by the following equation:

Radius = sqrt (((xn-xe)*(ye-yn))+ (xs-xe)*(ys-ye)+(xw-xs)*(ys-yw)+(xw-xn)*(yw-yn))/48)

where (xn,yn), (xs,ys), (xe,ye), and (xw,yw) are the north, south, east, and west points that define the breast region outline.

This radius corresponds to a circle of size equal to approximately one twelfth the entire breast region size. Any pixels within the circular automated search region that are outside of the breast region are eliminated from the automated search region.

The search is performed on the product of two planes, a gradient plane and average temperature plane. The average temperature plane is calculated across the frames of interest on a pixel-by-pixel basis from the onset of cooling to 45 frames after onset with no spatial averaging. Each point on the gradient plane is represented by the average of all points within two pixels of the given point minus the average of all points more than two pixels away, but within five pixels of the point. For each point in the gradient plane, let AVG81 represent the average temperature across all pixels within five pixels of that point and N81 represent the number of pixels included in the average. Let AVG13 and N13 represent similar quantities for all pixels within two pixels of that point. Note that N81 and N13 may be less than 81 and 13, respectively, if the regions being averaged have pixels outside of the breast region. The gradient plane value, GRAD1381, is calculated using the following formula:

GRAD1381 = AVG13 – ((AVG81*N81-AVG13*N13)/(N81-N13))

To create comparable values across all patients, rescaling is performed. The gradient plane and the average temperature plane are subset down to those points within the automated search region. The 1st and 99th percentiles of the values within each subset are used to rescale each plane to a 0 – 1 range, respectively. With P01_A and P99_A representing the 1st and

99th percentiles of the average temperatures, and P01_G and P99_G representing those for the gradients, the slope and intercept for those values are calculated as:

m2_A = 1/(P99_A-P01_A); b2_A = -1*m2_A*P01_A;
m2_G = 1/(P99_G-P01_G); b2_G = -1*m2_G*P01_G;

Using those slopes and intercepts, the temperature averages (AVG) and the gradient values (GRAD1381), the product of the rescaled values can be expressed as the index value VAL_PCT:

VAL_PCT = (m2_A*AVG + b2_A)*(m2_G*GRAD1381+b2_G)

The maximum and standard deviation of all the index values within the search region are calculated. If the standard deviation is greater than 0.1933273 (the 25th percentile of the standard deviations for the training set), the location where the maximum VAL_PCT value occurs within the automated search region is selected as the center of the ROI. If the standard deviation is less than or equal to 0.1933273, the center of the ROI circle placed by the physician is used as the ROI location.

APPENDICES