SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Digital Breast Tomosynthesis
Device Trade Name:	Selenia Dimensions 3D System
Device Procode:	OTE
Applicant's Name and Address:	Hologic, Inc. 35 Crosby Dr. Bedford, MA 01730
Date(s) of Panel Recommendation:	October 24, 2012

Premarket Approval Application (PMA) Number: P080003/S001

Date of FDA Notice of Approval:	May 16, 2013
Expedited:	Not applicable

The original PMA (P080003) was approved on February 11, 2011 and is indicated for generating digital mammographic images that can be used for screening and diagnosis of breast cancer. The Selenia Dimensions (2D or 3D) system is intended for use in the same clinical applications as 2D mammography systems for screening mammograms. Specifically, the Selenia Dimensions system can be used to acquire 2D digital mammograms and 3D mammograms. The screening examination will consist of a 2D image set or a 2D and 3D image set. The Selenia Dimensions system may also be used for additional diagnostic workup of the breast. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the Selenia Dimensions 3D System.

II. INDICATIONS FOR USE

The Hologic Selenia Dimensions system generates digital mammographic images that can be used for screening and diagnosis of breast cancer. The Selenia Dimensions (2D or 3D) system is intended for use in the same clinical applications as a 2D mammography system for screening mammograms. Specifically, the Selenia Dimensions system can be used to generate 2D digital mammograms and 3D mammograms. Each screening examination may consist of:

- a 2D FFDM image set, or
- a 2D and 3D image set, where the 2D image can be either a FFDM or a 2D image generated from the 3D image set

The Selenia Dimensions system may also be used for additional diagnostic workup of the breast.

III. CONTRAINDICATIONS

None

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Selenia Dimensions 3D System labeling and the C-View User Manual.

V. DEVICE DESCRIPTION

The Selenia Dimensions 3D System (P080003) is a hardware and software upgrade to the Selenia Dimensions 2D FFDM system (P010025/S013). The Selenia Dimensions 3D System enables the acquisition of tomosynthesis three-dimensional (3D) images for screening and diagnostic purposes. The system can acquire 2D and 3D images separately, or combined in a single compression. The 3D images are acquired by moving the tube head in a 15^{o} arc over the stationary, compressed breast capturing multiple images at multiple angles during a short scan. These individual images are then reconstructed into a series of thin high-resolution slices that can be displayed on a softcopy workstation. Images can be acquired in any orientation of the gantry, including the standard CC and MLO mammography views. The 2D and 3D images can be acquired during a single breast compression, or they can be acquired separately.

This PMA supplement (P080003/S001) was submitted for the Selenia Dimensions 3D System with C-View Software Module.

The addition of the C-View Software Module enables the system to generate a synthesized 2D image from the tomosynthesis images. The synthesized 2D image for a given view (e.g., CC or MLO) is essentially a maximum intensity projection created from collapsing the 3D DBT image set for that view to a single 2D image. The synthesized 2D images can be displayed together with the tomosynthesis images. The synthesized 2D images are an option that can be used to eliminate the separate 2D FFDM acquisition. *Note: the notation $3D_S$ is used in this summary to signify the combination of the 3D DBT exam with the synthesized 2D images.*

System configurations allow adjustments to two aspects of the synthesized 2D images. The default contrast of the overall image can be set to low, medium, or high (window level setting on the review workstation are still adjustable). The appearance of the skin line can be set as less prominent or more prominent. The synthesized 2D images will have “C-View” incorporated into the pixel data to alert users that they are not FFDM images.

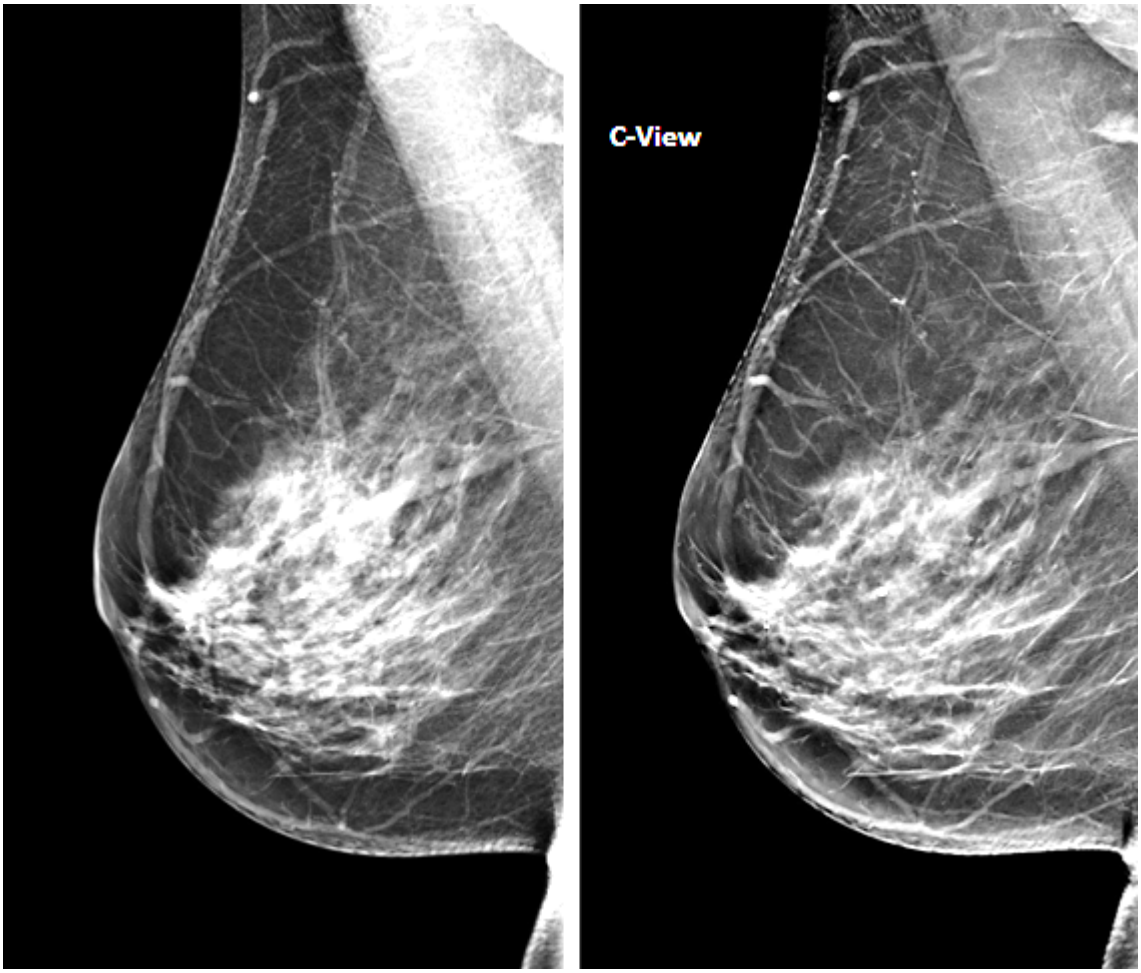

Figure 1. Example of 2D FFDM image (left) and synthesized 2D C-View image (right).

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are alternatives to digital breast tomosynthesis for the detection and diagnosis of breast cancer. Alternatives for breast cancer screening include a clinical breast examination, screen-film mammography, and digital 2D mammography. Specific ultrasound exams have also been approved when indicated. There are also additional diagnostic imaging options, including additional 2D diagnostic views with mammography, ultrasound, and/or magnetic resonance imaging. A biopsy of an abnormality detected with these exams is often obtained to diagnose cancer. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Selenia Dimensions 3D System is an upgrade to the commercially available Selenia Dimensions 2D System, which received FDA approval on December 22, 2008 via PMA Supplement P010025/S013. The Selenia Dimensions System (2D and 3D) was CE marked in September, 2008, and is commercially available in the countries of the European Union, markets in South America, Asia, Middle East, Asia, and Africa.

The Selenia Dimensions3D System (P080003) was approved by FDA for screening and diagnostic mammography on February 11, 2011.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device:

- excessive breast compression
- excessive x-ray exposure
- electric shock
- infection
- skin irritation, abrasion, or puncture wound

No serious adverse events were reported for the patients enrolled in the clinical study. The risks are the same as other screen-film or digital mammography systems.

IX. SUMMARY OF PRECLINICAL STUDIES

The addition of the C-View Software Module does not impact the image quality or performance FFDM or DBT of the Selenia Dimensions 3D System reviewed in PMA P080003. The design is otherwise unchanged since the approval.

Hologic provided design and test documentation to support that the C-View Software Module following FDA's "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices". The software design requirements document describes the method used to generate the synthesized 2D images from tomosynthesis data, including software integration, computational performance, input requirements to the software module and output requirements of the software module. The C-View software was validated using three sets of clinical cases, each set including normal cases, calcification cases, and cases containing masses. The resulting images were analyzed by an image quality expert according to pre-determined criteria for conspicuousness of lesions as well as absence of any artifacts.

All testing was successfully completed supporting the progression to the clinical study.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Hologic performed a clinical study to establish a reasonable assurance of safety and effectiveness of the Selenia Dimensions 3D System for the screening and diagnosis of breast cancer in the USA. Data from this clinical study was the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Case Acquisition Study Design

Hologic, Inc. designed and implemented a clinical case acquisition study to collect traditional 2D FFDM images as well as 3D tomosynthesis images to be used for the pivotal reader study. During the clinical case acquisition (September 2009 through February 2011), images and related patient information were obtained from 3521 subjects from twenty-two (22) pre-qualified clinical centers following the IRB approved pivotal clinical case acquisition study entitled "A Multicenter, Controlled Clinical Trial to Evaluate the Hologic Tomosynthesis Mammography System."

1. Acquisition Study Clinical Inclusion and Exclusion Criteria
   All subjects that enrolled in the study signed an IRB approved Informed Consent Form prior to any study imaging. All subjects underwent standard bilateral 2-view mammograms (MLO and CC) taken on an approved 2D FFDM system. The subjects additionally had both 2D and 3D images obtained on the Selenia Dimensions system. The 2D and 3D images for each projection (LCC, RCC, LMLO, and RMLO) were obtained under the same breast compression, thereby eliminating breast positioning as a source of variability in the study.

   Subjects were enrolled into the study from one of the following groups:

   - **Screening Group**
     - Subjects who are asymptomatic
     - Subjects scheduled to undergo a routine screening mammogram
   - **Biopsy Group**
     - Subjects scheduled for a biopsy

   Inclusion Criteria
   Enrollment in the study was limited to patients who met the following inclusion criteria:
   - Female
   - Any ethnic origin
   - No contraindication for routine bilateral mammography

   Exclusion Criteria
   Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:
   - Subjects who presented with any contraindications to mammographic screening, including, but not limited to:

    - Significant existing breast trauma
    - Pregnancy
    - Lactating
- Previous surgical biopsy
- Previous breast cancer
- Placement of an internal breast marker
- Breast implants
- Subjects who were unable to understand and execute written informed consent

2. Follow-up Schedule

Data was collected at two time points: first, at the time of imaging (study enrollment) and second, at the time of the one year screening mammogram. Data was collected for all patients who had not been previously discontinued at the time of their yearly screening mammogram and returned within the one year window. Subjects not returning and for whom contact had been made via, phone call, certified letter, or email were deemed lost to follow-up. The data collected at the one year time point consisted of a check of each subject's medical records to determine if any interval cancer was discovered prior to the next screening mammogram. The patient's record and one year follow-up was used to determine truth (cancer versus non-cancer for each case).

B. Accountability of PMA Cohort

A flow chart showing the subjects imaged, exclusions and eligible subjects is shown below. A total of 3521 subjects were enrolled in the acquisition study, 2299 of the subjects images were determined to be eligible for inclusion in the data set for the reader study.

One center enrolled 236 subjects for training only, no images from this site were part of the pivotal study reads, and therefore the 236 cases were counted as exclusions from the total enrollment.

The most common reasons for excluding cases at the site were: subject did not meet inclusion/exclusion criteria even though investigational imaging occurred (n=110), investigation equipment failure (n=20), subject withdrew consent (n=16), biopsy procedure was cancelled after investigational imaging occurred (n=16), incomplete image set obtained (n=13).

100 subjects were excluded because the images were obtained using the incorrect imaging technique tables.

19.8% (590/2985) of eligible cases were excluded for image quality control issues. The entire case was rejected and not used in the reader study if any of the FFDM or DBT images were rejected. The acquisition protocol did not allow for repeating any of the images. There were 300 FFDM images rejected and 171 DBT images rejected.

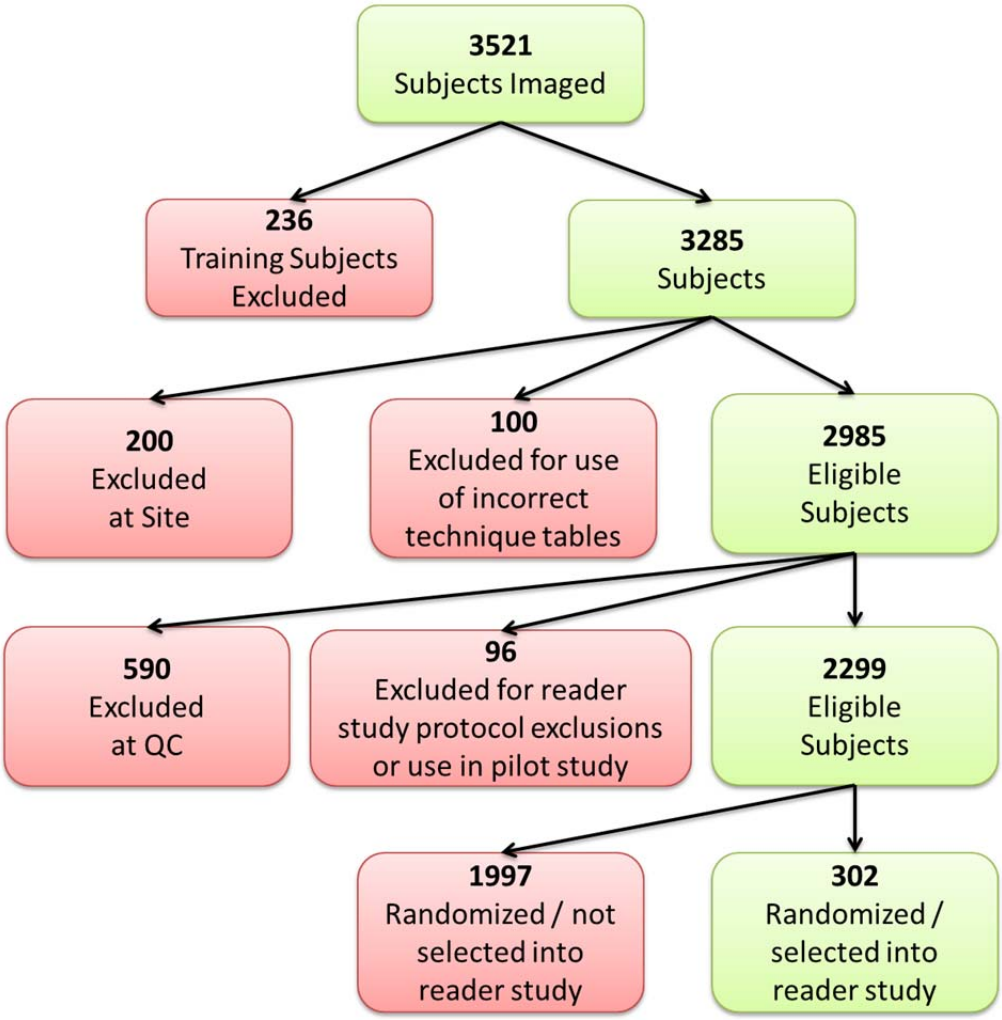

Figure 2. Accountability of Enrolled Subjects

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a mammography study performed in the US.

The 302 cases used for the reader study were randomly selected using stratified sampling from the 2299 eligible cases. The dataset included 157/1739 (9.0%) subjects from the screening cohort and 145/560 (25.9%) subjects from the biopsy group.

The 302 cases were randomized and used in the reader study before the one year follow-up on all cases was collected. One year follow-up information was not available for 9 of the 302 subjects (8 screening negatives; 1 benign biopsy) randomized into the reader study. Fourteen interval cancers were reported from the acquisition study, one of which was randomized into the reader study.

Of the 302 cases in the reader study 126/1339 (9.4%) were negatives, 24/161 (15%) were recalls, 76/512 were benign cases (15%) and 76/287 (26%) were cancer cases. The table below illustrates the cases randomized for the reader study from the acquired pool of eligible images.

Table 1. Distribution of subjects by case type

Case Type	Reader Study Cohort	Non-Reader Study Cohort	Total
Negative	126	1213	1339
Recall	24	137	161
Benign	76	436	512
Cancer	76	211	287
Total	302	1997	2299

The following tables present the distribution of cases by age, ethnicity, breast density, and calcifications/non-calcifications, and size of invasive cancers. Information on the distribution of cancer types was also reported, but is not presented.

Table 2. Distribution of subjects by age

Group	N=2299	Mean	Std Dev	Min	Max
Reader Study Cohort	302	54.2	10.6	27.0	84.0
Non-Reader Study Cohort	1997	53.6	10.2	28.0	85.0

Table 3. Distribution of subjects by ethnicity

Ethnicity	Caucasian	African American	Hispanic	Asian	Unknown and other	Total N=2299
Reader Study Cohort	260 (86.1%)	24 (8.0%)	9 (3.0%)	8 (2.7%)	1 (0.3%)	302
Non-Reader Study Cohort	1753 (87.8%)	95 (4.8%)	92 (4.6%)	24 (1.2%)	33 (1.6%)	1997

Table 4. Distribution of cases by breast density

Study Category	BI-RADS Breast Density Category	Cases (n=302)
Fatty	1	37 (12.3%)
	2	117 (38.7%)
Dense	3	118 (39.1%)
	4	30 (9.9%)

Table 5. Distribution of cases by calcifications/non-calcifications

Case Type	Calcification	Non-Calcification	Total
Cancer	24	53	77
Recall	8	16	24
Benign	24	51	75
Negative	0	126	126
Total	56	246	302

Table 6. Distribution of size for invasive cancers

Cancer Type	Mean Size (cm)	Median Size (cm)	Min (cm)	Max (cm)
Invasive (n=55)	1.35	1.4	0.1	2.5

D. Reader Study Design and Methods

Hologic conducted a multi-case, cross-over, multi-reader study using the collected set of cases. The objective was to compare the clinical performance of three dimensional breast tomosynthesis images with a synthesized 2D image ($3D_S$) to that of two dimensional full-field digital mammography (2D FFDM) images. The primary endpoint was to demonstrate non-inferior ROC performance as measured by the area under the curve of $3D_S$ compared to 2D FFDM. Two secondary endpoints included demonstration of non-inferior ROC performance for women with dense breasts and non-inferior recall rate for non-cancer cases.

1. Reference Standard

The following criteria were used to categorize cases:

- Negative screening cases: negative on clinical FFDM images and investigation FFDM plus DBT images at acquisition site (BI-RADS 1 or 2 score considered negative)
- Recalled screening cases: recalled by clinical FFDM images or investigation FFDM plus DBT images at acquisition site; determined to be non-cancer with additional follow-up (does not included benign biopsy cases)
- Benign biopsy cases: pathology proven benign cases
- Cancer cases: pathology proven malignant cases

The breast density score was performed at the acquisition site by two radiologists (with a third radiologists in the case of disagreement) using the standard of care FFDM images. Cases were categorized as either fatty (BI-RADS breast density type 1 or 2) or dense (BI-RADS breast density type 3 or 4).

2. Readers

   15 Readers with a range of clinical and tomosynthesis experience participated in the study. Readers were board certified and MQSA qualified and representative of the intended users. Readers were given two full days of training on the reading of 3D tomosynthesis with synthesized 2D images prior to the start of the reader study. No cases used for training or reader assessment were used in the pivotal reader study.

3. Image Scoring

   The study used a crossed reader study design. In Session 1, the readers scored half of the cases with FFDM and half of the cases with the combination of DBT and synthesized 2D images. In session 2, the readers scored each case using the other exam option. There was a one-month separation between reading sessions. The synthesized 2D images were provided to the reader when the corresponding DBT images were viewed. Patient history and prior 2D FFDM images were not used in the study.

   The following information was collected for each marked lesion:

   - Lesion location (used for cancer recall rate analysis)
   - Probability of Malignancy (POM) score of 0 to 100
   - Forced BI-RADS score of 1, 2, 3, 4a, 4b, 4c, or 5

   The following information was collected for cases with no marked lesions:

   - POM score of 0 to 100
   - BI-RADS score of 1 or 2

   The ROC and non-cancer recall analysis relied on case based scoring. For the non-cancer recall rate analysis, any case with a lesion marked was considered a recall (BI-RADS 0). For cases with multiple lesions, the lesion with the highest POM score was used as the POM score for the case.

   The cancer recall rate used lesion based scoring. When reviewing the combination of the DBT and synthesized 2D images, the lesion location was recorded on the slice of the DBT image that was determined to be at the center of the lesion.

4. Receiver Operating Characteristic (ROC) Analysis

   A multi-reader, multi-case (MRMC) ROC analysis using the probability of malignancy score was used to compare ROC area under the curve (AUC) performance. The parametric ROC curves were calculated using DBM MRMC 2.3 software and the "PROPROC" fit [1,2]. A bootstrapping method with replacement was used to compare average recall rates among all readers' pooled results for $3D_S$ to that for 2D FFDM.

E. Safety and Effectiveness Results

1. Safety Results

   The analysis of safety was based on the cohort of enrolled in the study. There were no adverse events (expected or unexpected) to report.

2. Effectiveness Results – Primary Endpoint

   The primary endpoint evaluated whether the ROC area under the curve (AUC) performance for 3D DBT plus synthesized 2D images ($3D_S$) was non-inferior to that of FFDM. The non-inferior margin was pre-specified: $3D_S$ was to be considered non-inferior to FFDM if the lower limit one-sided 95% CI for the difference in AUCs ($3D_S$ - FFDM) was greater than -0.05.

   The mean increase in the AUC was 0.040 (95% CI lower limit 0.014; p-value 0.005). The primary endpoint of non-inferiority was met.

   FDA also performed a non-parametric analysis using DBM MRMC 2.2 for all 15 readers and excluding the 9 of 302 cases with missing one year follow-up information. The mean increase in the AUC was 0.038 (95% CI lower limit 0.013; p-value 0.006). The results are consistent with the parametric DBM MRMC results used for the primary analysis.

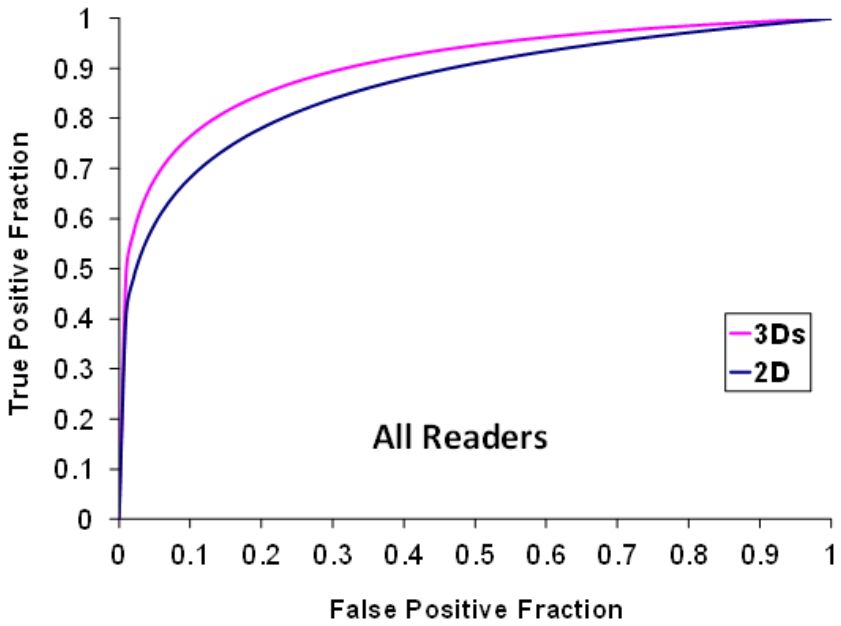

Figure 3. Mean ROC Curves for the 15 Readers (All Cases)

3. Effectiveness Results – Secondary Endpoint (Dense Breasts)

   A secondary endpoint was to show that the ROC AUC for subjects with dense breasts using $3D_S$ was non-inferior to that of FFDM. The non-inferiority margin was pre-specified: $3D_S$ was to be considered non-inferior to FFDM in dense breasts if the

lower limit one-sided 95% CI for the difference in AUCs ($3D_S$ - FFDM) is greater than -0.05.

The mean increase in AUC was 0.045 (95% CI lower limit 0.006; p-value 0.027). The non-inferiority endpoint was taking into account a Bonferroni adjustment for the two secondary endpoints.

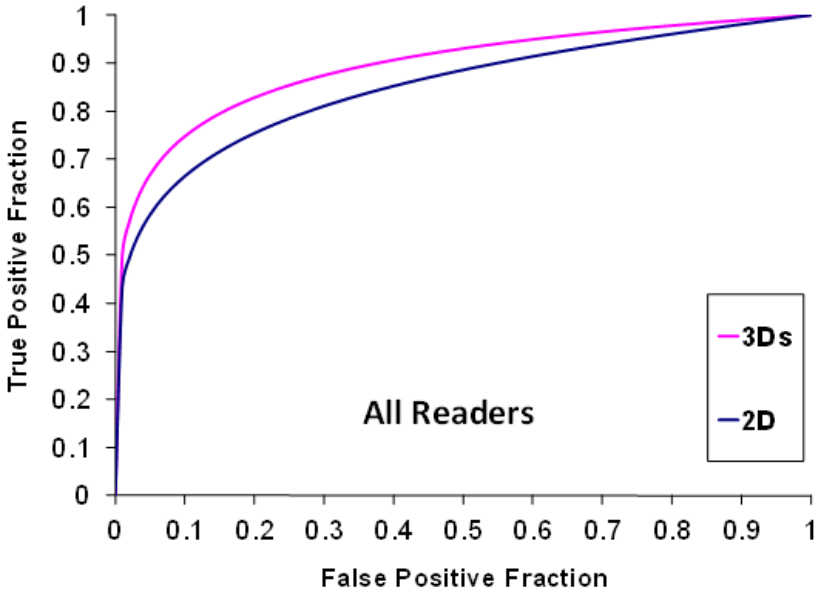

Figure 4. Mean ROC Curves for the 15 Readers (Dense Breasts Cases)

4. <u>Effectiveness Results – Secondary Endpoint (Recall Rate)</u>
The secondary endpoint for recall rate was to demonstrate that the non-cancer recall rate for $3D_S$ is non-inferior to that of FFDM. The non-inferiority margin was pre-specified: If the upper limit to the one-sided 95% confidence interval for the difference ($3D_S$ - FFDM) in recall rates among non-cancers is less than 0.05, then $3D_S$ is considered non-inferior to FFDM.

Bootstrapping with replacement was used to obtain average estimates of the recall rate. The bootstrap samples are based on pairs of reads (the FFDM read and the $3D_S$ read) to preserve the correlation structure from the original experiment and to maintain the ratio of cases in each group benign/negative/recall.

The non-inferiority endpoint was met. The average difference of the non-cancer recall rate with $3D_S$ was -13.9%, with the one-sided 95% CI upper limit of -10.1%. If a Bonferroni correction is made for the two secondary endpoints the one sided 97.5% CI lower limit is -9.6%.

Table 7. Mean difference in recall rates stratified by non-cancer categories for all readers.

Mode	Negative Screening (N=126)	Negative Recall Screening (N=24)	Benign (N=76)	All Negatives (N=226)
2D Recall Rate	32.7%	49.4%	67.1%	46.0%
$3D_S$ Recall Rate	17.4%	38.9%	54.8%	32.1%
Difference ($3D_s$ – 2D)	-15.3%	-10.5%	-12.3%	-13.9%

5. Effectiveness Results – Additional Analysis

The following table summarizes the additional analysis from the revised clinical analysis and also from the October 24, 2012 Radiological Advisory Panel Meeting:

Table 8. Summary of additional analysis

Additional analysis	Comments
Lesion Type (calcifications and non-calcifications)	The reader performance was equivalent or better with $3D_S$ for both lesion types as evaluated with ROC AUC.
Diagnostic Sensitivity and Specificity (based on BI-RADS Scores)	Diagnostic sensitivity, specificity, positive, and negative likelihood ratios were equivalent or better with $3D_S$ compared to 2D FFDM.
Fatty Breasts	The reader performance was equivalent or better with $3D_S$ for fatty breasts as evaluated with ROC AUC.
Cancer Recall Rate	The cancer recall rate was equivalent or better.
Reader Experience	The results suggest the readers' performance does not depend on mammography experience; although the trend suggests readers with less experience may benefit slightly more with $3D_S$.
Tomosynthesis Experience	The results suggest the reader's performance does not depend on tomosynthesis experience.
Case Distribution	The study was enriched with multiple categories of non-cancers (e.g., screening negatives, benign negatives, and recalled negatives). The AUC difference between modalities ($3D_S$ vs. FFDM) was relatively consistent regardless of the proportions among the non-cancer cases in the study.
Non-parametric analysis	FDA performed non-parametric analyses of the primary and secondary results, which were consistent with the parametric analysis.
Cases with missing follow-up	The results for the primary and two secondary endpoints were robust to the cases with missing follow-up (9 unconfirmed non-cancers) under multiple different scenarios (all non-cancer, all cancer, worst case).
Excluded Cases Q/C	FDA performed robustness analysis to examine the impact of 21% (524/2536) of non-cancers and 19% (66/353) of cancers were excluded for Q/C. The results for the primary and secondary endpoint were robust using missing-at-random, but the results were mixed when using a non-ignorable missing imputation analysis.

6. Effectiveness Results – Components of Variance

FDA computed the DBM Variance Component Estimates [1-5]. This information is helpful in appreciating the effects of reader and case variability on the study endpoints and confirming that reader and case variability were accounted for in the analyses. The components of variance results are shown in Table 9 and Table 10 below. The results

verify that, in "Effectiveness Results – Primary Endpoint" (section E.2), all the variance components (see the Description column in Tables 9 and 10) are appropriately accounted in calculating the primary AUC results. Note: These are unbiased ANOVA estimates which can be negative.

Table 9. DBM Variance Component Estimates [1, 2]

DBM Component	Estimate	Description
Var(R)	0.00012775	Reader variability
Var(C)	0.08509718	Case variability
Var(T*R)	0.00009464	Modality-reader interaction variability
Var(T*C)	0.02921675	Modality-case interaction variability
Var(R*C)	0.00503980	Reader-case interaction variability
Var(T*R*C) + Var(Error)	0.08179811	Modality-reader-case interaction variability and unexplained random errors

Table 10. Obuchowski-Rockette Variance component and Covariance Estimates [3, 4]

OR Component	Estimate	Description
Reader	0.00012775	Reader variability
Treatment*Reader	0.00009464	Modality-reader interaction variability
COV1	0.00029847	Covariance in diagnostic accuracies of the same reader in different modalities
COV2	0.00037852	Covariance in diagnostic accuracies of different readers in the same modality
COV3	0.00028178	Covariance in diagnostic accuracies of different readers in different modalities
Var(T*R*C) + Var(Error)	0.00066607	Modality-reader-case interaction variability and unexplained random errors

F. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical reader study included 15 radiologists of which none were full-time or part-time employees of the sponsor and 2 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 2
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTIONS

A. Panel Meeting Recommendation

At an advisory meeting held on October 24, 2012, the Radiological Advisory Panel voted 9-1-0 {yes, no, abstain} that there is reasonable assurance the device is safe, 9-1-0 that there is reasonable assurance that the device is effective, and 9-1-0 that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication. The meeting materials are available at:

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/RadiologicalDevicesPanel/ucm299053.htm

B. FDA's Post-Panel Action

FDA considered the panel's discussion on the clinical impact of the technology, the study design, labeling and training, and the generalizability of the results. The panel acknowledged the concerns related to the generalizability of the study results. The panel believed the results were generalizable, but more information would be preferred. Following the panel meeting, FDA asked Hologic to provide additional technical information on the device design and additional data to address concerns with subjects that were excluded from the study. The additional information supported that the study exclusions were made to accommodate the study design. The technical description of the device description was sufficient and did not raise concerns about imaging the excluded subjects. In addition, images of the types of subjects that were excluded were reviewed and considered to be of acceptable image quality for clinical use.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary endpoint evaluated whether the ROC area under the curve (AUC) performance for 3D DBT plus synthesized 2D images ($3D_S$) was non-inferior to that of FFDM. The mean increase in the AUC was 0.040 (95% CI lower limit 0.014; p-value 0.005).

A secondary endpoint was to show that the ROC AUC for subjects with dense breasts using $3D_S$ was non-inferior to that of FFDM. The mean increase in AUC was 0.045 (95% CI lower limit 0.006; p-value 0.027).

The secondary endpoint for recall rate was to demonstrate that the non-cancer recall rate for $3D_S$ is non-inferior to that of FFDM. The average difference of the non-cancer recall rate with 3DS was -13.9%, with the one sided 97.5% CI lower limit of -9.6%.

The primary, secondary, and additional analyses support that 3D DBT with synthesized 2D views is non-inferior to FFDM and can be considered an alternative exam option.

B. Safety Conclusions

The risks of the device are based on data collected in a clinical study conducted to support PMA approval as described above. There were no adverse events (expected or unexpected) to report. The risks from false positives and false negatives were considered as part of the review of the device effectiveness. The device is considered safe for its intended use.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above.

The potential benefits when using DBT plus synthesized 2D (3Ds) views include:

- The ability to perform 3D breast imaging at a dose that is comparable with the dose across 2D FFDM manufacturers;
- $3D_S$ may be more effective for breast cancer screening than FFDM alone; and
- $3D_S$ may reduce the number of non-cancer recalls, which could reduce unnecessary patient anxiety and radiation exposure from additional imaging

The potential risks when using DBT plus synthesized 2D views include:

- The radiation dose from the DBT image acquisition is slighter higher than a 2D FFDM acquisition for the Hologic system, which presents a slight increase in risk of future cancer development from the ionizing radiation; and
- The $3D_S$ acquisition will not include the standard of care FFDM images, which could potentially impact how mammography is performed.

The primary considerations of the benefit / risk analysis were the reader performance, radiation dose, and potential impact on performing mammography.

The study results met the primary and secondary non-inferiority endpoints. The general trend was that the reader performance with $3D_S$ was consistently equivalent or better across the secondary and additional analyses.

Additional factors considered in determining probable risks and benefits for the Selenia Dimensions 3D System include the uncertainty due to limitations of the study design and uncertainty from the radiation risk calculations. The MRMC design is

consistent with other mammography studies; however, there are limitations, such as the enrichment with cancers and the patient histories and prior images were not available to the study readers. Hologic performed as risk versus benefit analysis based on a number of assumptions from the study, cancer prevalence, and radiation risk. However, the study enrichment makes it difficult to generalize the estimates of recall, sensitivity, and specificity. The design is considered acceptable in order to reduce the size of the trial and avoid confounders; however, it does limit the benefit and risk analysis.

The potential impact on performing mammography was also considered. The standard of care FFDM images for breast cancer screening will not be acquired under the proposed 3D plus synthesized 2D images (3Ds) exam option. While the overall design to evaluate the diagnostic effectiveness is considered acceptable, FDA also recognizes that other aspects of performing mammography also need to be addressed (e.g., appropriate user training and labeling). The panel was asked to discuss these issues, and the general consensus was these issues could be addressed with the labeling and training (e.g., images marks and training so users know the synthesized are not the same at FFDM images). FDA agreed with the majority of the panel that benefits of the device outweigh the risks.

In conclusion, given the available information above, the data support that for mammography the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

The primary and secondary breast density endpoints were met based on the ROC analysis. ROC analysis is an accepted method for reader studies used to evaluate the effectiveness of a new imaging device. The ROC analysis evaluates the performance of a radiologist over a range of decision thresholds (i.e., over a range of sensitivities and specificities); thus, it is useful for measuring the performance of a new imaging modality for which doctors have not yet determined their decision threshold. In clinical practice, the decision thresholds at which a radiologist operates may move along the ROC curve depending upon experience and the desired tradeoff between sensitivity (cancer detection) and specificity (recall rate).

In clinical practice, there will likely be differences in the specific performance levels (e.g., AUC, recall rate) since the pivotal study relied on an enriched dataset and the readers were not given the patient history or prior images. However, the results indicate that DBT plus synthesized 2D images are non-inferior to FFDM alone, and this difference may be expected to translate into clinical practice since the study was designed to allow a comparison of the diagnostic ability of the systems with as minimal bias as possible, or if such bias exists, it should not reach the magnitude of the observed difference.

The reduction in recall rate was consistent across the stratifications of screening negatives, negative screening recalls, and benign cases.

In conclusion, given the available information above, the data support the approval of the Selenia Dimensions 3D System with C-View Software Module.

XIII. CDRH DECISION

CDRH issued an approval order on May 16, 2013. There were no conditions of approval.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

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