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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

RADIOLOGICAL DEVICES PANEL MEETING  
**PMA** 990066 FOR A DIGITAL **MAMMOGRAPHY** DEVICE

Thursday, December 16, 1999

8:30 a.m.

Double Tree Hotel  
1750 Rockville Pike  
Rockville, Maryland

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PARTICIPANTS

Brian S. Garra, M.D., Chairperson  
Robert J. Doyle, Executive Secretary

VOTING MEMBERS

Judy M. Destouet, M.D.  
Steven E. Harms, M.D.  
Arnold W. Malcolm, M.D.  
A. Patricia Romilly-Harper, M.D.  
Alicia Y. Toledano, Sc.D.  
James B. Smathers, Ph.D.

TEMPORARY VOTING MEMBER

Wendie Berg, M.D., Ph.D.

NON-VOTING MEMBER

Marilyn Peters, M.N. M.P.H.

TEMPORARY NON-VOTING MEMBER

Raymond P. Silkaitis, Ph.D.

FDA

Dan Schultz, M.D.

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1                   P R O C E E D I N G S

2                   Call to Order

3                   DR. GARRA: I would like to call this meeting of  
4 the Radiological Devices Panel to order. I would like to  
5 request everyone in attendance at this meeting to sign in on  
6 the attendance sheet at the door. Actually, I haven't done  
7 that myself.

a                   I note for the record that the voting members  
9 present constitute a quorum as required by 21 CFR Part 14.  
10 At this time, I would like each panel member at the table to  
11 introduce him or herself and state his or her specialty,  
12 position title, institution and status on the panel.

13                   I will begin with myself. I am Brian Garra. My  
14 position is Vice Chairman of Radiology at the University of  
15 Vermont, College of Medicine. I am the Chairman of this  
16 panel and a voting member.

17                   DR. MALCOLM: My name is Arnold Malcolm, Director  
18 of Radiation Oncology at Provident St. Joseph Medical  
19 Center, Burbank, California. I am a radiation oncologist  
20 and a voting member on the panel.

21                   MS. PETERS: My name is Marilyn Peters. I am the  
22 patient health education coordinator for the Department of  
23 Veterans Affairs, West Los Angeles Health Care Center. I am  
24 the consumer rep, a non-voting member.

25                   DR. SILKAITIS: My name is Raymond Silkaitis. I

1 am a temporary industry representative for this panel. I am  
2 Vice President of Regulatory Affairs for Gliatech. I have  
3 been in the medical-device industry for about twenty years.

4 DR. SCHULTZ: My name is Dan Schultz. I am the  
5 Acting Division Director for the Division of Reproductive,  
6 Abdominal and Radiological Devices, Office of Device  
7 Evaluation, Center for Devices, FDA.

a DR. SMATHERS: Jim Smathers, Professor of  
9 Radiation Oncology at UCLA. I am a voting member of the  
10 panel.

11 DR. ROMILLY-HARPER: Pat Romilly, Medical  
12 Director, Indianapolis Breast Center. I am a voting member  
13 of the panel.

14 DR. BERG: Dr. Wendie Berg, Director of Breast  
15 Imaging at the University of Maryland. I am a temporary  
16 voting member.

17 DR. DESTOUET: Judy Destouet. I am Chief of  
18 Mammography for Advanced Radiology in Baltimore, Maryland,  
19 and I am a voting member of the panel.

20 MR. DOYLE: I am Bob Doyle with the FDA. I am the  
21 Executive Secretary of this panel.

22 DR. HARMS: I am Steve Harms. I am Professor of  
23 Radiology at the University of Arkansas. I am a voting  
24 member of the panel.

25 DR. GARRA: At this point, Mr. Doyle would like to

1 make a few introductory comments.

2 **FDA Introductory Remarks**

3 MR. DOYLE: The following announcement addresses  
4 conflict of interest issues associated with this meeting and  
5 is made part of the record to preclude even the appearance  
6 of any impropriety.

7 To determine if any conflict existed, the agency  
8 reviewed the submitted agenda for this meeting and all  
9 financial interests reported by the committee participants.  
10 The conflict of interest statutes prohibit special  
11 government employees from participating in matters that  
12 could affect their, or their employer's, financial  
13 interests.

14 However, the agency has determined that  
15 participation of certain members and consultants, the need  
16 for whose service outweighs the potential conflict of  
17 interest involved, is in the best interest of the  
18 government. Therefore, a waiver has been granted to Dr.  
19 James Smathers for his interests in a firm that could  
20 potentially be affected by the panel's recommendations.

21 Copies of this waiver may be obtained from the  
22 Agency's Freedom of Information Office, Room 12A-15, of the  
23 Parklawn Building.

24 We would like to note for the record that the  
25 agency took into consideration other matters regarding Dr.

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1 Brian Garra who reported interests in a firm at issue but in  
2 matters that are not related to today's agenda. The agency  
' 3 has determined, therefore, that he may participate fully in  
4 all discussions.

5 In the event that the discussions involve any  
6 other products or firms not already on the agenda for which  
7 an FDA participant has financial interests, the participant  
a should excuse him or herself from such involvement and the  
9 exclusion will be noted for the record.

10 With respect to all other participants, we ask, in  
11 the interest of fairness, that all persons making statements  
12 or presentations disclose any current or previous financial  
13 involvement with any firm whose products they may wish to  
14 comment upon.

15 If anyone has anything to discuss concerning these  
16 matters, please advise me now and we can leave the room to  
17 discuss them. I don't see any.

18 The FDA seeks communications with industry and the  
19 clinical community in a number of different ways. First,  
20 FDA welcomes and encourages premeetings with sponsors prior  
21 to all IDE and PMA submissions. This affords the sponsor an  
22 opportunity to discuss issues that could impact the review  
23 process.

24 Second, the FDA communicates through the use of  
25 guidance documents. Towards this end, FDA develops two

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1 types of guidance documents for manufacturers to follow when  
2 submitting a premarket application. One type is simply a  
3 summary of the information that has historically been  
4 requested on devices that are well understood in order to  
5 determine substantial equivalence.

6 The second type of guidance document is one that  
7 develops as we learn about new technology. FDA welcomes and  
a encourages the panel and industry to provide comments  
9 concerning our guidance documents.

10 I would also like to remind you that the meetings  
11 of the Radiological Devices Panel tentatively scheduled for  
12 the first half of next year are February 7 and May 15. You  
13 may wish to pencil in these dates on your calendar but,  
14 please, recognize that these dates are tentative at this  
15 time.

16 DR. GARRA: Thank you.

17 We are ready to proceed with the first of the two  
18 half-hour open public hearing sessions for this meeting.  
19 The second session will occur this afternoon after the panel  
20 discussion. At these times, public attendees are given an  
21 opportunity to address the panel to present data or views  
22 relevant to the panel's activities.

23 Some individuals have already indicated they would  
24 like to address the meeting. If there are any others who  
25 would like to address the panel, if you could please

1 identify yourselves to Mr. Doyle at this time.

2 I don't see any others.

3 I would like to remind public observers at this  
4 meeting, while this portion of the meeting is open to public  
5 observation, public attendees may not participate except at  
6 the request of the Chairman.

7 I would ask, at this time, that the persons  
8 addressing the panel come forward to the microphone and  
9 speak clearly as the transcriptionist is dependent upon this  
10 means for providing an accurate transcript of the  
11 proceedings of the meeting. If you have hard copy of your  
12 talk available, please provide it to the Executive Secretary  
13 for use by the transcriptionist to help in the accurate  
14 recording of the proceedings.

15 We are also requesting that all persons making  
16 statements either during the open public hearings or during  
17 the open committee discussion portions of the meeting to  
18 disclose if they have any financial interest in any medical-  
19 device company before making your presentation to the panel.

20 In addition to stating your name and affiliation,  
21 please state the nature of your financial interest and the  
22 organization you represent. Of course, no statement is  
23 necessary from employees of that organization. A definition  
24 of financial interests in the sponsor company include  
25 compensation for time and services of clinical

1 investigators, assistants and staff in conducting the study  
2 and appearing at the panel meeting on behalf of the  
3 applicant.

4 The second is a direct stake in the product under  
5 review such as being the inventor of the product, patent  
6 holder, owner of shares of stock, et cetera and, finally,  
7 but not only, owner or part owner of the company, of course.

8 We can now begin the first open public portion of  
9 this meeting. Each speaker will be allowed a maximum of  
10 five minutes. We will start with Mr. Morgan Nields,  
11 President of Fischer Imaging Corporation.

12 **Open Public Hearing**

13 MR. NIELDS: Thank you and good morning. My name  
14 is Morgan Nields. I am Chairman and CEO of Fischer Imaging  
15 Corporation from Denver, Colorado. I would point out that  
16 Fischer Imaging is a public company. I am a significant  
17 shareholder in the company. Our company is engaged in  
18 clinical testing of digital mammography devices with the  
19 intent of providing an application to the FDA for approval  
20 shortly.

21 Secondly, I am also a direct shareholder in the  
22 publicly traded company, General Electric, who is presenting  
23 a PMA submission today in front of this panel.

24 My comments today on the PMA submission before the  
25 panel seek to improve upon the FDA approval process. No

1 matter what action is taken on the PMA, it may not  
2 facilitate our ability to bring appropriate technology to  
3 the public service unless we address elements of the process  
4 which are, clearly, defective.

5           The marginal gain from a PMA approach may be lost  
6 in the sea of related process problems. To clarify this  
7 point, I will offer a brief case study of what has actually  
8 been happening with the key advancement in diagnostic  
9 imaging technology digital mammography systems.

10           [Slide.]

11           I would like to show a couple of slides of what we  
12 are talking about. Just to orient some of the members of  
13 the panel, the image on the left, this is the same contrast  
14 detail phantom imaging with digital mammography on the left  
15 allowing one to see clearly small objects at very low  
16 contrast with approximately the same dose as a film-screen  
17 ACR-accredited system on the right.

18           [Slide.]

19           Just a couple of images of what digital mammograms  
20 look like printed on laser film, for those of you who are  
21 mammographers.

22           [Slide.]

23           In November, 1994, over five years ago, we first  
24 visited FDA to present information supporting a 510(k)  
25 clearance pathway citing both zero mammography and Fuji

1 computed radiography as predicate systems, particularly  
2 since they already cleared Fuji CR 510(k) cited breast  
3 imaging as one of its intended uses.

4 From then until now, this process has been  
5 nightmarish for our company as well as for the other  
6 companies and, in my opinion, contrary to the intent of the  
7 1997 Food and Drug Administration Modernization Act.

8 [Slide.]

9 Section 205 of FDAMA directed the agency to  
10 consider the least burdensome means of approval for new  
11 devices, in this section right here. The PMA process  
12 selected by FDA in September of this year essentially makes  
13 digital-mammography systems class III devices. Class III  
14 devices are the highest-risk devices regulated by FDA and  
15 include, for example, implantable devices where a failure or  
16 malfunction could cause death.

17 Sixteen months ago, this same advisory panel  
18 concluded that clinical trials were not necessary to clear  
19 the technology. The panel and the agency recognized that  
20 studies to measure the accuracy of mammography are very  
21 difficult to perform due to the high intra-observer  
22 variability of the readers.

23 The panel, including several invited mammography  
24 experts, concluded that a simple features analysis would  
25 suffice to establish equivalency to film mammography. The

1 panel's conclusions were ignored by FDA and, as importantly,  
2 sixteen months later, FDA has been unable to provide draft  
3 guidance to the public regarding the requirement for  
4 determining substantial equivalence.

5 [Slide.]

6 FDA has mandated that the 510(k) review should be  
7 limited to the minimum necessary to show substantial  
8 equivalence but industry and the agency have not reached  
9 agreement on this with respect to digital mammography. The  
10 FDA has, however, issued two policy letters to only four  
11 manufacturers. Because I believe these policy letters  
12 should be made available as a matter of public record, I  
13 have included these letters in the record of these meeting.

14 These letters are dated February 9 and  
15 September 13, 1999 and were sent to four manufacturers  
16 attempting to bring digital-mammography systems to the  
17 market. I am aware of at least five additional companies  
18 interested in this field who have no idea what types of  
19 requirements may be necessary for premarket clearance.  
20 Perhaps these policy statements will be of help to them.

21 I also have included two letters our company sent  
22 to FDA, a proposed clinical-trial design of May 20, 1999 and  
23 a follow-up letter of September 20 pleading for a response  
24 to the May 20 letter. The last letter includes a December 7  
25 letter from FDA, a belated response to our letter of May 20.

1 Both the February and September policy letters  
2 from FDA make it clear that any submitted studies must  
3 include ground truth, sensitivity, specificity or ROC,  
4 receiver operator characteristics analysis. The September  
5 letter further indicates a PMA pathway would essentially  
6 required in that a postmarket approval screening study would  
7 been to be conducted.

8 [Slide.]

9 FDAMA directed FDA to consider the benefits and  
10 risks of new life-saving technology and to utilize  
11 postmarket approval studies as a means of gathering crucial  
12 patient data for high-risk devices. FDA refers to this  
13 section of FDAMA in the September 13 letter regarding the  
14 imposition of a new requirement for postmarket approval  
15 studies.

16 I submit Congress never intended these types of  
17 expensive postmarket approval studies were to be used for  
18 class-II 510(k)-type devices. This regulatory quagmire  
19 could be avoided if the agency were to follow the mandate of  
20 FDAMA which directs FDA to consider outside scientific  
21 expertise and to develop a workable scientific dispute-  
22 resolution procedure for matters of scientific controversy.

23 [Slide.]

24 These sections here cover some of those thoughts.  
25 Given that there is unanimity among manufacturers, expert

1 radiologists and patient-advocacy groups the large-scale  
2 clinical trials are not necessary, I suggest digital-  
3 mammography clearance is an issue of "scientific  
4 controversy."

5           Requesting help, for example, from the National  
6 Cancer Institute or the RSNA to determine an appropriate  
7 premarket clearance pathway would meet the Congressional  
8 intent of FDAMA. We all know it is easy to be a critic but  
9 harder to solve the actual problem. There are several  
10 reasonable approaches to solve this regulatory conundrum.

11           In the December 7 letter, FDA stated that  
12 diagnostic and screening mammography are essentially the  
13 same procedure but, in fact, screening mammography is coded  
14 under CPT code 76092 and is reimbursed at a lower level than  
15 diagnostic mammography which has its own set of CPT codes.

16           HCFA reimburses based on FDA clearance and labeled  
17 indications for use and, therefore, is unlikely to reimburse  
18 a screening mammogram performed on a system that is cleared  
19 only for diagnostic mammogram. In addition, the American  
20 College of Radiology standards differentiate clearly between  
21 a screening mammogram and a diagnostic mammogram.

22           It would appear reasonable for manufacturers to  
23 label only for diagnostic mammography and even, at their  
24 choice, contraindicate screening in the labeling. Another  
25 approach to solve this problem is to use existing MQSA

1 regulations to measure the performance of digital-  
2 mammography systems.

3 [Slide.]

4 MQSA regulations require that mammography centers  
5 submit image quality and dose measurements to an accrediting  
6 body by means of specially designed breast phantoms and  
7 dosimeters. In addition, two sets of clinical films are  
8 submitted for scoring by a review panel of radiologists. If  
9 digital-mammography systems meet these criteria, and I am  
10 quite certain they do, it would be self-evident they are  
11 substantially equivalent to existing film-screen systems.

12 MQSA regulations already contain training  
13 requirements of at least eight hours each for radiologists,  
14 radiologic technologists and physicists for new modalities  
15 like digital mammography. This training goes beyond the  
16 applications training manufacturers would provide.

17 In addition, MQSA audit regulations require  
18 physicians to keep detailed outcome records for all  
19 mammographic procedures. A simple comparison of data will  
20 establish whether digital mammography finds more or less  
21 cancers per thousand women screened.

22 Call-back and false-positive rates and a host of  
23 other variables currently measured under MQSA will allow a  
24 continuous benchmark of digital mammography's performance.  
25 MQSA regulations provide an already designed framework for

1 the agency to monitor the relative performance of digital-  
2 mammography systems.

3 Requesting that radiologists and manufacturers  
4 provide access to FDA for this data would provide oversight  
5 to the agency. While large NCI-funded trials are expected  
6 to provide good outcomes data on the accuracy of both film-  
7 screen and digital mammography, at least four years will be  
8 required before results are known. I don't believe that  
9 these trials should be made part of a PMA postmarket  
10 approval study requirement.

11 CDRH is responsible for assuring that exposure to  
12 manmade sources of radiation is minimized as a matter of  
13 public health. Mandating the double exposure of thousands  
14 of healthy women is simply not justified given the many  
15 other alternatives available to clear this technology.

16 Regarding the application before the panel today,  
17 if the data presented comply with the February and September  
18 policy letters from FDA which detail requirements for  
19 statistically significant studies including ground truth,  
20 sensitivity and specificity or ROC analysis, then the  
21 application for clearance should be approved not as a PMA  
22 but as a 510(k).

23 Thank you for your attention.

24 DR. GARRA: Thank you very much. Some interesting  
25 points were brought up there.

1 Mr. Doyle has an announcement.

2 MR. DOYLE: I have been advised that Dr. Kopans  
3 would like to make a statement.

4 DR. GARRA: Please come forward, Dr. Kopans.

5 DR. KOPANS: Good morning.

6 DR. GARRA: Would you please state your  
7 affiliation and any financial interests.

a DR. KOPANS: I am Dr. Daniel Kopans. I am the  
9 Director of the Breast Imaging Division at the Massachusetts  
10 General Hospital in Boston and a Professor of Radiology at  
11 the Harvard Medical School.

12 I would like to read this and then I will be happy  
13 to submit it in writing. As an expert in breast-cancer  
14 detection and diagnosis, I am very concerned about the FDA's  
15 decision to require a postmarket approval for digital  
16 mammography. I believe that this will not only delay access  
17 to this important development in mammography but it will  
18 make it very difficult and expensive to improve our ability  
19 to detect and diagnose breast cancer.

20 This will be detrimental to American women. New  
21 film-screen technologies only require a 510(k) process for  
22 approval and digital detectors are merely electronic film-  
23 screen combinations.

24 FDA employees have suggested that digital  
25 mammography will provide radiologists with such new

1 information that they will not know what they are seeing and  
2 this will lead to unnecessary biopsies. There are  
3 absolutely no data to support this belief. I am unaware of  
4 any expert in breast imaging who would support this concern.

5 Digital mammography is nothing more than an X-ray  
6 image of the breast. All radiologists who are involved in  
7 the interpretation of conventional film-screen mammograms  
a can interpret digital mammographies. The adoption of  
9 digital chest radiography only required the submission of a  
10 few cases to demonstrate comparability.

11 The requirement of the FDA for a large screening  
12 trial for digital mammography is not warranted and would be  
13 a great waste of money. The efficacy of mammography has  
14 already been established. The only thing that large trials  
15 will do is to demonstrate well-established variation between  
16 observers.

17 This does not detect the detector systems but,  
18 rather, the individual radiologists. Direct image  
19 comparisons and physics evaluation should suffice to  
20 demonstrate that digital detectors are comparable to film-  
21 screen combinations.

22 Other observer studies will be misleading and an  
23 unnecessary expense. The postmarket approval process is  
24 unnecessarily onerous. Perhaps, of even greater concern, is  
25 that its use will mean that any future alteration in the

1 equipment will require a detailed resubmission. This will  
2 drastically slow and may curtail the future development of  
3 digital mammography to the detriment of women's health.

4 All of the experts in breast imaging that I know  
5 that have experience with digital mammography have supported  
6 a 510(k) process. It is unclear who, therefore, is advising  
7 the FDA. Dr. Henney and the FDA should explain why they  
8 have failed to respond to legitimate queries submitted by  
9 myself and Dr. Carl Dorsey from the University of  
10 Massachusetts and other queries submitted by the  
11 International Digital Mammography Development Group.

12 The failure of the FDA to respond to legitimate  
13 questions raised by international experts suggests that the  
14 FDA's motivation may be driven by politics. This is  
15 inappropriate and not acceptable when the health of American  
16 women is at stake.

17 Given the significance of this approval process,  
18 FDA should disclose all who have been involved in the  
19 agency's decision including any political pressures that  
20 have been employed to cause this major impediment to  
21 improving the healthcare of women. Approval for digital  
22 mammography should be accomplished through a 510(k) process.

23 DR. GARRA: Thank you.

24 Open Committee Discussion

25 DR. GARRA: Mr. Doyle has a quick announcement to make.

1 MR. DOYLE: For the record, I would like to read  
2 an appointment to temporary voting status that has been  
3 signed by Dr. David W. Feigal, the Director of the Center of  
4 Devices and Radiological Health.

5 Pursuant to the authority granted under the  
6 Medical Devices Advisory Committee Charter dated October 27,  
7 1990 and as amended August 18, 1999, I appoint Wendie A.  
a Berg, M.D., Ph.D., as a voting member of the Radiological  
9 Devices Panel for the meeting on December 16, 1999.

10 For the record, she is a special government  
11 employee and a consultant to this panel under the Medical  
12 Devices Advisory Committee. She has undergone the customary  
13 conflict of interest review and has reviewed the material to  
14 be considered at this meeting.

15 DR. GARRA: Thank you.

16 We are going to go back and proceed to the open  
17 committee discussion on PMA 990066 for a mammography system  
18 that uses as its detector a solid-state X-ray imaging  
19 device. However, before we get to the particulars of the  
20 PMA, I would like to ask Dr. David Feigal, Director of the  
21 Center for Devices and Radiological Health, to come forward  
22 to make a pair of special presentations.

23 Dr. Feigal.

24 **Special Presentation**

25 DR. FEIGAL: Thanks very much. Actually, in the

1 spirit of disclosure, I should mention that my first contact  
2 with the FDA was when I was asked to come and make a  
3 presentation to an advisory panel. Later, I served on a  
4 panel and one thing led to another. So I think this is just  
5 as a fair warning to those of you on the committee that  
6 there sometimes are adverse--I don't know if they are  
7 adverse, but there are unpredictable career effects of  
a getting involved with the FDA.

9 Let me begin with a task which is both pleasant  
10 but one which also reflects our deep appreciation of the  
11 service of two outgoing members of the committee. What I  
12 would like to present this morning is a letter and a plaque  
13 recognizing the contributions of Dr. Smathers and Dr.  
14 Destouet.

15 Let me just read the letter signed by Dr. Henney.  
16 "I would like to express my deepest appreciation for your  
17 efforts and guidance during your term as a member of the  
18 Radiologic Devices Panel of the Medical Devices Advisory  
19 Committee. The success of this committee's work reinforces  
20 our conviction that responsible regulation of consumer  
21 products depends greatly on the participation and advice of  
22 the nongovernmental health community.

23 "In recognition of your distinguished service to  
24 the Food and Drug Administration, I am pleased to present  
25 you with the enclosed certificate."

1 Let me present these to you right now.

2 [Applause.]

3 **Introductory Remarks**

4 DR. FEIGAL: Let me just make a couple of  
5 introductory comments to say how much I appreciate the  
6 committee's grappling with this issue with us. Today's  
7 focus will really be on one particular application and  
a whether or not that application meets the standards which  
9 are required and whether your recommendation on whether the  
10 approach suggesting in this application should be  
11 successful.

12 As you know, it has not been entirely  
13 straightforward to identify a regulatory path for approval  
14 for this technology. There are relatively few screening  
15 technologies used in healthy people that have paid their  
16 dues and have shown that there is actual clinical benefit.  
17 Pap smear is an example of that.

18 Recently, there was an approval of an automated  
19 Pap-smear reader and the **same** types of issues arose which is  
20 how much could we rely on small **datasets** and detailed  
21 technical analyses of the performance of such equipment and  
22 at what level did we need assurance that it would produce  
23 the same kinds of sensitivity and specificity and predictive  
24 accuracy that the Pap smear read by the human reader, all  
25 the same issues of inter-reader variability.

1           That was a technology that was approved with a  
2 dataset of about 33,000 slides. It was one where we were  
3 able to establish the relative sensitivity and specificity.  
4 The points that are made about changes in this technology  
5 being evolutionary are quite correct. That is one of the  
6 great difficulties in deciding when you ask for more data  
7 than some of the physics data or small datasets.

a           Different approaches have been suggested for this  
9 technology. As you are well aware, an initial approach was  
10 suggested that these technologies might be similar enough  
11 that it would be straightforward to demonstrate that there  
12 was agreement between two technologies in study designs that  
13 wouldn't even tell you why there was disagreement and, in  
14 fact, if there was high enough agreement, if the two  
15 results, if the two side-by-side technologies always led to  
16 the same result, you really couldn't argue about substantial  
17 equivalence.

18           But if one of the technologies was superior, all  
19 you would know was that there was a discrepancy between the  
20 two. YOU would not have any information unless you modified  
21 the study in some way as to which technology even had better  
22 sensitivity, and then the factors that lead to the  
23 variability which have already been alluded to, would be  
24 factors that would make it difficult to even know how much  
25 agreement there was because of the technology and where the

1 disagreement comes from.

2           There are other approaches. There are approaches  
3 which do not answer the question of whether or not this  
4 technology will identify cancers that screen film misses.  
5 Those types of technologies are where you identify patients  
6 who have already been referred because of a suspicious  
7 screen film and are now being evaluated in a more diagnostic  
8 setting.

9           Mammography devices that are on the market now are  
10 not separately labeled for diagnosis and screening but,  
11 clearly, that is a population. That type of study design,  
12 while it is a very good source for abnormal exams, it does  
13 not provide any insight into what is seen as one of the  
14 great promises of techniques with greater resolution which  
15 is the ability to improve the detection rate. It is a real  
16 question about when it is that we should forego this kind of  
17 information.

18           The final approach, and one that is, obviously,  
19 the most challenging and difficult, is to evaluate a new  
20 technology in a screening setting where you have the ability  
21 to assess the technology where it will be used.

22           In our regulatory letters, the initial approach of  
23 the agency to suggest agreement studies was realized to be  
24 too narrow an approach. There still remain manufacturers  
25 who are interested in pursuing agreement studies, in

1 pursuing the 510(k) route of approval. And there are other  
2 ways to get a 510(k) approval than an agreement study. You  
3 also could do that with a ground-truth study.

4           The reason that we proposed the PMA as an  
5 alternative to the 510(k) was because we felt that the  
6 substantial experience that many of the manufacturers  
7 already had could be put together in a PMA application which  
8 does not require that the application be complete because  
9 there is flexibility to extend some of the study  
10 requirements, some of the things you would like to know  
11 about the technology, into the postmarketing period with  
12 postmarketing commitments.

13           We realize that each company had a slightly  
14 different approach to the way they were collecting data and  
15 studying their equipment. What we were attempting to  
16 communicate, and I don't think we entirely succeeded, was  
17 that, in fact, the 510(k) mechanism is still open if someone  
18 wishes to complete enough of their studies to demonstrate it  
19 substantially equivalent, or they can use a PMA route if  
20 they wish to come in with data with a postmarketing  
21 commitment and, if that bring the technology to the market  
22 more quickly, then they have to weigh the business decision  
23 about the relative long-term and business effects of being  
24 in the 510(k) or the PMA stream.

25           As you may be aware, even those types of decisions

1 are not forever because there are times when **PMA**s are  
2 downclassified and technologies are used in different ways.

3 We essentially attempted to make this an option  
4 for the companies, to look at the information that they had  
5 and to choose the regulatory pathway that they wished to  
6 come forward with. As you look at this single application  
7 today, and as the company and as the FDA scientists present  
8 their perspectives on this, pay relatively less attention to  
9 whether this is setting a paradigm for how all companies  
10 should proceed because I can guarantee you we will be back  
11 with different types of information trying to accomplish the  
12 **same** end with other applications.

13 Our goal is to get these products into the  
14 marketplace as quickly as possible and to allow regulatory  
15 flexibility to allow companies to choose the pathway that  
16 they wish to choose.

17 Without any further comments, I think we should  
18 begin with the morning. Our first speaker this morning on  
19 introductory matters is the capable Dan Schultz.

20 **PMA Background**

21 DR. SCHULTZ: Welcome members of the panel and  
22 members of the audience.

23 [Slide.]

24 Would like to take this opportunity, once again,  
25 to welcome you here and, again, thank you for helping us

1 through what has obviously been a somewhat difficult and  
2 convoluted problem.

3           As you can see from the title of my introductory  
4 slide, what I intend to talk about very briefly is where we  
5 are today and how we got there. The fact that the fonts are  
6 different is not necessarily an accident. I think the  
7 important thing, really, is for us to move forward. I think  
8 that is important both to the agency and to the women of  
9 America.

10           We can spend some time going over how we got  
11 there, but I think that will be the brief part of this  
12 presentation.

13           I would like to say that, normally, as Division  
14 Director, I don't get to make these kinds of sort of  
15 detailed remarks. It is normally that I get to get up and  
16 give a couple of sort of perfunctory introductory remarks,  
17 but when we were deciding on who was going to give this talk  
18 today, for some strange reason, there were not a lot of  
19 volunteers so here I am.

20           [Slide.]

21           Briefly, and I think everybody in this room knows  
22 this probably as well as I do, and Dr. Feigal just went over  
23 some of it, the history of this product dates back to the  
24 early '90s. In 1995, we had our first panel meeting  
25 regarding digital mammography. The panel recommended

1 agreement as an alternative to large screening trials for  
2 the very reasons that have been talked about previously,  
3 that those trials are time consuming. They are costly.

4           There was a feeling at that time that, since this  
5 was, in fact, mammography, that that agreement paradigm  
6 would have a chance to show enough information to be able to  
7 determine that the two technologies were, in fact,  
8 substantially equivalent.

9           In 1996, the agency incorporated that paradigm  
10 into its guidance document. Between 1996 and 1998, we  
11 actually had the opportunity to look at data, to talk to  
12 companies, to look at different protocol ideas and,  
13 basically, came to the conclusion that, whether we liked it  
14 or not and, in fact, this is not something that we looked at  
15 with great glee because, in fact, the agreement paradigm  
16 would have been the simplest albeit not providing as much  
17 information as could be obtained in other ways, as Dr.  
18 Feigal mentioned.

19           But, the bottom line was that the agreement  
20 paradigm, at least as we proposed it in the guidance  
21 document, doesn't work.

22           In 1998, we asked you back here to discuss, once  
23 again, whether there were alternative clinical-study  
24 options. Again, as has been previously discussed, there  
25 were a number of opinions that were provided. There was a

1 lot of good information and, in fact, one thing I would like  
2 to correct is that the agency did not ignore those ideas and  
3 those recommendations.

4 We looked at all of them extremely carefully and,  
5 in fact, I think if you look closely at what we are  
6 suggesting today, there are elements of all of those  
7 opinions.

8 [Slide.]

9 September, 1999, FDA issued a letter to sponsors,  
10 again, as Dr. Feigal mentioned, trying to be specific to and  
11 requesting that each sponsor come in to discuss their  
12 individual applications given the fact that sponsors were  
13 and are in different points on the developmental curve.

14 So the letter was, in fact, directed at the  
15 sponsors that we had had discussions with regarding digital  
16 mammography and the letter suggested that there might be an  
17 alternative pathway to the market through the PMA process.

18 December 16, 1999 is where we are today and we are  
19 having the third digital panel. But this time, I think,  
20 there is a big difference. We, today, are actually going to  
21 be looking at an individual marketing application. For the  
22 first time, the panel will be asked not to talk about  
23 theories, not to talk about regulatory paradigms, not to  
24 talk about a variety of different approaches, but actually  
25 to look at data. We believe that that is a significant step

1 forward.

2           Where do we go from here? It has been mentioned  
3 that the revised guidance has not yet been issued. All I  
4 can tell you, at this point, is that we are working on it.  
5 It will come out in the next millennium, hopefully early in  
6 the next millennium but it will, I guarantee--and you can  
7 quote me on this--I guarantee that there will be a revised  
8 guidance in the next millennium. Thank you.

9           [Slide.]

10           A number of issues, again, without belaboring the  
11 point, one of the questions that has been raised is why is  
12 mammography different. It is, in fact, the only imaging  
13 technology currently indicated for both diagnosis and  
14 screening. While not a significant risk in the traditional  
15 sense of high-risk devices, I think the risk of this device  
16 is based upon the fact that it is, in fact, relied upon by  
17 millions in the United States for the early detection of  
18 breast cancer.

19           As Dr. Feigal mentioned, we know that this  
20 technology saves lives and we know that it leads to  
21 increased breast conservation, both of which we consider to  
22 be extremely important issues for American women.

23           [Slide.]

24           Other issues that have already been touched upon,  
25 why ground truth versus agreement. Again, our idea,

1 somewhat, I agree, simplistically, a few years ago, was that  
2 if you got perfect agreement you would, in essence, be  
3 mimicking ground truth. Unfortunately, what we have  
4 discovered since then is that anything less than perfect  
5 agreement does raise questions and, in fact, the poorer the  
6 agreement, and we all know the reasons why that agreement  
7 has not been as good as what we would have like to have  
8 seen, the poorer the agreement, the more questions are  
9 raised.

10 [Slide.]

11 Another issue that has been brought up on several  
12 occasions is the issue of enriched trials versus screening  
13 trials. What we think is that enriched trials do provide  
14 adequate information, at least for the diagnostic component  
15 of mammography and do, in fact, provide some important  
16 information on screening. However, we still believe that  
17 the screening trial is, in fact, a more sensitive measure of  
18 the ability to detect the earliest lesions and that that is,  
19 in fact, probably the most important aspect of mammography  
20 and, therefore, one that needs to be looked at in some form  
21 at some point in the developmental process.

22 [Slide.]

23 Finally, last but not least, PMA versus 510(k).  
24 Very simply, they answer different questions. They ask  
25 different questions and they are meant to answer different

1 questions. The PMA process looks at each individual device  
2 and the determination is made as to whether that device is,  
3 in fact, based on its own merits, safe and effective whereas  
4 the 510(k) process essentially lumps the technology together  
5 and looks at whether or not products are substantially  
6 equivalent.

7           How substantial that equivalence needs to be is  
8 basically dependent on the device itself and how critical  
9 those differences between devices really are. We feel that  
10 the PMA process provides us with some increased flexibility.  
11 We think that the labeling for an individual PMA can be  
12 tailored to reflect the data for that individual device. We  
13 think that the PMA lends itself to a regulatory paradigm  
14 which includes both a premarket component which gives us  
15 enough reassurance to put this device on the market as well  
16 as a postmarket component which answers some of the more  
17 difficult, harder-to-answer questions over a longer period  
18 of time once the device has actually been put on the market.

19           [Slide.]

20           We also think that, as counterintuitive as it  
21 might seem, in fact, for this and for some other  
22 technologies, that the PMA process may, in fact, provide a  
23 faster route to market while still maintaining the control  
24 and the data requirements that are necessary to assure the  
25 American public that these devices will do what they say

1 they will.

2           As Dr. Feigal has mentioned previously, again, and  
3 I just reiterate this one more time, we are not completely  
4 closing the door to 510(k). We think it is going to be  
5 difficult. We don't want that to be swept under the rug.  
6 Based on our experience over the last few years showing that  
7 these two products could be equivalent is not going to be an  
8 easy task, but the 510(k) process does remain open and does  
9 remain an option for those companies that wish to pursue it  
10 and we would be more than happy to discuss with any company,  
11 the ones that we have talked to so far, the ones that we  
12 haven't talked to, what those options might be and listen to  
13 their ideas on how to get their product to market.

14           [Slide.]

15           Finally, while all this may be very interesting  
16 and we could have long discussions and long debates on  
17 whether or not some of the ideas that have been presented  
18 today are right or wrong, in essence, the discussion and the  
19 comments that I have made so far are somewhat irrelevant for  
20 today's purpose.

21           Today, we are here to discuss an individual PMA  
22 and the questions that we are going to be asking you are not  
23 looking at whether the FDA is right or wrong. Today's  
24 questions are, in fact, and these will be read to you in a  
25 slightly different form later on, but, basically, I tried to

1 summarize them: does the data for this PMS provide  
2 reasonable assurance of the safety and effectiveness of this  
3 device; does the labeling for this PMA clearly and  
4 accurately reflect what is known and unknown about this  
5 device; and does the developmental plan, in its totality for  
6 this PMA, provide women and caregivers the data necessary to  
7 make informed decisions.

a We look forward to your deliberations. We look  
9 forward to your recommendations. And, once again, we thank  
10 you for being here and helping us with this very difficult  
11 problem.

12 Thank you.

13 DR. GARRA: Thank you, Dr. Schultz.

14 We are now going to proceed with the sponsor's  
15 presentation of the PMA, itself. The first speaker will be  
16 Scott Donnelly, General Electric's Vice President for Global  
17 Technology Operations. He will be followed by Dr. Edward  
18 Hendrick, the principle investigator from Northwestern  
19 University.

20 Mr. Donnelly?

21 **G.E. MEDICAL SYSTEMS PRESENTATION OF P990066**

22 **Introduction, Device Description, Non-Clinical Studies**

23 MR. DONNELLY: Good morning. I would like to  
24 thank the panel for their time.

25 [Slide.]

1 This morning, we are going to present the  
2 Senographe 2000D which is G.E.'s digital-mammography  
3 [Slide.]

4 My name is Scott Donnelly. I am the Vice  
5 President of G.E.'s Medical Systems Global Technology  
6 Operation. As such, I am an employee and shareholder in the  
7 General Electric Company.

a What I will be presenting this morning is an  
9 overview of the device and the technology as we have  
10 implemented it in our full-field digital-mammography machine  
11 at which point I will turn over the presentation to Dr. Ed  
12 Hendrick who will present the results from our clinical  
13 trials and studies.

14 [Slide.]

15 This is a very brief overview. G.E. Medical  
16 Systems in addition to being a developer of mammography,  
17 both in conventional as well as, now, digital systems also  
18 is in the business of the design and development of other X-  
19 ray equipment, both fluoroscopic and radiographic including  
20 other digital X-ray technology.

21 We also are a major developer, manufacturer, of  
22 CT, mR, ultrasound, PET and nuclear-medicine machines.  
23 Additionally, we provide solutions for managing that  
24 diagnostic information in terms of picture archival systems  
25 and radiological information systems.

1 [Slide.]

2 I will do an introduction and overview of the  
3 product and a device description as implemented in the  
4 technology that we have selected and a brief overview of the  
5 performance of the product in terms of its physics and  
6 engineering, and then Dr. Hendrick will cover the clinical  
7 data and also the postapproval study which we are proposing.

a [Slide.]

9 I think it is important when you look at our full-  
10 field digital-mammography product that it is really based on  
11 our current platform for analogues, film-screen mammography.  
12 The gantry, patient position and acquisition system is  
13 actually quite similar to what we do today in analogue film-  
14 screen mammography. Once you go into the digital world, we  
15 are actually leveraging quite heavily a product we call our  
16 G.E. Advantage Windows Platform which currently is used for  
17 out CT and mR product as well as in our other digital X-ray  
18 products.

19 [Slide.]

20 It is important to note, as indicated in the PMA,  
21 that the indications-for-use statement is for both  
22 diagnostic and for screening applications, so we are seeking  
23 approval for both diagnostic and screening use of this  
24 machine.

25 [Slide.]

1           The device description, on the left-hand side of  
2 the chart, shows the acquisition platform. If you look at  
3 the gantry, it is actually very, very similar to our current  
4 film-screen mammography product. The gantry, and,  
5 therefore, the patient positioning and the way the  
6 technician would use the equipment is the same, the only  
7 difference, really, being that, in place of a film-screen  
8 buckey, you now have a digital detector that is used in  
9 place of the film. I will go into some details later that  
10 explain how we have implemented the digital detector.

11           [Slide.]

12           New to the system is the acquisition work station.  
13 The acquisition work station is used to collect all the  
14 electronic data that is generated by the detector to do the  
15 image manipulation and image processing to generate the  
16 image. It is also used as a link to the rest of the  
17 information system.

18           Additionally, what you have, and one of the  
19 advantages of the technology, is the ability to do an  
20 immediate review of the exam to do basic quality-assurance  
21 checking to make sure the positioning was done properly and  
22 that the parameters were such that you received a good-  
23 quality film.

24           After that is done, you use the acquisition work  
25 station to then send the data over to a laser camera to

1 generate, for purposes of our clinical trials, hard copy  
2 review which is then reviewed on a conventional **viewbox** as  
3 you would with film-screen mammography.

4 [Slide.]

5 The acquisition process is actually very similar  
6 to film screen. The patient positioning and exam setting,  
7 demographic data, is entered in a very similar fashion.  
8 Where the difference is is because the acquisition process  
9 is very fast. In a very short time, you can acquire a  
10 series of acquisitions with the patient and then go over and  
11 review each of those acquisitions to insure quality is  
12 there.

13 In a post process, you will be able to send that  
14 data to a laser camera to generate the hard-copy review in  
15 the same form as a film screen. So one of the advantages of  
16 the technology is that it does dramatically increase the  
17 speed at which you can do the acquisition and it also  
18 provides you immediate feedback in terms of quality  
19 **assurance**, hopefully reducing the number of retakes based on  
20 later film processing which would show a gross positioning  
21 error or that something went wrong during the acquisition  
22 that resulted in a poor-quality image.

23 Those retakes can be taken immediately upon review  
24 of the QA.

25 [Slide.]

1           The detector is the new technology involved in  
2 this digital mammography. Effectively, you have photons  
3 coming into the detector the same as you would in a film-  
4 screen system. But, instead of a film screen, you have a  
5 solid-state digital detector that has a cesium-iodide layer  
6 across the top which brings the photons in and, through a  
7 crystalline structure, converts those into light.

a           That light then comes out and is placed directly  
9 onto an amorphous silicon panel which I will describe in the  
10 next chart in more detail which basically takes and converts  
11 the light to an electronic charge. And then you have read-  
12 out electronics which take the charge and scan across the  
13 panel and, therefore, take all the digital charge out of the  
14 panel, convert that to digital data and send that to the  
15 analysis work station where it is processed and the image is  
16 generated from that data.

17           [Slide.]

18           The detector is manufactured with semi-conductor  
19 technology. We start with a basic glass substrate. It is  
20 important that there are a number of digital technologies.  
21 This is unique to the G.E. detector.

22           After you take the glass substrate, you use  
23 conventional semi-conductor manufacturing processes to lay  
24 down an amorphous silicon array with 100-micron pixel sizes  
25 across the entire field of the array. You then have

1 electronics which scan from the individual rays. The charge  
2 would be stored here after it is converted from photons to  
3 light.

4 The signals are extracted on three panels. They  
5 are not extracted on the fourth panel in order to minimize  
6 the distance and how close you can get to the chest wall so  
7 there are no electronics or connector across the front  
a allowing perfect access in against the chest wall.

9 On top of that is deposited the cesium-iodide  
10 scintillator which, again, is a crystalline structure that  
11 converts the X-ray photons into light. And then, as you  
12 scan out, there is actually an electronics assembly that  
13 mounts to the back side of the glass substrate so all the  
14 electrons are swept out and converted to digital data to be  
15 transmitted to the acquisition work station.

16 [Slide.]

17 If you look at the nonclinical data on the system,  
18 our intent was to take what was available today in **screen-**  
19 film mammography and improve the most important  
20 characteristics that are necessary to get good image quality  
21 when doing a mammography screening or diagnostic exam. And  
22 so the critical functions of dynamic range, modulation  
23 transfer function or the spatial resolution of the image,  
24 the contrast and the signal-to-noise ratio I will address in  
25 this presentation.

1           In the end, the detective quantum efficiency which  
2 is really the overall measure of how effectively you convert  
3 from X-ray to an image is discussed in some detail.

4           [Slide.]

5           This chart shows the comparison between how a  
6 digital detector responds versus what you see in a  
7 conventional film screen. On the right-hand side is the  
8 a sensor-metric response that you would see in a typical film-  
9 screen mammography system. There is actually a considerable  
10 differentiation with very small changes in dose that is here  
11 in this region which is where normal tissue would be. A  
12 film screen performs quite well in this region.

13           Where you don't see as great a differentiation  
14 between the amount of exposure and, therefore, the  
15 sensitivity to different absorption of X-ray turning into a  
16 very significant change in optical density with a relatively  
17 flat line is in this area which would be a very dense area,  
18 either against the chest wall or glandular region of the  
19 breast or, at the other end of the spectrum, at the very  
20 high end, which might be typical of a very low contrast  
21 area, let's say, against the skin line.

22           One of the advantages of the digital detector  
23 response is if you look at the digital detector response  
24 through that same dose region, it is very linear from very  
25 low dose areas that would be typical of a high-density

1 breast or chest wall all the way up to very low density on  
2 the skin line.

3 Of course, in terms of optical density, the  
4 equivalent is the number of electrons that are converted as  
5 a function of that dose. So what you see is a very, very  
6 linear response across the whole range which gives you some  
7 superior physics to what you see in a film-screen system.

a [Slide.]

9 In the end, the most important thing for us, of  
10 course, is detectability. Detectability is a function of  
11 both the spatial resolution--so this is a very high spatial  
12 resolution moving to the lower spatial resolution and we  
13 start to see some blur but, also, and very importantly, the  
14 amount of noise that is in with the image.

15 So, if you see a very, very high-noise  
16 environment, even though you may have very high spatial  
17 resolution, it is very difficult to extract the signal you  
18 are interested in from the noise environment on the display.  
19 As you move to a lower noise environment, sometimes even a  
20 lower spatial resolution may be more detectable in terms of  
21 the radiographer's ability to extract a signal from the  
22 image.

23 The measurements which we used, which quantifies  
24 the overall performance in terms of detectability is what we  
25 call the detective quantum efficiency. This takes into

1 consideration both the balance between spatial resolution,  
2 or MTF, or the amount of noise that is in the image.

3 [Slide.]

4 So the most important thing, in terms of  
5 maintaining and achieving a very high DQE is that,  
6 regardless of whether you have a digital detector or screen-  
7 film system, the amount of signal to noise that impinges  
a upon that detector is the same. This is the system now X-  
9 rayed that is propagated from the tube through the patient  
10 and is received at the detector.

11 So the really important thing to optimize the  
12 image quality and/or patient dose is a function of how  
13 efficiently you convert the signal and to do that in such a  
14 fashion that you do not induce noise into the image. So it  
15 is a very good measure of both signal and noise.

16 One of the things that having high DQE gives you  
17 is also the tradeoff now to decide do you want to have the  
18 same image quality with a lower dose or do you want to have  
19 improved image quality by the same dose because they are  
20 relative, since really what you are talking about is a ratio  
21 of the signal to the noise in the system.

22 [Slide.]

23 This chart takes measurements which we have made  
24 on the Senographe 2000D digital system versus published data  
25 on an existing and typical film screening. So what you see

1 on the left-hand side is the percentage of detectable  
2 quantum efficiency or how efficient is the detector at  
3 converting signal into either electrons or, in the case of  
4 digital, sensorimetric response.

5           So you see that, in a digital system, you have a  
6 much higher DQE across the entire range of line pairs in  
7 terms of spatial frequency. This is the region of interest  
8 in terms of clinical benefit for mammography. So you can  
9 see, across that whole region, you have substantially  
10 improved DQE as compared to a typical film screen.

11           [Slide.]

12           This chart has similar information except instead  
13 of selecting two of the same dose, you look across the  
14 entire range of dose from very, very low dose to high dose,  
15 you see the response of the digital detector is actually  
16 very linear and quite flat across the whole range until you  
17 get to extremely low dose down in this end.

18           In terms of noise conversion, what you want to  
19 have is to not contribute additional noise. There is some  
20 noise called quantum noise which is inherent in the X-ray  
21 generation. What you don't want to do is contribute any  
22 more noise to that image through the conversion process.

23           If you look at--even in extremely low doses, you  
24 have the noise of the X-ray and you don't have any  
25 contribution of additional noise in a digital detector until

1 you are down, approximately--the quantum and the detector-  
2 contributed noise become equivalent down at about a dosage  
3 of 0.8 mR which is almost an order of magnitude below the  
4 region of clinical interest because you are not going to see  
5 dosages down to 0.8 to be clinically important in a  
6 mammography machine.

7 [Slide.]

8 So that is kind of a summary of the data that we  
9 have for you in terms of the physics and the engineering  
10 that we have incorporated in the full-field digital-  
11 mammography machine. I think it leverages quite well our  
12 long history in mammography taking advantage of a system  
13 that is already out in clinical use on a widespread basis.

14 We have invested and generated a lot of time and  
15 tried to come up with a digital detector that has superior  
16 physics and to make sure that we leverage our signal-  
17 processing expertise both in other digital radiography as  
18 well as CT and mR to try to optimize and take advantage of  
19 that digital-conversion technology.

20 The end results, of course, are to be proven in  
21 the clinical studies. I will introduce Dr. Hendrick who  
22 will take you through the results of the clinical trials  
23 using the G.E. F50M machine.

24 Thank you.

25 **Clinical Studies**

1 DR. HENDRICK: It is a pleasure to be here. It is  
2 also a pleasure to follow the person presenting the physics  
3 and to get the clinical results for a change.

4 My name is Ed Hendrick. I want to do the public-  
5 disclosure thing so I want to let you know I own a few  
6 shares of G.E., unfortunately not a significant fraction of  
7 the company. My wife owns some shares of G.E. as well.

8 I have had research agreements with G.E. at the  
9 University of Colorado Health Sciences Center where I was a  
10 professor prior to October and I hope to have a research  
11 agreement with G.E. at Northwestern University but that  
12 hasn't been executed yet. It might be in the millennium if  
13 we can keep it out of the hands of the lawyers from the two  
14 institutions.

15 [Slide.]

16 I want to present the clinical results that have  
17 come about from the trial that we have conducted. The goal  
18 of this is establish the noninferiority of digital compared  
19 to screen film. Based on the meetings that we had with the  
20 FDA and the public meeting in August of 1998, we adopted a  
21 noninferiority approach rather than an equivalence approach.  
22 That is what I want to discuss.

23 So we are following the guidelines that were laid  
24 out by Dr. Schultz in addressing the PMA approach which is  
25 to establish the safety and effectiveness of full-field

1 digital mammography both for screening and diagnosis of  
2 breast cancer.

3 [Slide.]

4 The presentation will first talk about the study  
5 cohort, the people that were enrolled, the women that were  
6 enrolled in the study. And then I will talk about the  
7 results of two reader studies and the results of a side-by-  
8 side analysis comparing features on digital to features on  
9 film screen side by side and then I will give some  
10 conclusions.

11 [Slide.]

12 For the enrollment of clinical subjects, all of  
13 these were consented by IRB and they were enrolled at four  
14 institutions consisting of women over the age of 40  
15 attending for diagnostic mammography. The four institutions  
16 were my former institution, the University of Colorado  
17 Health Sciences Center, the University of Massachusetts  
18 Medical Center, Mass General Hospital and the University of  
19 Pennsylvania Hospital.

20 [Slide.]

21 The exclusion criteria for women in the study were  
22 women under the age of 40, women who were pregnant or  
23 suspicious of being pregnant, women with breast implants,  
24 women with breasts too large to fit on a 24-by-30 CM image  
25 receptor which is the larger image receptor used for film-

1 screen mammography, women who didn't qualify for diagnostic  
2 mammography because they had non-focal or bilateral breast  
3 pain, and women who were unable or unwilling to execute the  
4 consent form.

5 [Slide.]

6 The study cohort for the diagnostic study  
7 consisted of 641 women enrolled as diagnostic subjects at  
8 those four institutions. There were an additional 21 women,  
9 and it was the first 21 women with cancer out of a total of  
10 about 4,000 women who had been screened at that time in an  
11 additional study of digital mammography comparing it to film  
12 screen which was being conducted at the University of  
13 Colorado Health Sciences Center and the University of  
14 Massachusetts Medical Center, and that was a screening-based  
15 study so there were an additional 21 women with cancer who  
16 were additionally consented to have their images included in  
17 the reading studies that took place for this PMA.

18 [Slide.]

19 The patient demographics of the diagnostic study  
20 population are given here. The mean age was 55 and the  
21 range from 40 to 86. The ethnicity is given in the table  
22 here as well. 34 percent reported a history of breast  
23 disease and 33 percent reported a history of hormone-  
24 replacement therapy.

25 [Slide. 1

1           The imaging techniques that were used were to  
2 views of each breast, the standard CC and MLO views, in both  
3 film-screen mammography and digital mammography. They were  
4 performed on each study volunteer. 59 percent were  
5 bilateral exams, 41 percent unilateral diagnostic exams.

6           [Slide. 1

7           The same target filter kVp and approximately the  
8 same mAs were used on both the full-field digital system as  
9 were used on the film-screen system. When the mAs couldn't  
10 be matched exactly, the full-field digital used a slightly  
11 lower mAs to insure that we had equal or slightly lower  
12 doses in full-field digital compared to screen-film  
13 mammography.

14           The technologists, in most cases, was the same  
15 person performing screen film and full-field digital and  
16 they used the same basic X-ray design for the compression of  
17 the breast and the positioning of the breast is the GED mR  
18 system for film screen and the prototype digital systems  
19 based on the GED mR so that positioning and compression  
20 forces were similar in the two modalities.

21           [Slide.]

22           Just to present one of the more important results  
23 in terms of safety, there were no adverse consequences,  
24 serious or otherwise, reported among all the study subjects  
25 in the study cohort in this PMA study.

1 [Slide.]

2 Let me talk about the different reading studies in  
3 the side-by-side analysis that were done. These were  
4 conducted sort of consecutively. The first reading study  
5 used an adjudication process where each image was read by  
6 two reviewers. So full-field digital was read by two  
7 reviewers and screen film was read by the same two  
8 reviewers.

9 One of the designs of this first reading study was  
10 that the readers would not be at the institutions in which  
11 the images were acquired. That is actually a design of both  
12 reader studies. In the first reading study, we had 646  
13 subjects getting both full-field digital and screen-film  
14 images. 47 of those were cancers. 599 were non-cancers.

15 When I say they were read by two or three, it is  
16 because of the adjudication process. If the two initial  
17 readers agreed on the positivity or negativity on a given  
18 modality--say, for screen film--then that was the  
19 determination for that modality. But if they disagreed for  
20 screen film on whether it was positive or negative, then it  
21 went on to an adjudicating reader. That was the third  
22 reader who was the tie-breaker and decided, in the  
23 adjudicated readings, whether it was positive or negative.

24 That design was eliminated in the second study  
25 which consisted of 625 subjects getting both digital and

1 screen film. In that study, there were five readers reading  
2 every image and each reader read both digital and screen-  
3 film images and, in each case, those were spaced out in time  
4 to avoid any kind of recall effect.

5 So there was at least a 30-day period between a  
6 reader reading a woman's, say, screen film and reading their  
7 digital image. Each reader read half the screen-film images  
a first and half digital images first.

9 I will talk about the side-by-side reading study a  
10 little later.

11 [Slide.]

12 The differences between the first and second  
13 reader studies were that, for the first reader study, each  
14 case had two primary readers and if they differed in  
15 positivity or negativity, a secondary reader, who was  
16 actually a third reader.

17 The data were analyzed in two ways based on the  
18 primary interpretations and also analyzed based on the  
19 adjudicated interpretation. In reader study No. 2, all five  
20 readers read each case on each modality. Part of the reason  
21 for going on and conducting reader study No. 2 was the  
22 analysis of data in reader study No. 1 was made more  
23 difficult by the fact that not all readers read all images.

24 So it eliminated some of the possible statistical  
25 methods that could account for multiple readings of the same

1 images or it made it much more difficult to conduct those  
2 kinds of analyses.

3 [Slide.]

4 Also, after conducting the first reader study, we  
5 learned some things about digital mammography that helped us  
6 do a better job in the second reader study. One of the  
7 things we learned was, in doing the side-by-side analysis  
8 between the first and second reader study, that in a few  
9 images, there were lesion markers on some films on one  
10 modality that were not visible in the other modality.

11 So, in preparation for the second reader study, we  
12 eliminated any images where there were different markers on  
13 one modality than on the second. Also, we learned a lot  
14 about printing digital images in the course of conducting  
15 the first study and recognized that the print quality on the  
16 digital images wasn't always up to par.

17 I, personally, reviewed the digital images not  
18 looking at the film screen but looking at the quality of  
19 printouts on the digital images and had some of those images  
20 reprinted prior to the conduct of the second study,

21 The readers used in the second study were from a  
22 single institution and they were tested and selected--we  
23 tested nine people and picked six readers out of that group,  
24 or five readers out of that group, of nine. Then the  
25 readers received uniform instructions prior to the study.

1           One of the things we didn't do in the first reader  
2 study that we should have done was tell readers that these  
3 images should have been read as a screening exam since there  
4 weren't prior films. And we didn't do that, so, in the  
5 first study, we learned some readers read these as screening  
6 cases, some read them as diagnostic cases, which led to big  
7 differences among the performance of the readers in the  
a first study.

9           In the second study, we instructed the readers to  
10 read these as if they were screening cases since there  
11 weren't prior films or the presence of a diagnostic workup  
12 on those images.

13           [Slide.]

14           In both readers studies, we asked to readers to  
15 provide a BIRADS code, 0, 1, 2, 3, 4 or 5, and the 0 was  
16 included because we did want them to read it as a screening  
17 study. And, in addition, for anything that had any BIRADS  
18 code other than 1 or 2, we asked them to provide a percent  
19 probability of that identified lesion or breast as having  
20 cancer. That was on an integer scale from 0 to 100 percent

21           In the side-by-side reader study, it was a  
22 different design with the Likert scale that I will describe  
23 in just a minute.

24           [Slide.]

25           The null hypotheses are the key to this non-

1 inferiority approach. The null hypothesis is sort of the  
2 straw man that you set up to see if you can reject that  
3 based on the data. The null hypotheses are in three areas  
4 in terms of recall rates, or specificity--and just bear in  
5 mind, the specificity is 1 minus the recall rate.

6 In terms of recall rates, the null hypothesis was  
7 that digital had a higher recall rate than screen-film  
8 mammography by 0.05 or more. One of the concerns that FDA  
9 had with this new technology was that digital would have a  
10 higher recall rate, prompt the recall of more women, but not  
11 find more breast cancer. So the straw man for recall rates  
12 is that digital has a higher recall rate by 0.05 or more.

13 For sensitivity, the null hypothesis is that  
14 digital has a lower sensitivity than screen film by 0.1 or  
15 more. And, for ROC curve areas, the null hypothesis is that  
16 digital has a lower ROC curve area by 0.1 or more compared  
17 to screen-film mammography.

18 We collected data and analyzed data in terms of  
19 recall rates, sensitivity and ROC curve areas to test the  
20 null hypotheses.

21 [Slide. 1

22 Here is the first set of data from the first  
23 reading study. These data are for recall rates. In this  
24 table, there are two columns, one for all cases and then for  
25 non-cancer cases. In each case, the recall rate for digital

1 was lower than the recall rate for screen film. When we  
2 tested the null hypothesis without taking into account the  
3 correlation that multiple readers read the same films, we  
4 would get a p-value of less than 0.001 in each case.

5 Also, in the adjudicated readings, which don't  
6 have the correlation problem because we get a single  
7 determination based on the best two out of three readings,  
a digital also had a lower recall rate and we were able to  
9 reject the null hypothesis with a high degree of statistical  
10 significance.

11 [Slide.]

12 This is where the statistics comes in. These  
13 terms PROC MIXED and PROC GENMOD are just fancy names for  
14 other statistical tests that were conducted to analyze the  
15 effect, and take out the effect, of multiple readers reading  
16 the same cases. In the case of PROC MIXED, it includes all  
17 the cases that were read.

18 In the PROC GENMOD method, it only includes the  
19 cases where the readers disagreed between the two  
20 modalities. So it only includes the cases where digital  
21 recalled the patient and film screen didn't, or film screen  
22 recalled the patient and digital didn't.

23 It doesn't include the data where the two  
24 modalities agree and because there are fewer data in the  
25 disagreement areas, the p-values are somewhat higher. But,

1 in all cases analyzing recall rate, digital had a  
2 statistically significantly lower recall rate in that it was  
3 able to reject the null hypothesis regardless of the  
4 specific statistical tests that were used to account for  
5 multiple readers reading the same images.

6 [Slide. 1

7 In terms of sensitivity in reader study No. 1,  
8 digital had a sensitivity rate of 78 percent, just combining  
9 the primary readings of all the cases, and screen film had a  
10 sensitivity rate of 74 percent. In either case, where we  
11 didn't take into account the correlation among the readings  
12 by the two primary readers of each case or where we did take  
13 that into account by the PROC MIXED method, we get a  
14 statistically significant rejection of the null hypothesis.  
15 So digital doesn't have a significantly lower sensitivity  
16 than film screen.

17 When we look at the adjudicated readings, the two  
18 modalities had exactly the same sensitivity and we were  
19 right on the edge of being able to reject the null  
20 hypothesis with statistically significance.

21 [Slide.]

22 One of the concerns the FDA had in the design of  
23 this kind of trial was that if there is some hand picking of  
24 the cases involved that the study could use larger, easier-  
25 to-detect, later-stage cancers that really make no

1 difference in the outcome for the woman.

2           What we did was took all women coming for  
3 diagnostic mammography plus this subset of cancers from the  
4 screening study without any selection process along the way.  
5 I think that is reflected in the stage distribution and the  
6 size distribution of the cancers that were detected in this  
7 study.

8           There were 47 cancers in reader study No. 1 and,  
9 in terms of the number of cancers with stage 0 or I, a total  
10 of 58 percent. The AHCPR guidelines recommend that, in a  
11 good mammography practice, you should have greater than  
12 50 percent of your cancers be stage 0 or I. The stage  
13 distribution of the study group exceeded that AHCPR  
14 guideline.

15           In terms of minimal cancers--that is, stage 0 or I  
16 cancers that are less than 1 centimeter in size, it was  
17 39 percent in this study group for reader study No. 1 and  
1 8 AHCPR recommends that, in a good mammography practice, that  
19 should exceed 30 percent. So we met those criteria for the  
20 kind of stage distribution and size distribution that you  
21 would hope to find in a good mammography practice.

22           [Slide.]

23           Looking specifically at the way digital compared  
24 in terms of sensitivity for these earlier stage and minimal  
25 cancers, digital actually did even better compared to screen

1 film in terms of sensitivity for stage 0 and I cancers based  
2 on 27 in those two categories. Digital had an 85 percent  
3 sensitivity compared to 74 for screen film. For minimal  
4 cancers, digital had a sensitivity of 83 percent compared to  
5 70 for screen film.

6 So for the cancers that are probably the most  
7 critical in terms of making a difference in saving the  
8 woman's life, digital did even better than screen film.

9 [Slide.]

10 Here are the ROC curve areas for digital compared  
11 to screen film. Digital had a lower ROC curve area. This  
12 is combining all the primary readings in study No. 1.  
13 Digital had a lower ROC curve area by 0.01, actually 0.009.  
14 So, for all practical purposes, the ROC curve areas were the  
15 same.

16 When we applied the statistical test to reject to  
17 null hypothesis that digital had a lower ROC curve area by  
18 0.1 or more, we were able to do that with either all primary  
19 readings combined or with the adjudicated readings.

20 [Slide.]

21 In summary, for reader study No. 1, we were able  
22 to show that digital did not have a significantly higher  
23 recall rate--in fact, it had a lower recall rate from screen  
24 film. We were able to show that it had very similar  
25 sensitivity to screen film and somewhat better sensitivity

1 for smaller earlier stage cancers, and the digital had a  
2 comparable ROC curve area to screen film. We were able to  
3 reject the null hypotheses of the core performance of  
4 digital in each case.

5 For reader study No. 2, we got very similar  
6 results to reader study No. 1. Remember, this is based on  
7 all the cases being read by five MQSA-qualified radiologists  
8 reading both digital and film screen with the separation of  
9 at least 30 days between the readings of the two different  
10 modalities.

11 All cases analyzed had digital with a 2 percent  
12 lower recall rate than screen film and we were able to  
13 reject the null hypothesis again, and, if you looked at just  
14 all non-cancer cases, the same 2 percent difference with a  
15 strong rejection of the null hypothesis.

16 When we used these statistical methods that took  
17 into account the correlation now among the five different  
18 readers in terms of recall rate, we were still getting a  
19 2 percent lower recall rate for digital compared to screen  
20 film and a highly significant rejection of the null  
21 hypothesis when you included all cases and a reasonable  
22 rejection, in terms of significance, of the rejection of the  
23 null hypothesis when we only included the cases where there  
24 was disagreement between the two modalities by a given  
25 reader in terms of recall.

1 [Slide.]

2 In terms of sensitivity in reader study No. 2,  
3 digital had a 68 percent sensitivity. Screen film had a  
4 70 percent sensitivity. But we were still able to reject  
5 the null hypothesis when we included--did the statistical  
6 evaluation without taking into account the correlation among  
7 readers or when we used all cases and took into account the  
8 correlation among the readers with this PROC MIXED method.

9 [Slide.]

10 In terms of the cancer distribution in reader  
11 study No. 2, 61 percent of the cancers in reader study No. 2  
12 were stage 0 or I so these were even a slightly better  
13 distribution toward earlier stage cancers and slightly  
14 better toward minimal cancers.

15 43 percent had cancers less than 1 centimeter in  
16 size in stage 0 and I meeting the AHCPR guidelines for this  
17 study as well.

18 [Slide.]

19 In terms of the sensitivity of digital in stage 0  
20 and I cancers, it was about exactly the same for digital and  
21 screen film, and for minimal cancers, digital did slightly  
22 better. But, again, this is a more limited number of cases  
23 on which these numbers are based.

24 [Slide.]

25 The ROC curves are remarkably similar between

1 digital and screen film in reader study No. 2. This is  
2 combining the results of all five readers in a breast-by-  
' 3 breast analysis. Not only are the areas the same within  
4 0.001, the areas under the ROC curves, but the shapes of the  
5 ROC curves are virtually identical.

6           When we use these data to test to reject the null  
7 hypothesis, the digital has an ROC curve area lower than  
8 screen film by 0.1 or more. Unadjusted for the correlation  
9 between readers, we have a high degree of significance.  
10 Even adjusted for multiple readers, we have a high degree of  
11 significance in rejecting the null hypothesis. The digital  
12 has a significantly lower ROC curve area.

13           So, from these results, we can conclude, also in  
14 reader study No. 2, that digital is noninferior in terms of  
15 recall rate. It doesn't recall more women than screen film.  
16 Digital is noninferior in terms of sensitivity. It has a  
17 comparable sensitivity and it has virtually identical ROC  
18 curves to screen film as well.

19           We are able, statistically, to reject the null  
20 hypothesis of digital being worse than screen film in this  
21 study.

22           [Slide.]

23           The side-by-side analysis was a different kind of  
24 analysis to look at how lesions appeared in digital images  
25 compared to screen-film images. We limited the case

1 election for the side-by-side analysis to the first  
2 0 cancer cases that were collected in the reader studies  
3 including some of the screening cancer cases.

4 So the readers sat with screen film on the  
5 viewboxes and the printed digital hard copy images on view  
6 boxes, looking at them side-by-side and used the Likert  
7 scale, which is a ranking scale with eleven points on it, to  
8 assess whether lesion conspicuity was better in one modality  
9 than another, whether there was more inclusion of tissue at  
10 the chest wall in one modality or another, or whether the  
11 visibility of tissue at the skin line was better in one  
12 modality or another.

13 Obviously, the most important of these is lesion  
14 conspicuity between the two modalities. But we also wanted  
15 to make sure that, in acquiring the digital images, that  
16 there was not a loss of tissue at the chest wall because of  
17 the digital detector design or some compromise in the  
18 appearance of tissue at the skin line because of the image  
19 acquisition.

20 [Slide. 1

21 The eleven-point Likert scale is shown here  
22 graphically. The five radiologists who did the side-by-side  
23 analysis could pick a score from 0 to 11. For example, on  
24 lesion conspicuity, if they thought the lesion was equally  
25 visible on both film screen and digital, they would give it

1 a score of 5.

2 If they saw the lesion only in digital and not in  
3 film screen, they would give it a score of 0 and, if they  
4 saw it only in screen film and not in digital, they would  
5 give it a score of 10.

6 We found, from our results, that the radiologist  
7 did use the full range of this scale.

8 [Slide.]

9 The null hypothesis was that screen film was  
10 better than digital in terms of each of these assessment  
11 areas by a score of one point or more on the Likert scale.  
12 Screen film being better is toward the high end of the  
13 scale, so the null hypothesis was that, in each of these  
14 areas, screen film, the score would be greater than or equal  
15 to 6. We tested against that.

16 [Slide.]

17 The actual results; in terms of lesion  
18 conspicuity, the mean score was 5.17. This range is  
19 averaging over the 40 cancers. Actually, two views were  
20 scored separately for each of the 40 cancers. This is  
21 averaging over the 40 cancers and looking at the range of  
22 reviewers averaged over the 40 cancer cases.

23 The view range is looking at the range averaging  
24 over the five reviewers and looking at the range applied  
25 over the 40 cancer cases. So the fact that there is a 0

at

ere means that all five radiologists gave it a score of 0, not just one of them, because this is an average over the five radiologists and the maximum score of 9.8 means that, in one case, four radiologists gave it a 10 and one radiologist gave it a 9 which would be strongly in favor of screen film.

So this is just to show that, in these different categories, generally the full range of scores was used. The fact that this number is less than 6 meets the criteria--the fact that each of these numbers is less than 6. One of the results that were pleased about is the score being significantly below 5.

Even when you look at the range over all the reviewers, each reviewer scored at less than 5 and almost every view was scored less than 5 for the visibility of tissue at the skin line. One of the explanations for that is that the images on digital were thickness equalized.

An algorithm was applied to the digital images that eliminated the thickness differences of the breast and only presented tissue consistency differences in the breast and it made it much easier for the radiologist to see to the skin line compared to screen film, even with hot lighting which was available for any of the images.

[Slide.]

We also did a subgroup analysis of the side-by-

1 side results for different types of lesions among the 40  
2 cancers. This is looking at the number of views. Some  
3 lesions had both a mass sign and a calcification sign so  
4 they may be double counted here, but this shows that where  
5 calcification were present, the scores were similar to the  
6 mean score that we got for all lesions.

7 Really, there was no significant difference in the  
8 means for any particular type of lesion. The full range was  
9 used across these different types of lesions.

10 [Slide.]

11 So, in conclusion, from the side-by-side analysis,  
12 we were able to show that, in a side-by-side comparison of  
13 screen film and hard-copy digital, that the readers saw the  
14 conspicuity of lesions to be the same. They saw the same  
15 amount of tissue at the chest wall and were actually much  
16 better to see skin line more easily with the digital  
17 presentation of the images.

18 [Slide.]

19 So the study conclusions are that in both the  
20 reader studies, recall rates demonstrated fewer recalls with  
21 digital than with screen film. In both reader studies, the  
22 sensitivity of digital was comparable to that of screen film  
23 for the detection of breast cancer and, in both reader  
24 studies, the ROC analysis gave virtually identical ROC  
25 scores for the areas under the curve for digital compared to

1 screen film.

2           In the side-by-side feature analysis, there were  
3 comparable lesion conspicuity and visibility of tissue at  
4 the chest wall with digital compared to screen film.  
5 Digital actually did significantly better for visibility of  
6 tissue at the skin line.

7           [Slide.]

8           The final conclusions are that product labeling is  
9 consistent with the data presented in this PMA and the PMA,  
10 we think, presents a strong case for the safety and  
11 effectiveness of digital mammography for the detection of  
12 breast cancer, both for screening and diagnosis.

13           [Slide.]

14           Let me just close by presenting a road map of  
15 where we go from here. What we have done so far is present  
16 the PMA data on the hard copy digital compared to screen  
17 film. Hopefully, with approval of hard copy digital, based  
18 on the data that have been presented, the next step will  
19 then be to go on and seek a soft copy--or perform a PMA  
20 supplement study that would validate soft copy digital by  
21 comparing soft copy presentation of digital images to hard  
22 copy presentation of digital images in a side-by-side  
23 comparison similar to the study that I presented here,  
24 comparing digital hard copy to film screen.

25           But this would be done in a side-by-side

1 comparison of digital hard copy with digital soft copy. It  
2 would require at least 45 cancers, a total of 100 lesions  
3 and would be done by five qualified radiologists performing  
4 the side-by-side comparison.

5 Obviously, the manufacturers want to be able to  
6 use either hard copy or soft copy presentation of their  
7 digital images to be read by radiologists. So this would  
8 close the PMA, the premarket approval, step for soft copy.  
9 We have conferred with the FDA about the design of a  
10 postmarket study and we would like to at least present some  
11 idea of what the postmarket approval study might look like  
12 based on those.

13 Those discussions, the design that has come up, is  
14 the multiple reader, multiple case study which would use ROC  
15 analysis like the multi-reader analysis presented in reader  
16 studies here but would include more readers, somewhere  
17 between six and ten readers and would include more cancers,  
18 and all of them screening generated cancers.

19 I think the concern is how digital will perform in  
20 the screening cohort and this postmarket study would collect  
21 cases only from a screening cohort, would collect at least  
22 50 cancers and then at least three to four times that number  
23 of non-cancers, so somewhere between a total of 200 and 250  
24 images.

25 And these six to ten readers would read both the

1 digital and screen-film images with a sufficient time  
2 separation in between to avoid recall effects. Those  
3 results would then be analyzed with multi-reader ROC methods  
4 to eliminate the correlation among the readers and compare  
5 the ROC results in this multi-reader, multi-case approach.

6 I think the FDA will be talking more about that in  
7 their presentation as well. So I will stop here and thank  
8 you very much for your attention.

9 DR. GARRA: Thank you, Dr. Hendrick.

10 We are running just slightly ahead of schedule so  
11 we could take one or two questions from the panel about Dr.  
12 Hendrick's presentation. Dr. Smathers?

13 DR. SMATHERS: Ed, as I understand the sequence,  
14 the film screen was done first and then, using the same  
15 radiographic techniques, the digital mammography was taken.

16 DR. HENDRICK: Yes; that is exactly right.

17 DR. SMATHERS: Were any of the recalls in film  
18 screen due to inadequate exposure of the film since that  
19 would prejudice that cohort to some extent.

20 DR. HENDRICK: No; that wasn't the reason for  
21 recall.

22 DR. SMATHERS: They were subtracted out or  
23 eliminated from the--

24 DR. HENDRICK: Yes; there was QC done on the  
25 quality of the screen-film images prior to the radiologist

1 making the decision about whether it was a positive or a  
2 negative case. The recalls were only because they thought  
3 the women needed further evaluation to work up the findings.

4 DR. GARRA: Thank you.

5 Any other questions at this point?

6 DR. HARMS: Ed, what was the gold standard? How  
7 do you establish that? Is that biopsy, the size of the  
8 lesion? How was that determined?

9 DR. HENDRICK: The gold standard is the presence  
10 of cancer and that was determined by biopsy in the cases  
11 that got to biopsy through the diagnostic workup. There  
12 were, obviously, lots of cases that were read as normal on  
13 both modalities that didn't get the biopsy. The only way  
14 that we have to determine whether cancer occurs in those is  
15 to follow those women for at least a year after the study  
16 and see if cancer occurs.

17 So the study was conducted between October of '97  
18 and January of '98, and follow up continues. But there was  
19 intense follow up through May of 1999 when MedTrials, who  
20 was monitoring this study, was collecting data and sort of  
21 hounding sites on a daily basis about, "Have there been any  
22 more cancers in the study group?"

23 That monitoring will continue but one of the  
24 things that we find in this kind of a study is that, because  
25 you are doing both modalities, and if one modality shows it

1 to be suspicious, you are going to do something about it,  
2 that there is better ascertainment of the presence of cancer  
3 than in the normal just doing a single modality in these  
4 studies.

5 The ascertainment is not biopsy in every case, is  
6 the simple answer to your question, but biopsy plus follow  
7 up.

8 DR. GARRA: Any other questions? Some of us have  
9 questions but I think we are going to hold them until after  
10 we hear the FDA presentation. We will all have an  
11 opportunity to ask additional questions later on.

12 Thank you.

13 I think, at this point, what we are going to do is  
14 take a fifteen-minute break. It is now 10:15 and we will  
15 reconvene at 10:30 in the morning here.

16 [Break.]

17 DR. GARRA: Thanks everyone. We are now going to  
18 begin with the FDA presentations. The first speaker is  
19 going to be Jack Monahan who is the lead reviewer for this  
20 PMA.

21 **FDA Presentations**

22 **PMA Overview**

23 MR. MONAHAN: Good morning.

24 [Slide.]

25 I would like to start my presentation today by

1 thanking the panel for taking time out of their busy  
2 schedules to have a look at the material that has been  
3 submitted by G.E. and to come here today to help us in our  
4 deliberations to bring this product to market.

5 This, I feel, is a really important step along the  
6 road that we have taken with digital mammography that we are  
7 here today to actually look at an application and to reach  
8 some decision. During the course of the review, I would  
9 like to point out that we have involved not just the Office  
10 of Device Evaluation but also the Office of Surveillance and  
11 Biometrics in the Center, the Office of Compliance and our  
12 Office of Science and Technology.

13 [Slide.]

14 You will notice that the manufacturer, when they  
15 got up today, used soft copy for display of their slides.  
16 FDA, on the other hand, is using hard-copy display. I don't  
17 want to panel to read anything into this about our distrust  
18 of technologies. But we are relying on the old technology  
19 here today.

20 I had the overall lead of this review but I was  
21 assisted by many people from the Center and I would like to  
22 thank each and every one of them for promptly giving their  
23 reviews and cooperating in this joint effort.

24 For the manufacturing review, we had Falidia  
25 Farrar from the Office of Compliance. There are no major

1 problems remaining with the manufacturing aspects of the  
2 submission. The labeling has been reviewed by Dr. Sacks,  
3 Phillips and Mr. Doyle who is the Executive Secretary for  
4 the panel. There may be some lingering issues relative to  
5 the labeling which is typical for a PMA, and the agency will  
6 work those out as we move along in the process. Most of  
7 those usually consist of editorial changes rather than  
8 anything of substance.

9 [Slide.]

10 The clinical studies and the statistical work in  
11 the application were reviewed by Dr. Sacks, Wagner and  
12 Bushar. The engineering and physics were reviewed by Robert  
13 Gagne, Robert Jennings and Kish Chakrabarti. I forgot to  
14 mention, Kish is with the Office of Mammography Quality  
15 Assurance and I didn't mention them when I was talking about  
16 offices. I apologize for that.

17 The disinfection and sterilization issues  
18 associated with the device were reviewed by Cathy Nutter.  
19 Again, there were no significant issues with the  
20 disinfection of the device. The information provided by the  
21 company is adequate.

22 [Slide.]

23 We will begin this morning with Robert Gagne  
24 **discussing** the physics. You have heard some of that  
25 discussed earlier. This will be from the FDA perspective as

1 will all the other presentations given today. As you are  
2 aware, the FDA had a slightly different perspective on  
3 applications than manufacturers, typically, and, hopefully,  
4 we come to agreement.

5 The clinical study and the statistics will be  
6 reviewed by Harry Bushar. Robert Wagner will give a semi-  
7 tutorial and then discuss some of the clinical data as it  
8 all relates to ROC analysis. The feature analysis study,  
9 the post-approval study design and, finally, the labeling  
10 will be discussed by Dr. Sacks.

11 We will start now with Bob Gagne.

12 **Physics Review**

13 DR. GAGNE: Good morning.

14 [Slide.]

15 My name is Bob Gagne. I work in the Office of  
16 Science and Technology here at the Center. My job today is  
17 to go ahead and try and give you a review of some of the key  
18 aspects of the physics that are present in this particular  
19 submittal.

20 [Slide.]

21 As a start to this presentation, what I would like  
22 to do is just give you an overview of where I am going with  
23 the presentation. Basically, what I would like to do is to  
24 quickly review for you what it is that we look for in terms  
25 of physics whenever we get an application in this manner. I

1 am going to spend some time, and this will be a little bit  
2 redundant with the manufacturer's presentation but I think I  
3 am giving a little bit different view here so, hopefully, it  
4 will increase the knowledge a bit. That remains to be seen.

5 I would like to define the DQE and show you a  
6 little bit its relation to imaging performance because we  
7 are going to talk about DQE data that the manufacturer has  
8 presented in their application.

9 I am only going to review some of the key data.  
10 The key data is defined, basically, by me in terms of the  
11 review of the physics--we are not going to go over all the  
12 physics aspects here from the PMA--and then give you some  
13 concluding remarks.

14 [Slide.]

15 What do we look for in terms of physics? I am not  
16 going to describe each item on this slide. I just want to  
17 say, however, that one thing that I will be doing is that  
18 the things that are in italics and the bolder color blue we  
19 will talk about some more as we go along in the  
20 presentation.

21 There are basically three major areas that we look  
22 at when we look at the physics for this type of device. The  
23 breakout of two of those areas are titled "detected **data**"  
24 and "display **data**." It is kind of a unique circumstance for  
25 a digital detector that, in fact, you can break those out,

1 you can get parameters that are strictly related with  
2 detector and you can get parameters that are strictly  
3 related with display.

4 So we itemize those kinds of parameters and they  
5 are all in the sponsor's application. That is different  
6 than the analogue system film screening that incorporates,  
7 basically, the display in the imaging system.

8 [Slide. 1

9 Let me go on to the next viewgraph. I would like  
10 to take a little bit of time here going over this slide. I  
11 wonder if you would make the translation for me here as I  
12 talk about DQE later on in the presentation that what I mean  
13 by DQE is the ability of the system to transfer information  
14 that is available at the input to the output.

15 It is defined in terms of signal-to-noise ratio,  
16 but it really is its ability to transfer information. So  
17 when I say that the system has a particular DQE value, what  
18 I am saying is that I am making some value judgment on how  
19 well it is able to transfer that information.

20 It turns out that, if you look at the first  
21 equation here--you saw this equation previously in the GE  
22 presentation--its DQE is a measure of system efficiency in  
23 terms of how much signal-to-noise ratio squared you had into  
24 the system compared to what you get out. It has a spatial  
25 frequency dependence. That is the  $(f)$  means.

1           You can express the DQE in a different manner when  
2 you look into the expression for signal-to-noise ratio. It  
3 turns out that you can describe the DQE in a different  
4 manner as the ratio of noise-equivalent quanta as a function  
5 of spatial frequency to the number of input quanta.

6           That is interesting because noise-equivalent  
7 quanta is made up of, and I hope you can see the light color  
8 blue there--noise-equivalent quanta wraps up three important  
9 imaging parameters for imaging systems and that is its gray  
10 scale transfer, in the large G, its resolution as measured  
11 by modulation transfer function and the noise in the system  
12 as measured through a noise-power spectrum.

13           What I have tried to do on the right-hand side  
14 with a set of images that I think some of you probably have  
15 seen before is if you think about noise-equivalent quanta as  
16 a measure of the amount of detected X-ray photons by the  
17 imaging system, the set of black-and-white photos there  
18 represents a set of images where that number of quanta is  
19 increasing when you go to the right and it is increasing as  
20 you go down the page.

21           I would like to focus a bit, just to give you sort  
22 of a practical description of this concept, at the two  
23 middle pictures. If you look at the right-hand side photo  
24 in the middle row, and assume that that would be the picture  
25 that you got if you had a perfect detector, a DQE equal to

1 1.0.

2 The image to the left of that represents what  
3 would be at the output of the system if the DQE were  
4 somewhere around 15 percent. So you see the differences,  
5 then, in terms of the transfer of information and what this  
6 quantity represents.

7 [Slide.]

8 One key piece of data that I want to bring up for  
9 you are the values of DQE for the sponsor's imaging system.  
10 I would like to spend just a little bit of time talking a  
11 little bit about the impact of design on these DQE values.

12 You can trade off certain aspects because of  
13 design constraints with respect to DQE. In the final  
14 analysis, what you would like to do is you would like to  
15 meet--if you look at the graph on the right-hand side--you  
16 would like to get the DQE value to go up in magnitude and  
17 over to the right in terms of spatial frequency. You would  
18 like to increase its band width if you want. Those are the  
19 things you would like to do.

20 But there may be circumstances where you might  
21 trade off one versus the other. One situation where that  
22 occurs is the choice of input phosphor. But I want to focus  
23 more on the size of the pixel.

24 There have been some recommendations in the  
25 literature, informally, about the size of the pixel. Should

1 it be 0.05 millimeter, 0.1 millimeter, or 0.15 millimeter?  
2 That is a difficult question to answer because choosing one  
3 of those sizes involves tradeoffs.

4 The Senographe 2000D has a 0.1 millimeter pixel  
5 size. Now, the immediate impact of that that I think I will  
6 show you in some of these slides is that you do get some  
7 tradeoff in terms of the band width of the DQE because of  
8 the size of the pixel, but you pick up other aspects in  
9 terms of image display because the total number of pixels is  
10 smaller.

11 So those kinds of tradeoffs, I think, make it  
12 difficult to make a definitive statement about pixel size.

13 [Slide.]

14 Let's go on to the actual data. This is another  
15 slide that I would like to spend a little bit of time  
16 explaining because the same motif will follow through in the  
17 next three slides. I am going to start from the top left,  
18 work my way over to the right and then down to the actual  
19 data.

20 First, let's consider the objects at the top of  
21 the slide. I have tried to show, in a cartoon  
22 representation, if you want, the imaging of a spiculated  
23 mass which is at the center of the breast. In this case,  
24 the exposure at the detector is close to optimum for film  
25 screen, about 11 mR. This results in an image of that

1 spiculated mass at the center of the breast.

2           Moving along now, I have three circles on that  
3 spiculated mass that I am trying to show represents a  
4 different amount of stress, if you want, on the imaging  
5 system in terms of its ability to image that particular  
6 structure. Starting with the top circle, which is really  
7 just detecting whether the mass is there or not, going down  
8 to the next one down which is to see something slowly  
9 changing in shape, and, finally, to the fast-changing end of  
10 the spiculation in the mass.

11           The arrows are intended, then, to represent this  
12 stress, if you want, how much of the DQE, how much of the  
13 information transfer is needed in order to picture these  
14 particular pieces of this cartoon representation of a  
15 spiculated mass.

16           Now, let's go on to the data itself. You saw this  
17 DQE route before. What I would like to do is summarize a  
18 little bit. Let me make a statement, first of all, about  
19 the film-screen system. The system that I have picked is  
20 intended to be representative of the performance of a  
21 typical film screen. I am not intending to take the  
22 absolute best, but it certainly is a good representation of  
23 the performance of a film-screen system.

24           Now, with respect to the graph, a couple of  
25 points. First of all, as for any digital detector, there is

1 a frequency at which faithful reproduction of signal when  
2 you are near or above that spatial frequency is no longer  
3 possible. That is really determined by the pixel size.

4 For the G.E. system, that frequency is 5 line  
5 pairs per millimeter related to the 0.1 millimeter pixel  
6 size.

7 Now, let's look at the data, itself, and see what  
8 conclusions we can draw from this. First of all, the  
9 sponsor's system has a higher DQE for almost all frequencies  
10 up to the Nyquist. But the film screen has response,  
11 transfer of information, DQE beyond the Nyquist frequency.

12 So, with respect to those particular imaging  
13 tasks, then, I hope this gives you a bit of a feeling as to  
14 the advantages and disadvantages for these systems at this  
15 particular operating point, 11 mR.

16 [Slide.]

17 In the next slide, I won't go back in terms of  
18 saying what is going on with the imaging task. What has  
19 changed in this particular slide is the exposure to the  
20 detector. We are talking, now, about a situation where we  
21 have a mass near the skin line. The higher exposure, in  
22 this case, 22 mR, is intended to show the conditions of the  
23 detector at or near the skin line.

24 Now, if you look at the DQE for the sponsor's  
25 system, you see it is quite a bit higher than film screen.

1 Film screen has fallen off considerably. Again, there is no  
2 response for the digital beyond five linepair and there is a  
'3 little bit for the film screen.

4 So, in thinking about the future analysis, I think  
5 this particular graph, to a certain extent, explains some of  
6 those results.

7 [Slide.]

8 At the other extreme, suppose we are in a region  
9 of the breast which corresponds to a dense area of the  
10 breast, now the exposure at the detector is less than the  
11 'typical 11 mR. It is 1 mR. Again, we see similar  
12 characteristics. The sponsor's system has higher DQE values  
13 on the order of two to five times than the screen film and  
14 it stops at 5 linepair per milligram per milligram.

15 [Slide.]

16 So, in summary, then, at the risk of being a  
17 little bit repetitious here, what I am saying is that the  
18 DQE for this system, for exposure which is close to optimum  
19 for film screen, indicates that the DQE for the Senographe  
20 is higher than film screen almost all the way up to the  
21 Nyquist frequency.

22 It is a digital detector so a faithful  
23 reproduction of signal is not possible near and beyond the  
24 Nyquist. As far as conditions of exposure that are near a  
25 skin line or in a dense area of the breast, we saw that the

1 transfer of information, as measured by DQE, falls off  
2 considerably for film screen and the digital system remains  
3 high on the order of two to ten times higher than the film  
4 screen.

5 So you get a significant increase in dynamic  
6 range. I am talking dynamic range in terms of transfer of  
7 information here for the applicant's imaging system.

8 [Slide.]

9 Let me talk about a couple of other key components  
10 associated with this type of imaging system. If you think  
11 about the major contributors to noise in these systems,  
12 there are two major pieces. One is the quantum noise that  
13 comes strictly from the X-ray photon statistics. But then  
14 there is also additive noise from the detector in the  
15 electronics.

16 What you would like to have in an imaging system  
17 is you would like to have the total noise be dominated by  
18 the X-ray photon statistics, not by the additive noise of  
19 the electronics. You would like to have this quantum-  
20 limited operation over a range of exposures that are  
21 appropriate for mammography.

22 So we are looking at this particular parameter  
23 because of this characteristic--you want this to be  
24 dominated by quantum noise--and because, formally or  
25 informally, there have been circumstances where sometimes

1 the electronics are, in fact, quite noise.

2 If you have significant additive noise, it will  
3 have an impact on this summary measure, DQE. The impact  
4 that will be such that it will impact the value of DQE at  
5 low exposure values.

6 [Slide.]

7 So, going on to the sponsor's data, now, you saw  
8 this graph previously. This is a different graph than what  
9 I had before. Previously, the abscissa represented spatial  
10 frequency. Now I am showing you the value of DQE at a  
11 particular spatial frequency, 2 linepairs per millimeter, as  
12 a function of exposure to the detector.

13 The DQE is essentially flat until you reach  
14 exposure levels on the order of about an mR or less. So the  
15 significance of the additive noise doesn't come in until you  
16 are almost out of the range of operation for mammography  
17 exposures. As a comparison, I have shown you a film screen  
18 plot for the same exposure, the same film screen that I was  
19 showing you before.

20 In this particular case, what dominates the noise  
21 on the low and high exposure for film screen is not, of  
22 course, electronic noise but additive noise brought out by  
23 the film grain. And so when the relative contribution of  
24 film grain versus quantum noise starts to be large, the film  
25 screen's DQE or transfer of information goes down.

1           As you can see, this particular system, G.E. full-  
2 field digital mammography, at this spatial frequency,  
3 outperforms the film screen.

4           [Slide.]

5           Going on to a couple of other datapoints with  
6 respect to the physics, there is image conditioning and  
7 display which is going on with respect to the digital data.  
8 Some of this conditioning involves the thickness  
9 compensation so that when you look at a laser-film-recorded  
10 image of a breast from the digital system, you don't see the  
11 wide range and optical density that you would see in a  
12 regular analogue film.

13           There is processing going on. There is  
14 linearization associated with perceptual linearization for  
15 the display device and linearization on the device, itself.  
16 All of this is conditioning associated with getting a final  
17 display on the laser film recorder.

18           [Slide.]

19           There is really not very much consensus or  
20 standards on relating necessary performance levels for these  
21 display devices, whether it is soft copy or, in this case,  
22 we are talking hard copy to the characteristics of the  
23 digital data. In our view, in looking at the submission,  
24 the steps that have been taken seem reasonable and  
25 appropriate.

1 But, in the final analysis, at this point, we  
2 really have to rely on the demonstrated clinical performance  
3 associated with the protocols and the algorithms that are  
4 being used for conditioning and display.

5 [Slide.]

6 Lastly, one aspect that is unique to visual  
7 detectors is the fact that you can have artifacts on the  
8 image that come from bad or defective pixels. The  
9 manufacturer specifies limits with respect to these bad and  
10 defective pixels. Again, there are no standards or  
11 guidelines. There is no consensus here with respect to  
12 pixels, bad pixels.

13 So what is reasonable is really somewhat up in the  
14 air. Not only is what is reasonable up in the air but there  
15 are no requirements to provide any information in terms of  
16 where the bad pixels reside with respect to the detector.

17 Just to go over a couple of the criteria that are  
18 used by the sponsor in this area, bad pixels, before you  
19 correct them, a lot of these pixels can be corrected. The  
20 tolerance is being specified as a maximum of 1100 isolated  
21 pixels or pixel pairs--this is a maximum now--and no large  
22 clusters--that is, you can't have any large clusters of  
23 greater than, for example, 15 or more adjacent pixels in the  
24 line.

25 After correction of these pixels, you can't have

1 more than one bad pixel in any 2 centimeter by 2 centimeter  
2 area. Again, as I said, there is no consensus here but it  
3 looks to us, in terms of these tolerances, that these are  
4 reasonable tolerances for this particular kind of device.

5 [Slide.]

6 In conclusion, the data pertaining to the physics  
7 aspects in the PMA I think provides important information on  
8 comparative imaging performance between a digital system and  
9 its analogue counterpart and actually between other digital  
10 systems, if you want, also.

11 System parameters like DQE and quantum-limited  
12 operation provide the means to evaluate the advantages and  
13 disadvantages of the different imaging modalities. There is  
14 a summary of this data in the labeling and so, looking at it  
15 in terms of adequacy and availability, this data is in the  
16 labeling of this particular device.

17 We think, and it is my opinion, that this sort of  
18 information is not only appropriate for the device labeling  
19 but can also serve in the future as a point of reference for  
20 the community.

21 Thank you.

22 DR. GARRA: Thank you.

23 The next speaker for the FDA is Dr. Harry Bushar  
24 who is going to be talking about the statistical review of  
25 the clinical data.

1                   **Statistical Review of the Clinical Data**

2                   DR. BUSHAR: Good morning.

3                   [Slide.]

4                   My name is Harry Bushar. I will be doing the  
5 statistical review. I looked at what the sponsor had  
6 presented in their clinical trials and what I will be  
7 presenting is my review of the sponsor's analysis.

8                   [Slide.]

9                   I focussed primarily, or entirely, on the second  
10 reader study for the simple reason that this study was done  
11 a little bit better in that all five radiologists read all  
12 of the mammograms from all of the women. The sponsor  
13 compared the digital mammography to the screen-film  
14 mammography in a clinical trial which consisted of 625  
15 women.

16                   There were 581 from a diagnostic series that did  
17 not have cancer. There were 24 in the series that did have  
18 cancer. And then there were 20 women with cancer taken from  
19 a screening series. Each women received both a two-view  
20 screen film and an equivalent two-view digital which was  
21 performed using technique factors that were matched. Notice  
22 the digital was matched to the screen-film technique.

23                   [Slide.]

24                   In the second reader study, the diagnostic cohort  
25 consisted of 605 consecutive women who were attending for

1 diagnostic mammography at four sites, one in Colorado, one  
2 in Pennsylvania and two in Massachusetts. The screening  
3 cohort consists of 20 cancers--that is, the first 20  
4 cancers--selected from approximately 4,000 women in an  
5 ongoing screening study which was conducted at two of the  
6 above four sites, namely Colorado and one in Massachusetts.

7 [Slide.]

8 In the second reader study, the sponsor used five  
9 MQSA-qualified radiologists to independently interpret each  
10 digital and each screen-film mammography which were obtained  
11 from a total of 997 breasts from the 625 women enrolled.  
12 Some women only had mammography done on one of the breasts.

13 The digital images were stored digitally and laser  
14 printed for reading. The printing was done at the Colorado  
15 and Massachusetts facility to provide the comparability to  
16 screen film; that is, everything was hard copy in this  
17 particular reader study.

18 [Slide.]

19 What I will be looking at here is patient  
20 management. In other words, I am going to look at the ACR  
21 BIRADS categories which were defined to be negative when  
22 they were one, normal, or two, benign, for breast cancer for  
23 both the screen film and the digital, In the other ACR  
24 BIRADS categories, namely 0, needs further evaluation, 3,  
25 probably benign, 4, suspicious of breast cancer and 5,

1 highly suspicious of breast cancer, are all considered  
2 positive. This was done for both the screen film and the  
3 digital, so my sensitivity and specificity will be relative  
4 to these definitions.

5 [Slide.]

6 The specificity, or 2 negative rate, was estimated  
7 by the sponsor for digital to be 55 percent. It was  
8 slightly numerically larger than the corresponding estimate  
9 of screen film which was 53 percent, The sponsor did an  
10 equivalence test where he looked at the difference delta  
11 between the digital specificity and the screen film  
12 specificity. He used a model--he used a SAS PROC MIXED and  
13 he was able to adjust for the fact that there were five  
14 readers for each mammography to obtain a confidence  
15 interval, a 95 percent confidence interval, for this  
16 difference which extended down as far as -0.6 percent up to  
17 about 4 percent.

18 He was also able to reject his equivalence null  
19 hypothesis. The equivalence null hypothesis was that the  
20 delta would be less than -5 percent; in other words, the  
21 digital would be worse in specificity than the screen film  
22 by more than five percentage points. This was done with a  
23 p-value of 0.001, so it was a highly statistically  
24 significant result in terms of equivalence.

25 [Slide.]

1           Correspondingly, he looked at sensitivity, or the  
2 true positive rate, and his estimate of digital sensitivity  
3 was 68 percent which was now slightly numerically smaller  
4 than the corresponding estimate of screen film which was  
5 70 percent. Here, I have presented the delta in the same  
6 form as I did for specificity, so as not to be confusing.  
7 But the sponsor looked at digital sensitivity minus screen  
8 film sensitivity and used the same type of model in the SAS  
9 PROC MIXED to take care of the correlation between the  
10 multiple readers and obtain the 95 percent confidence  
11 interval now that went all the way down almost to  
12 -10 percent and up to 7 percent.

13           But, still, he was able to reject the equivalence  
14 null hypothesis that delta was less than -10 percent. In  
15 other words, he rejected the null hypothesis that the  
16 digital sensitivity would be worse by ten percentage points  
17 than the screen film sensitivity, but just barely because  
18 the p-value now is less than 0.03.

19           [Slide.]

20           So, therefore, in conclusion, the sponsor's second  
21 reader study demonstrates that for patient management in a  
22 diagnostic population which was enriched with cancer  
23 selected from a screening study that the digital specificity  
24 is not lower than 5 percentage points below the screen film  
25 specificity and also that the digital sensitivity is not

1 lower than ten percentage points below screen film  
2 sensitivity.

3 We have to realize, here, that there are some  
4 biases because we are dealing with a diagnostic population  
5 and there may even have been some bias in favor of analogue  
6 because the women, perhaps going to the digital clinic, had  
7 been screened previously with analogue.

8 But the way the sponsor did this study, they tried  
9 to minimize, if not eliminate, this bias. They took  
10 consecutive women showing up at the diagnostic center so  
11 that each women that was selected for the population  
12 received both an analogue and a digital. That analogue was  
13 not used to select that woman for the study.

14 In the screening study, all women who entered the  
15 study received both digital and analogue so there was no  
16 obvious bias on that study.

17 That's it. Thank you.

18 DR. GARRA: Thank you.

19 The next speaker for the FDA is going to be Dr.  
20 Robert Wagner who is going to review some of the ROC  
21 analysis features that are found in this study.

22 **ROC Analysis**

23 DR. WAGNER: Good morning, panel, sponsor and  
24 guests.

25 [Slide.]

1           Our sponsor did a multiple-reader ROC study. I  
2 would like to explain to you what these words mean and ask  
3 Dr. Toledano to indulge me. Dr. Toledano works at the  
4 frontier in this field.

5           Here is an outline of the presentation I have this  
6 morning. I will first talk about the ROC paradigm and the  
7 sources of variability that it controls for. And then I  
8 will just give you a quick flashing of two classic papers on  
9 the variability in mammography. These papers explain a lot  
10 of the predicament where we were in the last few years.

11           Then I will define what was meant by multiple-  
12 reader, multiple-case ROC study and, in the jargon of the  
13 land, and many people just refer to this as a reader study,  
14 in the interest of saving three or four words. And,  
15 finally, we will get to the sponsor's multiple-reader and  
16 multiple-case ROC analysis.

17           [Slide.]

18           Here is a one-page ROC tutorial. The ROC paradigm  
19 was invented to accommodate the situation where you have two  
20 populations, one disease, which is here, the cancer  
21 population, and another population that is nondiseased or  
22 the noncancer population. You would like to be able to  
23 separate the two populations with some kind of a diagnostic  
24 test.

25           If you would think in terms of prostate cancer,

1 this decision axis is--for example, it could be PSA assay so  
2 there would be the test measurement. In diagnostic imaging,  
3 you don't have a nice scale and so people reporting in ROC  
4 analyses give a scale which is considered the probability of  
5 malignancy, the probability of disease or, in the jargon,  
6 the reader's subjective judgment of the probability or the  
7 likelihood that the case is a cancer.

8           So some people call this the probability of  
9 cancer, probability of malignancy or what have you. The  
10 idea is that you would like to separate the two populations  
11 and you would like to have a place where you could totally  
12 separate the cancers from the noncancers. Of course, as in  
13 all real-world problems, those two populations overlap quite  
14 a bit.

15           If you put your cut at a certain point, then all  
16 of those cancers to the right of your threshold would be  
17 true positives but then there will always be some noncancers  
18 that would leak past that threshold so the people from the  
19 noncancer that leak past that threshold are the false  
20 positives.

21           If you try to be more aggressive and to catch more  
22 cancers, we all know that that means you have to pay with  
23 more false positives. That tradeoff was just described by  
24 the ROC curve.

25           [Slide. 1

1           What we don't see in the curve is the hidden  
2 parameter which is where you set the threshold. Where you  
3 set it is determined by what is called the reader's mindset  
4 or a level of aggressiveness.

5           So, as the reader gets more aggressive, you just  
6 move up the ROC curve and trace a figure something like I  
7 have shown here. When people start making measurements of  
8 sensitivity and specificity, you realize that it going to be  
9 very expensive to pin down the sensitivity and specificity  
10 at every point in the curve.

11           So, early in the study what people frequently do  
12 is they summarize the ROC curve by the area underneath the  
13 curve. When you do that, you are essentially giving the  
14 sensitivity averaged over all specificities so you are  
15 essentially replacing the curve with a line at the level of  
16 the area under the curve. So you have just reduced a nice  
17 dataset to a simple average number.

18           A test that is guessing has an area under the  
19 curve of 0.5. A perfect test would come up and hug the  
20 corner and would have an area of 1.0. So that is the simple  
21 paradigm of what ROC is about.

22           [Slide.]

23           Now let me move on to two of the classic papers on  
24 variability and ROC analysis. The first classic paper is  
25 from Joanne Elmore and company who studied ten radiologists

1 not randomly selected. That is the point of this overhead.  
2 She reported on the wide range of patient management  
3 decisions on this number, nine cancers, and that number of  
4 cancers.

5 If you just look at that range of performance, it  
6 looks like it is all over the map, But Carl Dorsey and John  
7 Swets came along and took Joanne's data and showed that, at  
8 least for these ten radiologists, their performance  
9 straddled a model ROC curve. So what you were seeing in the  
10 variability seen in her study was a rather homogenous range  
11 of reader skill level because a low skill is here, a really  
12 good skill is up here.

13 So this is a rather homogeneous level of reader  
14 skill. What we are seeing is a difference in the mindset or  
15 the level of aggressiveness of those readers. This is one  
16 of the problems for agreement studies is that they would not  
17 control for that.

18 Enough on the Elmore study and its interpretation.

19 [Slide.]

20 Craig Beam, Peter Layde and Dan Sullivan went to  
21 great effort not just to select some readers but to select  
22 over 100 readers randomly from the population across the  
23 country. When you keep score in the same way, based on the  
24 recommendation for biopsy or not, if you were to look at ROC  
25 space, you would have a true positive, false positive. If

1 you look in sensitivity space, you have the complement.

2 So Craig Beam put his data out in this way. Here  
3 we now see that the radiologist's performance is really all  
4 over the map. This is one of most celebrated figures. In  
5 fact, I have xeroxed this so many times it has come out as a  
6 parallelogram, as you can see. It is a very population  
7 figure.

8 So, here, we see among these 108 radiologists  
9 operating on these samples not only quite a range of  
10 variability of their mind set or level of aggressiveness, we  
11 also clearly see that there is a range from level of reader  
12 skill. I say "clearly;" I did not do this analysis. Craig  
13 Beam later came along and showed that this spread of  
14 performance is not consistent with the finite sample  
15 statistics of one single ROC curve. There really is a range  
16 of ROC curves.

17 [Slide.]

18 One more wrinkle I have to put you through before  
19 we go on to the sponsor's results. If you had one  
20 diagnostic test--we are here, today, to compare two  
21 diagnostic tests. If you had one diagnostic tests, you  
22 might get these two populations, schematically, and you  
23 might have another diagnostic test in which they are  
24 slightly different in the way the two populations overlap.  
25 I failed in doing that nicely.

1           But, to analyze the comparison of two modalities,  
2 you have to put the problem into two dimensions. Now, the  
3 new dimple, if you will, is that you now see the correlation  
4 between the two tests. The egg shape of the cancer  
5 population and the egg shape of the noncancer population is  
6 a measure of the correlation of patients across tests.

7           If you just squeeze the cancer population into a  
8 cigar, in that case, we have what we call 100 percent  
9 correlation across modalities. That would mean that, from  
10 the probability of malignancy from the one test as this as a  
11 cigar cloud, you could just go up from the probability in  
12 the one test and get the probability in the other test.

13           But we know that, in the real world, that it has  
14 been discovered in comparing digital to conventional  
15 mammography, this correlation is not high, particularly as  
16 Dr. Lewin suggested in the Diagnostic Imaging article,  
17 because of repositioning, at least for many of the  
18 modalities.

19           When you take the patient out of the room and into  
20 another room, repositioning, there is enough variability  
21 there that these clouds are not 100 percent correlated. In  
22 fact, you would know from following the literature and the  
23 public discussions, at least some of the ones we have had at  
24 the National Cancer Institute, that that correlation is less  
25 than 0.5.

1 So that is another problem for agreement studies.

2 [Slide.]

3 Now I will define what all those words meant up  
4 front. The multiple-reader, multiple-case, ROC paradigm  
5 means the following: it means every reader reads every case  
6 and, where possible, reads every case in both modalities.  
7 When you do that, you can actually start to enter a more  
8 complicated world than we had up front.

9 Now you can start to do what is called  
10 multivariate ROC analysis. What that means is that you  
11 start to account for the variance due to the range of case  
12 difficulty in the patients and its finite sampling. You can  
13 get some feel for the variance due to the range of reader  
14 skills and its finite sampling.

15 You can get a feel for those egg shapes that I  
16 talked about a moment ago, the correlation of the case  
17 variance across modality and the correlation of reader  
18 variance across modality. You would do that with some other  
19 egg figures that look something like what I just showed you.

20 And then there is something that is called within-  
21 reader variability or reader jitter. When you ask the  
22 reader to get the probably of malignancy and the reader  
23 says, "Well, that is like 70 percent," and you come back a  
24 month later, it could be 30 percent. We call this  
25 radiologist jitter. I think Dr. Elzeraki or Dr. Destouet

1 last time said that perhaps this could be called a rumble.

2 This is not a subtle effect.

3 Most models actually involve more parameters than  
4 we have here but you can get a good feel from the ones I  
5 just mentioned. Now what you can do is, collecting data in  
6 this format, you can now use software that is available on  
7 the web from the University of Chicago. Dr. Toledano has  
8 developed software to solve this problem and our own group,  
9 Sergie Beiden, Greg Campbell and myself, have an algorithm  
10 and a paper on that. If anyone is interested, we can tell  
11 you how we solved this problem.

12 [Slide.]

13 Again, before we get to the sponsor's results, I  
14 just want to give you a feel for how the various variances  
15 play out. We are interested in comparing two modalities and  
16 so we will compare the difference in ROC areas between the  
17 two modalities.

18 We saw earlier today that the ROC curves, and I am  
19 talking about reader study 2, here, the ROC curves lie right  
20 on top of one another essentially for the two modalities,  
21 digital and analogue in that study, but there is something  
22 called sampling statistics. What is the sampling  
23 variability? How uncertain are we about the areas under the  
24 ROC curves.

25 To do that, it is actually not a trivial problem.

1 The difference in the ROC areas between two modalities  
2 requires three pieces. I have it in the unexpurgated  
3 version. The panelists have this in your notes. You can  
4 study it on the plane tonight, if you like.

5 I have translated it and I have written "i.e.,"  
6 here. Every school child today knows that "i.e." is Latin  
7 for "in English." In English, what contributes to your  
8 uncertainty and your ability to see the difference between  
9 two modalities has three pieces.

10 It has a piece that is inversely proportional to  
11 the number of cases. This is the piece that most people  
12 carry around in their gut, but that is not the whole story.  
13 There is a second piece that is inversely proportional to  
14 the number of readers, as you might expect, if you are going  
15 to start to average readers together.

16 And then there is third piece that is within-  
17 reader jitter or any remaining lack of experimental  
18 reproducibility. That scale is inversely with the product  
19 of the cases and the readers.

20 There is something really important for these  
21 first two terms, which is the uncorrelated part of the case  
22 variance. I am going to put you through a little exercise  
23 for a minute to explain what we mean by that.

24 Picture that you were on a shore and you have a  
25 laser and you are trying to measure the height of a mast on

1 a ship. Suppose that ship is in very choppy waters. Well,  
2 you might think, at first, it is going to be very difficult  
3 to measure the bottom of the mast because it is very noisy  
4 and it is going to be very difficult to measure the top of  
5 the mast. But those two are 100 percent correlated.

6 So, actually, with a good enough laser, you can  
7 measure the height of that mast perfectly, almost perfectly,  
8 until it starts to get choppy and there are other sources of  
9 noise. That would enter, then, a random component. So what  
10 happens in these models if you only generate uncertainty  
11 from the uncorrelated part. The correlated part is in your  
12 favor.

13 So what I am trying to say to you is even though  
14 the reader variability can be very great, as it is in  
15 mammography, if the boats that the readers are on rise  
16 together, if the readers' digital and analogue rise  
17 together, they are pretty highly correlated and you may not  
18 have to pay an awful lot for that term.

19 That was the reader term. The same thing for the  
20 case term. But, remember, this is only of the order of 0.5  
21 and this is the last term that comes in like the product.

22 [Slide.]

23 Finally let's get to the sponsor's study. You  
24 heard from Dr. Bushar just a few moments ago about this  
25 cohort. This is the reader study No. 2. There were 44

1 breasts with cancer, no known bilateral cancer. There were  
2 five readers, five MQSA-qualified radiologists. All cases  
3 were imaged with both modalities.

4 Here is the essence of what a multiple-reader,  
5 multiple-case study is. All readers read all images from  
6 both modalities. The readers in the study used what we call  
7 the quasi-continuous scale. They used the range from 0 to  
8 100 for the probability of malignancy. That is sort of  
9 their test measurement readout scale sort of analogous to  
10 using a diagnostic clinical test.

11 The readings in digital and analogue were  
12 separated by 30 days to minimize the memory effect and there  
13 was a balance of the reading that you heard about earlier.  
14 Half of the cases were read digital first and half of them  
15 analogue first to try to minimize two other learning and  
16 memory sources of bias.

17 Now, I am going to give you the sponsor's results  
18 in two pieces; first, the easy piece that you heard about a  
19 little while ago. We are thinking now of the individual  
20 readers and uncertainties based on just readers one at a  
21 time. In a minute, we will put all the readers together.  
22 But, one at a time--let me just say this again.

23 We are going to average all five readers' ROC  
24 areas. When we do this for analogue, the areas were 0.77 on  
25 the average. The film screen, on the average, was 0.76. It

1 is actually closer than 0.01 there. I am going to ignore  
2 that difference for a moment because the readers'  
3 uncertainty was of the order of 0.1, ten times that, so you  
4 didn't see that on those average curves we showed earlier.

5 So that is what some of the work going on here is  
6 about; do we want to live with a 0.01 uncertainty. If you  
7 took the five readers' error bars, they move around 0.1. If  
8 you average them together, the mean 95 percent confidence  
9 interval about that difference is plus-or-minus 0.11. So  
10 that is a question for society, whether this level of  
11 uncertainty--how it strikes us.

12 When you go to the multiple-reader analysis, now,  
13 the idea here is you would think you could just average all  
14 these scores together and you ought to be able to get the  
15 error bars for the average reader's ROC area. That turns  
16 out not to be an easy problem. That is why I went through  
17 that exercise.

18 People worked on that problem for a number of  
19 years, including ourselves and one of our panelists. But  
20 when you do that and, in this case, when you use the  
21 University of Chicago software, and it is available on the  
22 web, now the 95 percent confidence interval about the  
23 difference has been narrowed. It is down to plus-or-minus  
24 0.064. Now we are starting to zero in on some kind of  
25 precision estimate of this difference.

1           We reproduced the sponsor's study with the Chicago  
2 software. We got the same results. We have our own  
3 software and I have some information on that in a paper if  
4 people are interested in how we do it. Our group has  
5 developed an independent algorithm. When we do the problem,  
6 we get plus-or-minus 0.068, almost the same result.

7           Another nice feature of our treatment is that we  
8 can tease out all those components of variance that I  
9 mentioned before, with some uncertainty, but this is what  
10 you do in a pilot study. You can look at that data and say,  
11 what do these results and the components of variance say  
12 about the size of a larger study that tried to narrow the  
13 error bars.

14           For example, if you wanted to narrow those error  
15 bars to plus or minus 0.05, here are the combinations that  
16 you would need if the patients you are about to sample from  
17 look like the patients they studied in the pilot study. You  
18 can see that, with 44 cancers in ten readers up to 59  
19 cancers in five readers, with our current estimates, you  
20 could get the error bars down to about plus-or-minus 0.05.

21           Now, suppose people are uncomfortable with that.  
22 We are talking postapproval now. Suppose people are  
23 uncomfortable with that and they said, "We would really like  
24 to get it down to 0.01 or 0.02 or 0.03." If you tried to  
25 put that to 0.03, the numbers go up very quickly. Now you

1 need 78 cancers and 100 readers, or 100 cancers and 20  
2 readers, especially when you realize that you get about five  
3 cancers per 1000 screened.

4 This study, then, is 10,000; is that right? And  
5 this study would be 20,000 people screened. So you can see  
6 how prohibitive these studies would become. But, perhaps,  
7 this study is within reach.

8 [Slide.]

9 So, in conclusion, the individual reader studies  
10 bring the error bars to the neighborhood of 0.1. The  
11 multiple-reader study cut to about 0.06 to 0.07. We showed  
12 what you could do to get it down to 0.05 if one would like  
13 and the panelists have the references, and the last two  
14 references have a star; one is the Chicago software and the  
15 other is a paper written by my colleagues and myself.

16 Thank you very much.

17 DR. GARRA: Thank you, Bob. I am glad you  
1 8 provided me with some reading for the flight home tonight.  
19 I will have to read that, but I am going to be drinking at  
20 the same time, so I don't know.

21 We would like to go on to the next speaker which  
22 is Bill Sacks. He is going to be talking about labeling  
23 review and the proposed postmarket study.

24 **Labeling Review and the Proposed Postmarket Study**

25 DR. SACKS: Good morning, everyone.

1 [Slide.]

2 I am a radiologist and an ex-physicist, although I  
3 don't know if there is such a thing as an ex-physicist, with  
4 the Office of Device Evaluation in the Radiology Branch. I  
5 will be discussing three items.

6 [Slide.]

7 First, I will say a little bit in addition to what  
8 Ed Hendrick told you about the side-by-side comparison.  
9 Secondly, I will go into the error bars that we feel should  
10 be included in the labeling. And, thirdly, I will go into  
11 the company's proposal for their postapproval study.

12 [Slide.]

13 With regard to the side-by-side feature  
14 comparison, as Ed explained, it was based on 40 cases with  
15 cancer, biopsy-proven cancer, in which the radiologists had  
16 in front of them at the same time the digital mammography  
17 and the film-screen mammography on the same woman, and they  
1 8 were asked a series of three questions to judge these with  
19 respect to the conspicuity of the cancers which were marked  
20 on the films; secondly, the question of inclusion of tissue  
21 near the chest wall; and, thirdly, visibility of tissue near  
22 the skin line.

23 [Slide.]

24 That is a particular selection of features that  
25 were compared by the company. They are not the only ones

1 that can be compared. This is just an example of two  
2 others. There are many. One might compare the ability to  
3 discriminate between benign and malignant calcifications.  
4 One might compare the ability to detect fine marginal  
5 irregularities of masses which would also relate to the  
6 question of whether they were benign or malignant. And  
7 there are others that one could come up with.

a One of the things about a side-by-side feature  
9 analysis, of course, is anybody who has looked at these  
10 knows that it is impossible to hide which is the analogue  
11 and which is the digital mammography. There are certain  
12 appearances which indicate to you which is which.

13 Since this is not a blinded study, a certain  
14 amount of subjective bias can come into play. Just bear  
15 that in mind as we talk about this.

16 [Slide.]

17 This is the Likert scale that is the same picture  
18 that Ed showed. I just have it filled in with the points  
19 here. And bear in mind that when you are looking at this  
20 side-by-side pair of mammograms on the same woman, if you  
21 feel that the digital is better with respect to the index  
22 that you are looking at, you give it a lower number. If you  
23 feel that analogue is better, you give it a higher number.

24 The extremes can either represent not visible at  
25 all on the other film or simply much better seen. Clearly,

1 5, being right smack in the middle, means that, well, as far  
2 as I am concerned, each one is as good as the other.

3 [Slide.]

4 This is the results in tabular form. I will show  
5 them in graphic form in a second with respect to these three  
6 indices. The conspicuity of cancer--these are figures that  
7 you have seen before, today. The average was about 5.17  
8 meaning just slightly to the side of analogue or film screen  
9 being better.

10 As far as inclusion near the chest wall, again, it  
11 is very close to 5. With visibility near the skin line, it  
12 is actually much closer to 0 which is in digital's favor, as  
13 you will remember from that scale. I will talk about these  
14 ranges, but it is easier on the next slide because this is  
15 the same information in pictorial form.

16 [Slide. 1

17 The range of each of these lines is the range of  
18 readers. It has all been averaged over--each reader had had  
19 their reading averaged over all 40 cancers so that with  
20 respect to conspicuity of cancer, there was one reader down  
21 there. There was one reader up here. And the other three  
22 fell in the middle. That is all that means. And the  
23 average came out to be just barely above 5.

24 Again with inclusion of tissue within the chest  
25 wall, there was one reader down at that extreme, another at

1 that extreme, because these are ranges. These are not  
2 standard deviations or anything. It is just the range over  
3 the five readers.

4           And then with visibility near the skin line,  
5 again, there was one that was way down here, one that was  
6 here and, on average, they came out at 2.95, as we saw. It  
7 is significant that all of the readers felt that, on  
8 average, the films were better on digital with regard to  
9 visibility near the skin line which would surprise nobody  
10 who has ever looked at a mammogram. They tend to be very  
11 dark near the skin line and the dynamic range that you have  
12 seen in both the company and the FDA's presentation on the  
13 physics shows the tremendous dynamic range that digital has.  
14 That is one of its major advantages over analogue.

15           [Slide,]

16           This can be broken down, again data that you have  
17 seen, with regard to the particular sign of cancer; that is,  
18 whether it is calcifications. Here this is broken down even  
19 farther than you saw before. This is whether calcifications  
20 were present or whether calcifications were the primary way  
21 that this cancer was identified, and so on.

22           Again, it is striking that all of these are just  
23 above 5 but, essentially, right in the middle. The range--  
24 now, this is not a range from one reader to the next but a  
25 range from one view to the next averaged over the five

1 readers--in other words, there was one mammogram, at least,  
2 and again this is a range; this is not a plus-or-minus a  
3 standard deviation or confidence interval.

4           There was at least one mammogram down here where  
5 none of the radiologists could see it on the analogue film  
6 at all. The only way you can average 0 is to have every one  
7 of them essentially giving you a 0, particularly when you  
8 are just using integral--well, maybe one may have gone as  
9 high as 1, but basically, they all thought that the digital  
10 was much better and, probably, that represented a case where  
11 it wasn't visible on the analogue.

12           You have got another mammogram, at least one, that  
13 was at the high end where they thought the analogue showed  
14 the cancer much better, or the calcifications, in this case.  
15 Similarly, as you go down masses, the range goes from fairly  
16 low to fairly high, again architectural distortion, fairly  
17 low to fairly high.

18           That means that some mammograms were much better--  
19 the cancer was much better seen by this sign on the digital  
20 and others in which the cancer was much better seen on the  
21 other.

22           Perhaps, this range can be explained by what was  
23 found in John Lewin's article in the November Diagnostic  
24 Imaging that Dr. Wagner mentioned in which he pointed out  
25 that repositioning causes two-thirds of the reason for the

1 variation between the way the analogue and the digital look  
2 which suggests that if you were to repeat every woman's  
3 analogue mammogram, even if digital didn't exist, you would  
4 pick up quite a bit more cancer.

5           So if everybody came in to get a mammogram once a  
6 year, if you did two copies of each view, the sensitivity  
7 might go from roughly 80 percent, as is said for  
8 a mammography, up to maybe 90 percent which is about the same  
9 advantage you get if you use a second reader on one set of  
10 films, and so on.

11           There has been a paper in the literature recently--  
12 -Dr. Kopans was one of the authors--modeling what would  
13 happen if you did mammograms more frequently like every six  
14 months or every three months, and so on, and the sensitivity  
15 goes tremendously close to 100 as you get down towards every  
16 three months.

17           One comment I would make in answer to something  
18 that was said earlier today that the idea of double exposing  
19 women in these trials may not be ethical. If you take into  
20 account what I just said, there is a definite benefit to  
21 that risk of everybody having both an analogue and a digital  
22 mammogram at the same time because they are read and they  
23 do, in this kind of a trial, determine the woman's follow up  
24 and care.

25           [Slide.]

1           The second issue that I want to discuss is what  
2 error bars should go in the labeling.

3           [Slide.]

4           Now I, like Dr. Bushar, am showing only the data  
5 from reader study No. 2. There are the three indices that  
6 we feel are important here; that is, the area under the ROC  
7 curves for FFDM, which means full-field digital mammography,  
a and this is screen-film mammography sensitivity and  
9 specificity with regard to the dichotomous decision, does  
10 this woman need to come back for anything based on these  
11 four views as though, as Dr. Hendrick explained, being  
12 looked at as though this was a screening mammogram with no  
13 other information.

14           One can deal with sensitivity and specificity at  
15 later stages, as we will see in a minute. Almost half of  
16 the mammograms were read as BIRADS 0 which means "needs  
17 further imaging" to the point where I can't even make a  
18 decision whether to assign this a BIRADS 1, 2, 3 or 5. Once  
19 you do that further imaging and you make that determination,  
20 then you could do sensitivity at other cutpoints; for  
21 example, at the BIRADS 3 cutpoint which would be where a  
22 woman can either come back next year, there is nothing wrong  
23 at all, or if they are 3 or above, that means, well, there  
24 is low probability of malignancy but I want to see here  
25 again in six months and repeat the mammogram.

1           That is one possible cutpoint. The next  
2 reasonable cutpoint would be at the BIRADS 4 level which  
3 would make the decision between, this woman I am  
4 recommending for a biopsy, versus, she doesn't need a  
5 biopsy. So sensitivity and specificity, in this particular  
6 study, the only thing measured was at the original four-view  
7 that was treated as though it were a screening study and,  
a therefore, was separated just into negative and positive  
9 with respect to, does anything else need to be done even as  
10 minor as having her come back next Tuesday for a repeat,  
11 say, spot magnification view.

12           Now, given that, the ROC area for digital was  
13 0.758 and 0.767 for film screen which gives a very small  
14 difference. We have seen these figures before. The error  
15 bars on this--I have highlighted the worst case. This is  
16 what we feel needs to go into the labeling. Based on the  
17 data here, and the numbers of women involved, the numbers of  
18 cancers, the numbers of noncancers, this point estimate for  
19 the difference which makes it look trivial actually could be  
20 as bad as 0.07 less or it could be as good as 0.05 better  
21 for digital.

22           A wide range like that means that, of course, a  
23 point estimate can be very misleading. For the  
24 nonstatistician, you would like to ignore error bars and the  
25 rest of that complication and just look at point estimates

1 but the fact of the matter is that this information is  
2 compatible and, even here, is an arbitrary cutpoint. But it  
3 could be compatible with the usual standard of significance  
4 with an area under the digital ROC curve which is as much as  
5 0.07 below that of the ROC curve for screen film.

6 With sensitivity, if you look at the point  
7 estimates, digital was 68.18, the screen film, 69.55  
a sensitivity with a difference of -1.3 which looks trivial  
9 but, again, because of small numbers--sensitivity always  
10 deals with the cancers and specificity always deals with the  
11 noncancers, in this case disease or non-disease--the small  
12 number of cancers, only 44 cancers in reader study No. 2,  
13 gives a fairly wide range.

14 What that means is that, while these point  
15 estimates look close enough to say, "oh, well, that is no  
16 problem; they are obviously equivalent," the fact of the  
17 matter is they are compatible with a sensitivity for digital  
18 that is as much as almost 10 percent lower than that of  
19 screen film.

20 Now, one has only to think about the fact that  
21 25 million women are screened each year in the United States  
22 with about 180,000 cancers found in the last few years,  
23 anyway, each year, and 10 percent smaller sensitivity can  
24 mean a lot of cancers missed.

25 On the other hand, of course, it is also

1 compatible with digitals possibly being 7 percent higher.  
2 So anywhere in between there, the fact is, we just don't  
3 know, based on these figures and bear that in mind as we go  
4 on to the next topic which will be the postmarket study.

5           With regard to specificity, again, digital and  
6 analogue were very close, 1.89, although, in this case,  
7 digital was better. They had a better specificity; that is,  
8 they had a lower recall rate for the noncancers by a small  
9 amount. Here, the worst-case scenario is that it could have  
10 had a specificity only 0.58 less than that of the analogue.  
11 So this is, actually, a better range.

12           [Slide.]

13           Finally, in talking about the postapproval study  
14 proposal, the first thing I want to talk about is, then,  
15 just to summarize, why is it that the FDA is requiring a  
16 postapproval study on a PMA such as this one?

17           There are two broad reasons. One is that the  
18 modest size of the study in this PMA which, as I just showed  
19 you, gives fairly broad confidence intervals on the  
20 difference between digital and screen film, in particular  
21 with respect to ROC area and sensitivity which are two very  
22 important issues, but, secondly, and possibly even more  
23 important, a study that is performed in part on a diagnostic  
24 cohort, and this was primarily a diagnostic cohort, although  
25 the cancers were almost equally drawn from the screening

1 study, a separate screening study and a diagnostic study,  
2 introduces a potential bias, let's say, of case mix towards  
3 larger, more advanced cancers.

4 For example, women who come to a diagnostic clinic  
5 come for one of two broad reasons, either because they have  
6 some symptom, such as a palpable lump which, I think, is  
7 most of them, maybe a nipple discharge, something like that,  
a but a large number of them have a palpable lump.

9 In order for a lump to be palpable, it already has  
10 to be about a 1-centimeter size cancer and that already  
11 takes it out of the range of the kinds of things that  
12 mammography can be the first to detect down at the 1 to 2  
13 millimeter range. So there is a bias towards larger, more  
14 advanced cancers.

15 It may not test digital's ability with respect to  
16 the smaller, earlier, more curable cancers, although I will  
17 show in the data, in a minute, that it was surprisingly well  
18 distributed.

19 [Slide.]

20 First of all, let's just talk about the  
21 distribution of the cancers with regard to the BIRADS  
22 categories--not the cancers, but all of them. I am just  
23 going to base this on the analogue. It would be very  
24 similar if I did it just on the digital readings.

25 This is the BIRADS category, 1, 2, 3, 4, 5, 0.

1 The first column here is the distribution with regards to  
2 these BIRADS categories of the analogue mammograms in the  
3 PMA by their category. What this means is that 50 percent  
4 of them were in the BIRADS 1 and 2 category. 47 percent,  
5 almost the other half, were in the BIRADS 0 category which I  
6 mentioned a minute ago. And there was a scattering, a small  
7 number, in the BIRADS 3, 4 and 5 category.

a Just to give you a sense in a screening population  
9 to show the difference between what is partially a  
10 diagnostic population and a screening population, just to  
11 get a sense of a little bias here, the kinds of figures--  
12 there is, perhaps, a wider range than I have given here but  
13 these is fairly representative figures from a couple of  
14 papers that, in a screening population, you can expect that  
15 about 90 to 93 percent, somewhere in that range, will be  
16 BIRADS 1s and 2s.

17 The initial assignation of BIRADS 0s will range,  
18 it depends on the center--some go as far as 5 percent,  
19 perhaps, some as high as 15 percent, but somewhere in the 8  
20 to 12 range is what you will get in a screening population.  
21 But those will, ultimately, once the woman does come back  
22 for further imaging, whether it be extra mammographic views  
23 and/or ultrasound, every one of them will be redistributed  
24 among the 1, 2, 3, 4, 5 category.

25 So these numbers actually represent that final

1 after they have been through the added evaluation. You get  
2 figures for BIRADS 3 that is on the order of 3 to 4 percent  
3 of the total. For BIRADS 4, about another 3 to 4 percent  
4 and for BIRADS 5, maybe 0.3, 0.5 percent, somewhere in  
5 there. This just gives you a flavor for the figures.

6 You can see that the BIRADS 5 category, even in  
7 the study as it was is fairly close to the range that you  
8 will get. The BIRADS 1 and 2 category was only about half  
9 and the BIRADS 3 and 4, which could be considered the more  
10 difficult mammographic cases--these are the subtle ones  
11 where, gee, you don't know quite what to do. You are always  
12 sitting there thinking, do I need her to come back in six  
13 months or should I recommend a biopsy.

14 A lot of women that you recommend a biopsy on, you  
15 know have a fairly low suspicion of probability of  
16 malignancy but it is high enough that you really don't want  
17 to risk waiting six months. These are the more difficult  
18 cases. You can see that they are underrepresented in this  
19 partially diagnostic cohort by a factor of maybe 3 or 4.

20 So this is one of the biases that is introduced by  
21 using a partially diagnostic cohort which is why we want to  
22 see, in a postmarketing study, a study done in a screening  
23 population.

24 [Slide.]

25 We actually are able to break down the 44 cancers

1 that were included in reader study No. 2 into those that  
2 were derived from the diagnostic cohort which was 24 of them  
3 and those that were derived from the screening cohort which  
4 was 20 of them with respect to size.

5 As you can see, the numbers here are small, but  
6 two-thirds of the diagnostic cancers were greater than a  
7 centimeter in size and only 45 percent of the screening  
a cohort were over 1 centimeter.

9 These numbers, in fact, the difference here is not  
10 statistically significant if you do the appropriate tests.  
11 The error bars are very large because the numbers are small.  
12 It just gives you a flavor of the kind of trend that one  
13 might reasonably expect.

14 [Slide.]

15 Another way to break these down is by the stage of  
16 cancer. Ed Hendrick showed you the figures that actually  
17 combined these two. He gave you the sum of the second and  
18 third row. If you break it out into the diagnostic cohort  
19 and the screening cohort, you can see, again, and I will  
20 preface this by saying, again, there is no statistical  
21 significance here in the difference between this second row  
22 and the third, again because the figures are small, the  
23 numbers are small.

24 But you get, again, a sense of the trend one would  
25 reasonably expect and that is if you look at stage III and

1 IV, for example, you have got about 12 percent of the  
2 cancers here and, in the screening cohort, you have only got  
3 about 5 percent. Again, and I don't want to make too much  
4 of this, I am just trying to illustrate the fact that in a  
5 diagnostic cohort you might expect that kind of trend, that  
6 there would be a shift toward the higher stage cancers away  
7 from the lower stage, although if you look at the curable 0  
a and I stages, they are 58 percent of the diagnostic,  
9 65 percent in the screening cohort, not very different.

10 As a matter of fact, there is a surprising  
11 similarity here. One would expect even more of a bias in a  
12 diagnostic cohort, but, again, the numbers are small and,  
13 again, this is one reason why we would like to see this in a  
14 screening population.

15 Now, I just want to make one other point. Ed  
16 Hendrick showed you the figures. If you just looked at the  
17 sensitivity, and I don't have a slide on this because I  
18 haven't seen those figures before--if you just look at the  
19 sensitivity on the stage 0 and I's, he showed a sensitivity  
20 for digital that was about twelve points, eleven or twelve  
21 points, higher for the digital than for the analogue.

22 Certainly, those are the most important cancers  
23 for mammography to find. If you are finding the 0s and Is,  
24 you are able to cure. If you are finding the 111s and IVs,  
25 the cure rate is much, much lower. So what we would like to

1 see, and he pointed out, is that the AHCPH, the Agency for  
2 Health Care Policy Research, likes to recommend that you  
3 like to see at least 50 percent of your cancers in these two  
4 lowest stages in any good screening study.

5 In fact, this was exceeded in this diagnostic  
6 cohort, a little more so in the screening cohort, but that  
7 is still to the good. But the point is that the numbers  
8 here are very small, but to see 12 percentage points higher  
9 if we didn't see the error bars there, again, this is the  
10 question that we have; the error bars may be very broad and  
11 we don't know, while that point estimate may be encouraging,  
12 again point estimates can always be misleading unless you  
13 have much tighter error bars.

14 [Slide.]

15 Finally, the proposed study design by the company  
16 in broad outline involves a screening population, as I have  
17 said is necessary. They do propose to double expose every  
18 subject to both analogue and digital mammography. This is  
19 very important to avoid a selection bias. Some studies have  
20 enriched by exposing everybody to analogue and then taking  
21 all of the say, BIRADS 4s and 5s, or even 3s, 4s and 5s, and  
22 then double expose those and only take a random subselection  
23 of the 1s and 2s which, you will remember, was 90 to  
24 93 percent, to sort of match that number.

25 When you do that, you don't give digital a chance

1 to show that it can pick up the small cancers that the  
2 analogue happened to miss and assigned to BIRADS 1 and 2.  
3 So, by exposing every subject, you do avoid that kind of  
4 selection bias.

5 Their analysis, they propose to show  
6 noninferiority again in these three important indices--that  
7 is, ROC area, sensitivity and specificity. Of course, we  
8 will have to discuss further with them the question of at  
9 which cutpoints.

10 Now, I have hard copy written down here because  
11 that was, in fact, what was proposed in the hard copy of the  
12 PMA that we had although the company has already mentioned  
13 today and, in discussions with us a couple of weeks ago, or  
14 last week, I think, we have discussed the idea that a side-  
15 by-side comparison analysis of hard copy to soft copy, if  
16 that is approved ahead of time, then there is no reason not  
17 to use soft copy in the postapproval study.

18 Finally, the propose to analyze all of the cancers  
19 that they find. Again, these are ground-truth cancers,  
20 cancers based on biopsy or a cancer turning up a year later  
21 through a year of follow up and only a random selection of  
22 the noncancers. Now, that does not introduce the selection  
23 bias that I described up here because you have already got  
24 the ground truth and you are selecting not on how the  
25 analogue looked but whether the woman really has cancer or

1 doesn't have cancer.

2           While there are some details yet to be worked out,  
3 in broad outline, this is an acceptable study design.

4           Thank you.

5           DR. GARRA: Thank you.

6           It is seven minutes to 12:00. I guess we can  
7 entertain--if there are any clarification points that need  
8 to be made from the last several presentations, we can take  
9 a couple of questions on those. We will hold questions that  
10 deal with the substantial nature of the PMA until the  
11 discussion session after lunch.

12           Okay. Not seeing any panel members that want to  
13 ask any questions at this point, then what we will do is  
14 break for lunch at this point. We will do an hour for lunch  
15 and plan to be back here at about five minutes to 1:00.

16           Thank you very much.

17           [Whereupon, at 11:55 a.m., the proceedings were  
18 recessed to be resumed at 12:55 p.m.]

## A F T E R N O O N   S E S S I O N

[1:05 p.m.]

DR. GARRA: I would like to call the meeting back to order. I would remind the observers of the meeting that, while this portion of the meeting is open to public observation, public attendees may not participate unless specifically requested by the Chair.

We will continue the meeting with the panel's discussion of the PMA that will be led by Dr. Destouet. Judy, are you all set?

**Panel Discussion**

DR. DESTOUE: I want to thank the manufacturer and Dr. Hendrick for excellent presentations this morning as well as the FDA. With that, I have a couple of questions for you, Dr. Hendrick, if you will approach the podium.

In the design of the study, the manufacturer chose to select diagnostic mammography patients enriched with a number of cancers from previous screening programs and tell the readers that they had to read them as though they were screening mammograms. It seems that there is, indeed, certainly an inherent bias toward probably larger lesions in that population because there would be a certain number of patients with palpable lesions who you would not expect to have in the screening population.

I just wonder why did you choose that as opposed

1 to having a screening population as one of the two series of  
2 studies?

3 DR. HENDRICK: Primarily because we set up the  
4 patient recruitment for this study based on the guidance the  
5 FDA put out in '96 which was based on an equivalence study  
6 in the diagnostic cohort. So we began with that approach.  
7 And then, when the meeting occurred in August of '98, it was  
8 clear that an equivalence approach wasn't feasible and it  
9 was switched to a noninferiority approach. We didn't want  
10 to throw away all the patients that we had recruited.

11 In response to your mention about it being more  
12 biased toward larger lesions, that is what we would have  
13 expected from a strictly diagnostic cohort but, in fact, the  
14 stage and size information suggests that it was remarkably  
15 close to a screening cohort in that distribution, probably  
16 somewhere in between but close to a screening cohort in  
17 terms of stage of detected cancers, at least.

18 DR. DESTOUET: The recall rate of 44 percent and  
19 higher clearly was significantly much higher than one would  
20 see in a screening population.

21 DR. HENDRICK: Absolutely.

22 DR. DESTOUET: Where your recall rate would  
23 approach 10 to 15 percent. Do you have any data to show  
24 that the lesions that were recalled from screen film were  
25 the same lesions that were recalled on the full-field

1 digital images?

2 DR. HENDRICK: We have the data in terms of the  
3 two-by-two tables for recall rates that are in the documents  
4 that you have. If I get my document, I can point to the  
5 table.

6 DR. DESTOUET: Okay.

7 DR. HENDRICK: It is table No. 24.

8 DR. DESTOUET: What page?

9 DR. HENDRICK: It is page 0108 in the larger  
10 printed numerals. It is table 24 in the study report. If  
11 you look at, for instance, the noncancer cases, and this is  
12 the composite results of five readers on 625 cases, so, out  
13 of 3125 readings, there were 936 cases or readings that were  
14 read positive on both and a total of about 800 that were  
15 read positive by one but not the other.

16 So there was a considerable amount of disagreement  
17 between the two modalities. That sort of is an indication  
18 of why the equivalence approach, as originally formulated by  
19 the FDA, was not achievable. There was agreement on 1150  
20 being negative on both.

21 DR. DESTOUET: You also mentioned that there were  
22 lesion markers in some cases and you had to eliminate those  
23 cases because of "lesion markers." I didn't understand.

24 DR. HENDRICK: Oh; it was simply when you put the  
25 film-screen and digital cases side-by-side, some

1 institutions marked lesions with PVs on the films if they  
2 were palpable lesions and some institutions--most  
3 institutions do that, but what we found is, in a few cases,  
4 there was a marker visible in one modality that wasn't  
5 visible in the other.

6           So we eliminated those cases where there might be  
7 more of a suggestion of a finding in one modality than  
8 another. If the lesion markers were equivalent in the two,  
9 we kept them. But it was just to make the study as pure as  
10 possible in terms of avoiding any kind of bias toward one  
11 modality or the other.

12           DR. DESTOUET: Ed, as you look at the technology,  
13 do you feel that the difference in position that has been  
14 described, that can, indeed, obscure some lesions, whether  
15 they be malignant or benign, is such that it would be  
16 difficult to really compare the two modalities in any kind  
17 of study?

18           DR. HENDRICK: I agree with the speakers that have  
19 gone before that have pointed to the reader variability as  
20 being a big issue. The positioning variability, I think, is  
21 a bigger issue than we have given it credit for, not so much  
22 in that you do see a lesion clearly in one positioning and  
23 in the same positioning with the other modality you don't  
24 see it clearly. It is the little signs that throw it from  
25 being, say, a 1 or 2, usually a 2, into being something that

1 would be called back, a slight sign of spiculation,  
2 something like that that is visible in one position and not  
3 visible on the other modality in the corresponding position.

4           There is no reason to believe that you would get  
5 different results even if you were using a single modality  
6 and repositioned the patient. So I do think that has an  
7 effect. And, certainly, the reader variability has an  
8 effect on not being able to exactly compare these modalities  
9 without those sources of variability.

10           It just makes it much harder to do reader studies  
11 because of that.

12           DR. DESTOUET: Do you believe that the flexibility  
13 that we will have with manipulating window settings with  
14 full-field digital will, indeed, offset some of the problems  
15 that we are seeing with, perhaps, changes of position? Is  
16 there anything in this new technology that will help us to  
17 eliminate women having to come back for call-back?

18           DR. HENDRICK: Yes; the data that we have so far  
19 that you are looking at are all, obviously, hard-copy  
20 interpretations of full-field digital. The data that you  
21 don't have in front of you are the data on soft-copy  
22 interpretations of full-field digital. My experience with  
23 that comes from data in the Army study at Colorado and U.  
24 Mass. There we also see a significantly lower recall rate  
25 with digital primarily because the radiologists do have the

1 flexibility of the soft-copy display to window through the  
2 lesions and they are not stuck with sort of the opaque  
3 glandular tissue that you sometimes have on film-screen  
4 mammograms.

5           You can window through and better visualize the  
6 extent of the lesion than you can on a fixed hard copy,  
7 whether it is on digital or film screen. So I think that  
8 will offer some real advantages if radiologists are able to  
9 do soft-copy review of digital mammograms.

10           DR. DESTOUET: I want to open it to the panel now.  
11 I have some further questions but are there any questions  
12 from the panel?

13           DR. BERG: I have a question that is kind of a  
14 two-parter. I think one of the issues, obviously, that will  
15 be the subject of additional discussions as we get other  
16 applications from other manufacturers will be the issue of  
17 the resolution. I know G.E. has shown the 0.1 millimeter,  
18 Obviously, there are malignant calcifications, at least,  
19 that might be smaller than that limiting resolution.

20           So there is sort of a fundamental question out  
21 there, at least in the mind of many of us, until we have  
22 seen enough of these very subtle lesions on digital to  
23 really be satisfied.

24           I noticed, in looking--I will let you answer that  
25 part, but I wanted to address the ROC curve from reader

1 study No. 1. Looking at the middle ground, if you will, in  
2 what would sort of what would be BIRADS Category 3 and 4  
3 type lesions, it looked like full-field digital did worse  
4 than screen film.

5 I guess one of the possible interpretations of  
6 that, and I don't know that it is even was statistically  
7 significant if you just looked at that subset--but one of  
8 the interpretations could be that you are not seeing some of  
9 the very tiniest calcifications that might push you to be  
10 more concerned or that you are not seeing the border  
11 characteristics of a mass lesion as being clearly  
12 indistinctly marginated as opposed to being partially  
13 obscured.

14 Some of these issues that are right on the fringes  
15 where I think the only real remaining concern that some of  
16 us have, I was wondering if you could address. Also, then,  
17 I didn't see that difference in reader study No. 2 so I was  
18 wondering if the same readers learned, if you will, or if  
19 they were even different readers in study 2 versus study 1.

20 DR. HENDRICK: Right. They were different readers  
21 in study 2 versus study 1. I think you are right in seeing  
22 that in the places when the curves do differ, it is in the  
23 2 percent, 3 percent probability of cancer range. The low  
24 probability--and there were cases where readers, I think, in  
25 that study were reading the digital mammograms with less

1 confidence of what they were seeing which, in some cases,  
2 turned out to be cancer than the screen-film mammograms.

3           Partly, I think that was an effect of the readers  
4 not all being trained to the same level of familiarity with  
5 digital. Some of the readers started digital cold,  
6 basically. We basically had readers at two institutions as  
7 primary readers. Some had experience through reading Army  
8 cases in the Colorado/U. Mass Army Study. And then there  
9 were two other readers who didn't have that experience.

10           I think a lot of the differences in the curves,  
11 especially in that low probability of cancer range come from  
12 those readers that didn't have experience in the Army study.  
13 When we did study No. 2, we got everyone to the same level  
14 of experience with digital and we made sure that they were  
15 all reading the cases as if they were screening cases.

16           The two readers that we had that weren't in the  
17 Army study and reader study No. 1 were really reading them  
18 more as if they were diagnostic cases.

19           DR. BERG: I think that I certainly have concern  
20 about that issue just because a lot of the cancers that we  
21 see are not spiculated masses or obvious tracking branching  
22 calcifications. Many of them are in that middle ground. I  
23 think one of the issues that we all have to wrestle with a  
24 little bit is what kind of training we are going to require  
25 of people before they start doing this just so that we are

1 not misinterpreting those subtle lesions.

2 DR. HENDRICK: Right. But if I could address the  
3 first thing you brought up about were these the cases that,  
4 for instance, might have had subtle calcifications that  
5 digital didn't see and screen film did see. Those would  
6 have showed up in the side-by-side analysis specific for  
7 calcifications or specific for other lesion types and they  
8 didn't.

9 The scores were virtually identical even for those  
10 different lesion subtypes. So I really think, based on the  
11 data that we have, it was a reader issue in study No. 1 and  
12 not a shortcoming of the modality in either study.

13 DR. BERG: Do you have any specific information  
14 on, like, amorphous calcifications, the tiniest ones, side-  
15 by-side, or any breakdown on future analysis including  
16 benign lesions in terms of conspicuity, some of these subtle  
17 ones? It is hard to answer, from what I have seen and hear,  
18 one way or the other.

19 DR. HENDRICK: We don't have data on the smallest  
20 calcifications detected, but I just would want to make one  
21 point which is that calcifications tend to be fairly high  
22 contrast relative to rest of the breast. Even if they are  
23 smaller than 100 microns, they can be detected in that 100-  
24 micron pixel. Where you may have a limit is in breaking it  
25 apart into more than one calcification, but you should

1 still, with these high-contrast objects, detect things  
2 smaller than 100 microns. You just may not be able to have  
3 a good idea about the shape of the calcifications from when  
4 they are that small.

5 DR. BERG: Right.

6 DR. HENDRICK: I think there is another clinically  
7 interesting question which is how small calcifications do  
8 you really depend on detecting with screen film. If you  
9 compare specimen radiographs that are taken after the  
10 excision of the sample, you can see much, much smaller  
11 calcifications in the lesion than you tend to see on the  
12 screen-film mammograms or the digital mammograms.

13 So the question is is it making any diagnostic  
14 difference. Our data to date support that there isn't a  
15 difference, but I think that needs to be studied in some  
16 specific studies that look at calcifications as well.

17 DR. ROMILLY-HARPER: Excuse my voice, but in, I  
18 think, the last study, the laser printer--actually, the  
19 quality of the digital mammograms for the study were  
20 produced at one institution, as far as you ship them out to  
21 one place and then--correct me if I am wrong--

22 DR. HENDRICK: There were actually two  
23 institutions, Colorado and University of Massachusetts.

24 DR. ROMILLY-HARPER: But one person was in charge  
25 in printing out the digital studies for review; is that

1 correct?

2 DR. HENDRICK: There was one person at University  
3 of Massachusetts. Actually several people at Colorado  
4 printed them out.

5 DR. ROMILLY-HARPER: Are we going to have--if this  
6 is approved, how do you plan to do that for the multiple  
7 institutions? Do you have set criteria for the copies, how  
8 the copies are going to be made on the laser printers?

9 DR. HENDRICK: Yes; we have actually learned a lot  
10 from doing these studies and printing them out on hard copy.  
11 There will be criteria for how to print them out. For  
12 example, one of the things that we have learned is that the  
13 way laser printers are set up, and they are based on other  
14 modalities, typically is that the sort of middle range of  
15 signal--you window and level it on the monitor and then the  
16 median grey scale on the monitor on a laser camera gets  
17 printed out at an optical density of around 1.0.

18 That means that more glandular tissues would get  
19 printed out at even lower optical densities on the film. We  
20 have learned, in doing this, that that makes no sense for  
21 digital mammograms, just like you wouldn't want to take a  
22 film-screen mammogram and have the average optical density  
23 of the breast be at 1.0 and have all the glandular tissues  
24 be at lighter grey scales on the image.

25 So one of the things that we have learned is that

1 you need to set the median density in the laser printers to  
2 a higher level so that you have more signal values to work  
3 with in the most important part of the breast which is in  
4 the glandular parts of the tissue and in the grey scales  
5 that would represent cancers in the breast.

6           So there are guidelines that need to be put in  
7 place for people doing this kind of printing and it also  
8 depends on the setup of the printer with the monitors from  
9 which the images are printed. So you need to have the  
10 printed images looking like they look on the monitors that  
11 are being printed and to have advice to the people printing  
12 the images.

13           DR. ROMILLY-HARPER: That means that, as they  
14 purchase the unit, they will have dedicated laser printers  
15 for the digital mammography and not the typical laser  
16 printers that you see in a department. In other words, the  
17 unit will be sold with the printers.

18           DR. HENDRICK: In the initial digital-mammography  
19 systems that are out there, they have to use hard copy, so  
20 they have to be equipped with these printers.

21           This is Amy Sitzler who works with G.E. Medical  
22 Systems. She has some comments, if she may, about the QC on  
23 printed images.

24           MS. SITZLER: I am the Program Manager for the  
25 Digital Mammography Programs at G.E. There are two printers

1 which are qualified to be used with the system, and only  
2 those two so far. So we don't just allow images to be  
3 printed anywhere.

4 We have been working with the same QC procedures  
5 as you would be used to with MQSA so that you would do the  
6 same qualifications with your printer for the digital system  
7 as you would be used to doing with your screen-film system.  
8 So you should have the same daily kind of check that is on  
9 the QC menu like you would be used to in your normal film-  
10 screen system.

11 DR. ROMILLY-HARPER: Thank you.

12 DR. DESTOUET: Actually, I have a question for  
13 you. Is it anticipated that there will be one single  
14 setting, then, for the hard copy as opposed to what we have  
15 now with CT where you may have a couple of different window  
16 levels and settings?

17 Can we, indeed, produce a single hard-copy image  
18 that will give us the latitude as well as the resolution  
19 that we need?

20 MS. SITZLER: There is the capability. Because we  
21 have a lot of experience with a lot of images, we have tuned  
22 the algorithm for the automatic setting of the contrast so  
23 that the image will appear at a certain contrast setting  
24 which is selected automatically based on that breast.

25 It can be printed automatically based on that

1 setting. Of course, the technologist always has the  
2 opportunity to make her own adjustments, but we have  
3 actually designed an algorithm that allows the optimal  
4 setting immediately on presentation of the image, and that  
5 is automatically sent to the printer.

6 DR. MALCOLM: I just had a question. I looked  
7 under the training program--we were talking about, as we  
8 always talk about in issues like this, readability and  
9 variations. It was unclear to me the QA or QC program for  
10 the radiologist in making sure that he or she has the proper  
11 tools to understand the digital radiography. I wasn't quite  
12 clear. I didn't see much of that in this proposal.

13 What I am saying is you are not going to sell the  
14 units and say, okay, go out here and just start using it.  
15 What is the plan?

16 DR. HENDRICK: MQSA requires eight hours of  
17 training specific for radiologists on digital mammography.  
18 One of the ways to satisfy that is the plan to set up a  
19 training facility actually at Northwestern to provide those  
20 eight hours of training to the radiologist. Part of it  
21 would be--a large component of it, actually, would be  
22 working with the radiologists there who have experience  
23 reading digital mammograms and looking at the presentation  
24 of digital mammograms with the thickness equalization  
25 applied both on film and on soft-copy display so that they

1 are familiar with the kind of presentation.

2 It is not that it is that different from film  
3 screen, but they need to see an adequate number of cases  
4 where there are subtle cancers presented with digital  
5 images.

6 The artifacts are different. One of the great  
7 things about digital is you eliminate the artifacts due to  
8 the processor on film-screen mammograms, so those artifacts  
9 are basically eliminated. There are some other artifacts  
10 that come if the digital detector isn't performing properly  
11 that need to be recognized.

12 There are artifacts that come if the printing  
13 isn't occurring properly that need to be recognized. So the  
14 training would include recognizing those kinds of features  
15 in the image and then understanding the process by which the  
16 images is created and produced.

17 So it is to give them a broad picture but to focus  
18 on interpretation of both hard-copy and soft-copy digital  
19 mammograms. I don't know if I have given you enough  
20 information or not.

21 I don't think Northwestern will be unique in  
22 offering the training of radiologists in this. There also  
23 needs to be training for the physicists and technologists  
24 that will have to be provided as well.

25 DR. DESTOUET: Dr. Harms, do you have any

1 questions?

2 DR. HARMS: No; not at this time.

3 DR. GARRA: I have a couple. The first question I  
4 would have, in study 2, you talked about testing nine  
5 radiologists and picking five of those.

6 DR. HENDRICK: Yes.

7 DR. GARRA: Could you tell us a little bit about  
8 what selection criteria you used for that?

9 DR. HENDRICK: One of the things we learned in our  
10 first reader study was that there was a wide range of  
11 sensitivity and specificity among the different readers.  
12 Part of it, actually, had to do with this difference of two  
13 reviewers reading the images more as diagnostic studies and  
14 others as screening studies.

15 What was done is to--Craig Beam has developed a  
16 test set of images. In fact, the ROC data were presented  
17 here from his test set and there were something like 108  
18 datapoints. So we used his test set to test these nine  
19 readers.

20 The goal was not to take the best five out of  
21 those nine but to find readers that had a similar sort of  
22 range. It was really to eliminate those that were not good  
23 readers of mammograms at all. We actually, I think, threw  
24 out one reader at the very top of the ROC scale and three  
25 readers at the bottom of the ROC scale to get the five that

1 we picked, in terms of ROC areas.

2 DR. GARRA: Another question I had was you asked  
3 the readers to rate the probability of cancer being present.  
4 I see that on your form.

5 DR. HENDRICK: The form does not mention that they  
6 should not be rating BIRADS categories 1 and 2, yet you  
7 mentioned that in your talk, I believe, earlier. And even  
8 if you do eliminate BIRADS 1 and 2, what assurance do you  
9 have--why did you eliminate BIRADS categories 1 and 2?  
10 Because a person classifies something as BIRADS 2 does not  
11 mean they are 100 percent certain.

12 So I am just wondering if you created a little bit  
13 of a bias by excluding those people, the ratings from those  
14 people.

15 DR. HENDRICK: I would appeal to the radiologists  
16 on the panel. Would anyone give something, even a 1 percent  
17 probability, of cancer if you called it a BIRADS 1 or 2?

18 DR. DESTOUET: No.

19 DR. HENDRICK: That was the reason for that.

20 DR. GARRA: Okay. That is what I wanted to know.  
21 Did you get ratings for those categories, though, at all?

22 DR. HENDRICK: In terms of probability of cancers?

23 DR. GARRA: Yes.

24 DR. HENDRICK: Let me ask Karen White who works  
25 with MedTrials to answer that because she collected all

1 these data and I get confused between three studies, these  
2 reader studies and the Army study.

'3 DR. GARRA: When you talk about asking somebody to  
4 make sort of a binary decision, there is a big difference  
5 between getting him to grade on a grading scale versus a  
6 binary decision. People will often make a decision, this is  
7 absolutely not cancer, but when you actually pin me down, it  
8 will probably be something like 98 percent or 99 percent.

9 I think a lot of radiologists, when they think in  
10 terms of categories, 3 or 4 or 5 categories, think in terms  
11 of binary decisions, what am I going to call this. But when  
12 you ask them to really nail down percentages, they might  
13 answer slightly differently.

14 I just wanted to see what your numbers actually  
15 were.

16 MS. WHITE: Karen White. I work with MedTrials.  
17 We were the company that G.E. asked to help with the  
18 monitoring and project management for the collection of the  
19 clinical data.

20 In the first study, the collection of  
21 probabilities of cancers was something that, with the  
22 changes in study design through the different means of the  
23 FDA that evolved. So, in the first study, we only collected  
24 probabilities of cancers for BIRADS 3, 4, 5 and 0. It was  
25 an assumed, and correct me if I am wrong, probability of

1 cancer of 0 for BIRADS 1 and 2.

2 And then, in the second study, is the one where we  
3 did collect. We asked them to give a probability of cancer  
4 for any BIRAD. Part of the instructions to the radiologist  
5 that Dr. Hendrick and Dr. John Lewin also provided to the  
6 radiologist was based on ACR categories of how you should  
7 grade probabilities of cancer, so it was based on ACR BIRADS  
8 recommendations.

9 DR. HENDRICK: So I guess we did collect in reader  
10 study No. 2. I had forgotten that. Is that summarized  
11 anywhere?

12 MS. WHITE: Yes; on page 0165 under the clinical  
13 study, summary No. 2. It is under tab D.

14 DR. HENDRICK: That is the form, but do we have  
15 results? But do we have results? I guess the question is  
16 did anyone who gave it a BIRADS 1 or 2 give it anything  
17 other than a 0 probability of cancer?

18 MS. WHITE: We had a couple, I believe, that were  
19 between 0 and 2 percent.

20 DR. GARRA: I presume that those people did not  
21 figure into your--were they assigned the number they  
22 actually were given or were they assigned 0?

23 DR. HENDRICK: No. In reader study No. 2, the  
24 analysis was done based on what they gave.

25 DR. GARRA: Okay; great. Thank you.

1 DR. DESTOUET: Are there any other questions from  
2 the panel? Dr. Toledano?

3 DR. TOLEDANO: So when you set up the studies, you  
4 made a choice that had great public-health impact. You  
5 chose a delta of 0.05 for your recall but a delta of 0.10  
6 for sensitivity and ROC curve area.

7 Can you explain those choices, what motivated the  
8 difference in the criteria?

9 DR. HENDRICK: Partly, that was motivated by the  
10 understanding that we don't have as good a determination of  
11 sensitivity or ROC-curve area as we do of recall rate due to  
12 the numbers involved in those categories. The categories,  
13 specifically, for sensitivity, you need number of cancer  
14 cases, as you know. And, for ROC curve, the power depends  
15 largely on the number of cancer cases as well.

16 So we recognize that, without doing an immense  
17 study, we wouldn't have the ability to refine the delta as  
18 well as we could for the recall rate.

19 DR. TOLEDANO: So if you were approved and went  
20 into your postmarket study, you would be looking for smaller  
21 deltas.

22 DR. HENDRICK: Yes; the suggestion, based on what  
23 Bob Wagner presented, is the delta on the ROC-curve area  
24 would be closer to--would be; not closer to--would be 0.05.  
25 The study design would be set up to be able to see a

1 difference as small as 0.05.

2 DR. TOLEDANO: Thank you.

3 DR. HENDRICK: In a non-inferiority approach.

4 DR. TOLEDANO: Correct.

5 DR. HARMS: The false negatives would be a patient  
6 that you did not see a lesion on a study and then,  
7 subsequently, found either a lesion on the other study or on  
8 your follow up. How many cases did you have that had false  
9 negatives on both interpretations and that you caught on the  
10 one-year follow up?

11 DR. HENDRICK: That is in one of the tables in the  
12 study report. If you look at, say, study No. 2--table 26 on  
13 page 0110. This is, again, five readers reading the 44  
14 cancer cases, so there are 220 readings. There were  
15 36 readings and this table only includes cancers so there  
16 were 36 readings that were negative on both modalities.

17 DR. HARMS: But that doesn't say that they were  
18 false negatives.

19 DR. HENDRICK: Yes; those were false negatives,  
20 In fact, if you want the false negatives for screen film,  
21 you sum the column that was read negative on screen film.  
22 If you want the total number of false negatives for digital,  
23 you would sum the row across the bottom as the total number  
24 of false negatives for digital.

25 MS. PETERS: This is just a little different

1 focus. I notice that the device is being used in a number  
2 of different countries, or other countries. Do you have any  
3 data, or any information, from those countries about how  
4 they are experiencing the equipment?

5 DR. HENDRICK: I think I need to defer to the G.E.  
6 people on this one because no one lets me out of this  
7 country.

8 MS. SITZLER: Could you restate your question? I  
9 am not sure I understood exactly what--

10 MS. PETERS: Just is there any information or any  
11 data from any of the other countries that are using the  
12 device.

13 MS. SITZLER: So far, the device is installed in  
14 ten different sites in Europe and the data is--we haven't  
15 done this kind of detailed analysis, but the data is  
16 consistent with what we found already in this study.

17 DR. SMATHERS: A follow up on that. You say it is  
18 used in ten other sites. Are they using soft copy readout  
19 or are they constrained to this hard copy readout that has  
20 been proposed here?

21 MS. SITZLER: They are not constrained and they do  
22 both. It seems to be a site preference and a learning  
23 curve. But they are very much using soft copy.

24 DR. SMATHERS: Can I pursue this? Ed, I am a  
25 little concerned that you are essentially releasing this

1 device in what I see as its least favorable light. I think  
2 hard-copy readout puts it in the worst-case scenario as far  
3 as its capabilities go. I guess I am troubled by the fact  
4 that you are not going to put soft copy with it initially  
5 because of the greater flexibility in windowing and so forth  
6 that would give the radiologist a look at a given mammogram.

7 I would like to have some insight as to why you  
8 chose that other--and statistically what you did made it  
9 easy for the statisticians, but actually I don't think it  
10 makes good medical sense.

11 DR. HENDRICK: No; that wasn't the main reason.  
12 The main reason was based on earlier advice from the FDA,  
13 specifically the guidance document that, in writing, said  
14 these proposals--the digital mammograms have to be done in  
15 hard copy. Part of the concern I think they had justifying  
16 that point was that they wouldn't have a record of what the  
17 radiologist looked at in a soft-copy display of the digital  
18 images.

19 If hard copy were used, they would at least have a  
20 record that they could go back and look at to say, this is  
21 the way the image was displayed to make that interpretation.

22 I agree with you that the true flexibility of  
23 digital and the true benefit of digital is primarily  
24 realized in a soft-copy display of the images. I think the  
25 plan would be to move very rapidly after approval of digital

1 and hard copy to proceed to this comparison study of hard  
2 copy and soft copy to make sure that digital was available  
3 to radiologists with soft-copy interpretation.

4 Scott, do you want to--

5 MR. DONNELLY: I think that is exactly right, Dr.  
6 Smathers. The genesis of the study originally, since it was  
7 initially conceived as an equivalency, meant that we had to  
8 take the digital and turn it into an the equivalent medium  
9 in order to have a fair equivalency study and not to have  
10 the media be the difference between the studies, to  
11 eliminate that.

12 But I think you are absolutely right. In fact, a  
13 question earlier about window leveling and all the various  
14 techniques which you would expect today in doing, say, a CR  
15 or mR review, to lose those degrees of freedom in a  
16 mammogram exam certainly takes the digital and, to some  
17 degree, levels the playing field, if you will, with hard-  
1 8 copy review to conventional film screen.

19 That is why we have proposed that the first thing  
20 we want to do is do the soft-copy amendment to the PMA, get  
21 that passed, before we proceed with the broader post-  
22 clinical trials because I think, in order to really fairly  
23 compare and see the effectiveness of the device, it is going  
24 to be much more clear in a soft-copy environment than a hard  
25 copy.

1 I think, however, what we have shown is that, in a  
2 hard-copy environment, it is at least reaching the same  
3 levels, at least as the clinical data showing the same  
4 levels, of effectiveness as a film screen. But we would  
5 also expect it to be much better in soft copy.

6 DR. TOLEDANO: More on the public-health  
7 questions. In the request for expedited review, G.E. notes  
8 that we would expect wider patient acceptance because there  
9 would be shorter exam times. Also, I notice that there  
10 might be a decreased need for additional magnification  
11 views.

12 In light of the fact that the machines and the  
13 systems are being used in other countries, has that been  
14 their experience?

15 MR. DONNELLY: If I could comment on the other  
16 country installations. We have ten sites. The product has  
17 been in production in non-U.S. countries for a very short  
18 period of time so I think that, in all fairness, at this  
19 point, that we would say that we have any statistically  
20 relevant data from those sites would be presumptuous. So it  
21 is installed in other countries where they have already  
22 passed the regulations, but I don't think I would use that  
23 data for purposes for our approval at this time.

24 DR. TOLEDANO: What about anecdotal data from your  
25 previous studies in the states? Still just anecdotal?

1 MR. DONNELLY: Again, I think, at that point, we  
2 would probably prefer to call on radiologists that have  
3 actually been using it, some of whom have used it in the  
4 soft-copy evaluation review. Anecdotally, we have certainly  
5 had very positive feedback but I think I would have to defer  
6 to the radiologists that have actually used it to make a  
7 fair assessment.

8 DR. TOLEDANO: Thank you.

9 DR. HENDRICK: Part of your question was about the  
10 speed of doing digital acquisitions. One of the steps that  
11 is eliminated is that the technologist taking the film-  
12 screen cassette after, say, four films are taken, walking to  
13 the processor, putting them, one-by-one, through the  
14 processor by whatever means and then waiting for them to  
15 come out of the processor.

16 The acquisitions can take place as quickly as  
17 every ten seconds for different views on the system and the  
18 images pop up, and somebody is going to have to help me  
19 here, in less than ten seconds after the exposure is done.  
20 So that speeds that part of the process and that is part of  
21 the reason that it will speed the overall acquisition of  
22 images and increase the throughput.

23 DR. BERG: I have a question. You are asking for  
24 approval for diagnosis. From the data presented here, you  
25 were presenting screening views, what amounts to screening

1 views to your readers. We don't really know, with spot  
2 magnification views done on a digital unit or with  
3 additional spot compressions done on a digital unit, that  
4 the readers would have reached the appropriate conclusion to  
5 biopsy the lesion. Am I wrong in that statement?

6 DR. HENDRICK: We don't have direct data here on  
7 the performance of digital in that spot magnification mode.  
8 There are data collected but not in the PMA application for  
9 that. Northwestern has done a big study of digital versus  
10 film screen for workup but the expectation is that the unit,  
11 the small focal spot, is the same as the DMR unit which is  
12 very good for film-screen spot magnification.

13 The magnification stands are essentially the same  
14 as the on G.E. DMR. The only replacement is the digital  
15 image receptor replacing the film-screen image receptor. So  
16 the expectation is that actually digital will do even better  
17 there than film screen because the only change is the change  
18 in the image receptor and you are spreading the lesion out  
19 or the calcifications out over more pixels in that  
20 situation.

21 DR. BERG: I think one of the other issues is that  
22 you are also asking for approval in the labeling at least  
23 for screening and, yet, we are being presented with what  
24 amounts to data from a diagnostic trial. I don't know for  
25 sure that these are big problems but I am just trying to go

1 from the data that we are being handed today to review a  
2 consideration of this approval.

3 DR. HENDRICK: My only comment on the is that as  
4 far as the evaluation of the two views of each breast, you  
5 are doing essentially the same thing in screening or  
6 diagnostic. The only motivation for using the diagnostic  
7 population was so that we wouldn't have to image thousands  
8 of women to get an adequate number of cancers to be able to  
9 validate the device.

10 When you turn to a screening population, you can  
11 expect 5 per 1000. So, to get 40 cancers, we are talking  
12 8,000 women at least imaged with both modalities.

13 DR. BERG: I guess I was a little surprised just  
14 because we are all familiar with John Lewin's presentation  
15 and the recent Diagnostic Imaging article. I think there is  
16 a lot of data that G.E. has collected and, as part of the  
17 Army trial, I guess I would have appreciated seeing some of  
18 that as part of this application.

19 But I don't know enough about the entire logic  
20 that went into that.

21 DR. HENDRICK: Well, that is not G.E.'s data.  
22 That is an independent study that is not funded by G.E. or  
23 in any way affected by G.E. I think the idea is to keep it  
24 that way. The images are read completely independently of  
25 this. It is funded independently of G.E.

1           It was a concession to get the twenty cases that  
2 had cancer for inclusion in this case but, going back to the  
3 original guidance, it was to evaluate a diagnostic  
4 population. That is the course all the manufacturers had  
5 been instructed to embark on and that is what was done here.

6           DR. DESTOUET: Are there any other questions from  
7 the panel?

8           DR. GARRA: I have a couple more.

9           DR. DESTOUET: Yes; go ahead, Brian.

10          DR. GARRA: This has to do, again, with the work  
11 station and image processing. The first question I have is  
12 the work station that you are supplying, the so-called non-  
13 diagnostic work station is the Advantage Windows platform.  
14 I just want to know if that is the system you are supplying  
15 overseas for soft-copy reading or are you supplying a  
16 different system?

17          MS. SITZLER: It is identical. It is not the  
18 Advantage Windows system. The platform is the Advantage  
19 Windows platform. We built a specific mammo application on  
20 top of that.

21          DR. GARRA: So you are basically running that  
22 SunSpark station, then.

23          MS. SITZLER: It is the platform for both work  
24 stations.

25          DR. GARRA: You are talking about hardwarewise?

1 MS. SITZLER: More softwarewise than hardwarewise  
2 use the same software tools.

3 DR. GARRA: If the hardware and the software the  
4 same as the Advantage Windows, then it sounds like it would  
5 have to be the Advantage Windows for the film applications.

6 MS. SITZLER: The mammo application includes--the  
7 non-diagnostic review station includes the 2k by 2.5k  
8 monitors which are specifically for mammography.

9 DR. GARRA: So assuming that you might get a  
10 number of users--if you were to market this, you might get a  
11 number of users who might use it in a so-called off-label  
12 mode where they do start doing soft-copy readings. That is  
13 the reason for asking that question, to see what the  
14 capabilities of the system were.

15 The second question I have is regarding image  
16 processing. You mentioned about the thickness correction.  
17 Are there other image processing parameters that can be  
18 performed on the system and, if so--first of all, I will let  
19 you answer that one.

20 MS. SITZLER: Right now, we do the thickness  
21 compensation and automatic-contrast determination before  
22 presenting the image.

23 DR. GARRA: Those are the only two currently?

24 MS. SITZLER: Yes.

25 DR. GARRA: No edge enhancement or anything like

1 that?

2 MS. SITZLER: Not now.

3 DR. GARRA: What steps did you take to optimize  
4 those parameters? How were they optimized, in other words?

5 MS. SITZLER: How were the parameters optimized?

6 DR. GARRA: Did somebody say, "Oh; this looks  
7 pretty good?" and say, "That is what we are going to use?"

8 MS. SITZLER: I am hesitating because the whole  
9 design process is described in the larger PMA documentation  
10 and is part of that whole process where we got feedback from  
11 users on the presentation of the images and optimized the  
12 parameters based on their feedback.

13 DR. GARRA: The reason for asking that question is  
14 that regardless of how it was selected, the use of improper  
15 parameters or of non-optimal parameters could lead to  
16 compensation in terms of higher exposure which would be a  
17 violation of ALARA. That is the reason for asking.

18 DR. HENDRICK: These are all post-processing  
19 steps.

20 DR. GARRA: Right. But if you get a poor image,  
21 you might be tempted to say, "We have to use more  
22 technique." For instance, if you set your brightness or  
23 contrast settings to the wrong settings, you might be  
24 tempted to compensate by reexposing at a higher dose level.

25 DR. HENDRICK: I think that is why we need

1 training for people making those determinations on the  
2 system.

3 DR. GARRA: I just want to be sure that you did  
4 have a thorough process of optimization and did arrive at  
5 what you think are the lowest reasonably achievable doses.

6 DR. HENDRICK: All these images were required at  
7 the same doses as film screen. The images that went into  
8 their optimization of the thickness equalization algorithm,  
9 they were images acquired in ongoing studies that equalized  
10 the dose between film screen and digital.

11 DR. GARRA: Again, that is a matter of  
12 interpretation as to whether--that may not be the lowest  
13 reasonably achievable dose.

14 DR. HENDRICK: No; I am not suggesting that.

15 DR. GARRA: I will defer to the FDA on whether  
16 they want to follow that regulation or not. Do they want to  
17 go for lowest reasonably achievable dose or do they want to  
18 go for what is currently achievable with film screen. That  
19 is a question that maybe should be addressed in the follow-  
20 on study at the end if the device is approved.

21 'That's it for me.

22 DR. DESTOUET: I have one last question before we  
23 dismiss the panel. On the user end, if we, indeed, choose  
24 to use soft copy and have to compare with the hard-copy  
25 image from previous mammograms, does G.E. have any advice to

1 the radiologists how to eliminate the layer? How does one  
2 have a t.v. monitor with soft-copy display right next to a  
3 **viewbox**. That is something else that Dr. Lewin also  
4 addressed in his article.

5 It is going to be difficult to interface those  
6 viewing conditions.

7 DR. HENDRICK: One of the things we have learned  
8 from the Army study with soft-copy display is that you have  
9 to have the soft-copy display monitors in a very dark room  
10 because the brightness output isn't as high as the  
11 brightness coming through a film to your eye on a **viewbox**.  
12 So the viewing conditions are very important.

13 There will be the need, if people do soft-copy  
14 display, to have a viewing setup where they can compare,  
15 say, prior film-screen mammograms to current soft-copy  
16 displayed mammograms. But that needs to be worked out at  
17 each site that is going to do soft copy. That is a future  
18 **step**, not in the current application.

19 MR. DONNELLY: I don't think anybody should  
20 underestimate the need for quality control regardless of  
21 whether it was a digital or a film-screen read. But, to go  
22 **back** to some of the questions, the need, in terms of monitor  
23 resolutions--there has been a lot of work done with a lot of  
24 radiologists and a lot of evaluation of different kinds of  
25 equipment and some parameter settings to optimize basically

1 o the current radiologist's view so that when the hard copy  
2 ame out, it looked equivalent to what the doctors were used  
3 o seeing on the piece of film screen.

4 But all those kinds of issues, all the way back to  
5 he printer settings to is the room the right darkness, have  
6 ou selected the right monitor, these are all things that we  
7 ave worked through and established standards for. So when  
8 ve conducted the trials, these were in place.

9 Obviously, the right mechanisms have to be in  
10 lace so that as these machines are deployed in a large  
11 umber of settings, that that same level of quality control  
12 .s always in place. We have guidelines, as I said, for  
13 rinters. We have guidelines on the monitors that must be  
14 sed. We have guidelines and recommendations on the room,  
15 larkness.

16 But there are things that are outside of what you  
17 would expect for a normal film-screen room. A lot of  
18 ractices that, today, you see for people who are doing  
19 high-res imaging in a CTRM modality where you run into a lot  
20 of those same kinds of issues, what is the right environment  
21 to do reads on a live monitor as opposed to a light panel.

22 So those have to go with the product to see that  
23 it is applied in the proper fashion.

24 DR. DESTOUET: Any other questions from the panel?

25 MR. DOYLE: The FDA has three discussion points

1 that they would like to have the panel address. We will put  
2 them up on the screen and I will read them.

3 The first one is, please discuss whether or not  
4 the PMA contains sufficient data to conclude that the  
5 Senographe 2000D is safe and effective for mammography.

6 DR. DESTOUET: Is there anyone on the panel?

7 DR. ROMILLY-HARPER: I think that the PMA does  
8 contain enough data to conclude that the Senographe is safe  
9 and effective.

10 DR. DESTOUET: Any dissenting opinions? Any  
11 seconds?

12 DR. GARRA: We don't need a second. This is just  
13 discussion.

14 DR. DESTOUET: We are dealing, basically, with the  
15 same piece of equipment that has been on the market for many  
16 years except for the image receptor. So it seems as though  
17 the Senographe, indeed, is safe and effective and the PMA  
18 outlines it as such.

19 DR. GARRA: I would agree. At least, it seems  
20 totally safe and effective to me based on this data.

21 DR. HARMS: I would agree. I think it is safe and  
22 effective and the data provided more than validate that.

23 DR. MALCOLM: I have no additional comments. I  
24 agree with the comments that were made; it is clear it meets  
25 the criteria.

1 MR. DOYLE: I guess we can move on to the second  
2 discussion point; please discuss whether the labeling of  
3 this device, including the indications for use, is  
4 appropriate given the data provided in the PMA application.  
5 Are the biases, errors and limitations of the clinical study  
6 adequately described in the labeling?

7 DR. DESTOUET: Dr. Berg, do you have any questions  
8 about labeling?

9 DR. BERG: My only concern was whether we have  
10 really established that people will be able to make the  
11 right decisions for final diagnosis. Is it a 0, an abnormal  
12 or a normal; I think that has been very well established  
13 with the data we have been presented. I think there is data  
14 that supports the application but it is not necessarily  
15 fully included in the application. That is my only comment  
16 on that.

17 DR. HARMS: There was discussion earlier in the  
18 public forum about the 510(k) versus the PMA. The  
19 demonstration of equivalence to mammography is, on the basis  
20 of the PMA, by direct clinical comparison whereas other  
21 devices, other digital devices, have not had to do that.

22 The problem with the PMA is that it doesn't fully  
23 demonstrate equivalence to screening mammography because of  
24 the patient population. As Wendie mentions, there are some  
25 concerns about the diagnostic side as well. Perhaps a

1    etter way of approaching this is on the 510(k) mechanism  
2    rather than a PMA.

3           I think the paradigm for this was the Pap  
4    screening study where the automated readers of Pap smears  
5    are compared with standard readers of Pap smears. I think  
6    that may be, in essence, the problem because that focusses  
7    on the diagnostic side of things rather than how the data is  
8    gathered whereas the data in the case of digital mammograms,  
9    the gathering of the data is what we are trying to measure,  
10   not the interpretation.

11           Unfortunately, the PMA focusses on the  
12   interpretation. Actually, the interpretation is the biggest  
13   variable that we have. So I have some concerns about the  
14   mechanism of approval and the FDA guidelines for this, but I  
15   would agree that the indications of the device are  
16   appropriate. But I am not sure that the PMA actually  
17   answers that appropriateness.

18           DR. GARRA: I would like to make a comment about  
19   the labeling. Just looking through the proposed labeling  
20   section of the PMA, it is basically a slightly truncated  
21   version of the study results and you really have to work to  
22   tease out the meaningful differences between this study and  
23   a pure screening study. It took us most of the day today to  
24   do that.

25           I would suggest that the labeling needs to be

1 modified with a summary paragraph that surely summarizes the  
2 difference between the data collected here and a true  
3 screening study and also emphasizes the fact that, although  
4 the patient population was a mixture of diagnostic and  
5 screening populations, the study, itself, was run in  
6 screening mode rather than diagnostic mode so you don't have  
7 complete information about either one.

8           It is enough to be approved, but they have to  
9 realize those limitations. That needs to be summarized  
10 succinctly at the front end, I think.

11           DR. DESTOUET: Dan, can the FDA work with the  
12 manufacturer to come up with a statement to that effect?

13           DR. SCHULTZ: Absolutely.

14           DR. MALCOLM: I agree with the comments that Brian  
15 just put forward. Otherwise, I think it fits the question 2  
16 with the modifications that were just suggested.

17           DR. ROMILLY-HARPER: I would like to make just one  
18 comment. Just to the G.E. people, the fact that you do have  
19 this type of equipment in other countries, especially the  
20 European countries, part of our problem with screening  
21 devices in the United States is just the nature of the beast  
22 here. Maybe you should make some effort in collecting data  
23 from the European countries that will be applicable to  
24 describe to this population down the road.

25           It is very difficult to get true screening data in

1 the United States. It is almost impossible.

2 DR. DESTOUET: Any other comments about discussion  
3 point 2?

4 MR. DOYLE: Discussion point 3, then; there are  
5 issues not fully addressed in the PMA that require a  
6 postmarket study to resolve. Will the proposed study  
7 resolve these issues?

8 DR. DESTOUET: Dr. Toledano, have you looked at  
9 the proposed study by the manufacturer? Do you have any  
10 comments?

11 DR. TOLEDANO: I think I asked some of my most  
12 important questions earlier. I do have one remaining issue  
13 with the postmarket study is that I would like to see some  
14 plan to describe the variability across mammographers when  
15 they are interpreting the digital mammograms.

16 We know that that is one of our largest problems  
17 with the film screen. That is what waylaid the guidance  
18 from 1996 and we are still all trying to get back on track.  
19 So I would like to know, for digital, is everybody on the  
20 same curve as in the Elmore study? Is everybody on  
21 different curves as in the Beam study? How much does  
22 training affect that, and just what kinds of variability we  
23 would see. So I would add something in, some plans to  
24 address that.

25 That is a huge concern for women going to get

1 mammograms, that they don't know, depending on who you go to  
2 and what kind of day they are having. It would be nice to  
3 be able to quantify that for our population.

4 DR. HARMS: Unfortunately, that is probably not  
5 device-driven. That is probably more radiologist-driven.  
6 The concern I have here is that, in screening mammography,  
7 we are trying to provide an examination at low cost. If we  
8 increase the cost of that examination, then it will no  
9 longer be beneficial to society to screen.

10 I wonder what gain--the further study would be a  
11 study of screening. What is the relative gain of screening  
12 compared to the cost and the safety issues. We are mandated  
13 to make this a safe device and an effectiveness device. The  
14 safety, I think, is pretty apparent. The effectiveness for  
15 screening is the question here.

16 It looks like, from the physics data and the data  
17 presented so far, that it is likely to be equally effective  
18 as standard mammography. But the costs of doing a study to  
19 prove that are enormous. That will probably be passed on to  
20 the patients, ultimately, and I have a great deal of concern  
21 of whether this is worth the effort.

22 DR. DESTOUET: Any other comments?

23 DR. GARRA: I also have that concern and, because  
24 of that, I sort of hesitate to add an additional study to  
25 the postmarket one. The postmarket one that I see proposed

1 here is basically an extension of the screening protocol.  
2 If you are labeling it for screening and diagnosis, I think  
3 at least a small trial in the diagnostic modes--and the  
4 mammographers here would be better able to figure out what  
5 needs to be tested, the magnification modes, things like  
6 that, would be appropriate as a postmarket study.

7 I am concerned about the screening component from  
8 the cost standpoint as well. I like the alternate proposal  
9 where they tag onto some of the Army data as sort of a  
10 generic way of increasing number of cases more quickly and  
11 more cheaply.

12 DR. HARMS: The other issue was, again, with the  
13 Pap smear paradigm. You could take the same slide and have  
14 it read two different ways. But, with this, we actually  
15 have to expose the patients twice. That is a significant  
16 problem, a significant cost as well as X-ray exposure.

17 DR. GARRA: I did like Dr. Sacks' comment, though,  
18 that it is not like you are gaining nothing by doing the  
19 double exposure, as long as it is explained to the patients  
20 and they understand that they get an additional exposure  
21 risk but they also derive, probably, a significant benefit  
22 from the extra exposure. But, again, you still have that  
23 cost issue.

24 DR. DESTOUET: It is going to cost a lot of money  
25 and we certainly will have to radiate a lot more women. It

1 seems that the data that has been presented shows that  
2 digital mammography is effective in screening. I am not  
3 sure how much more data we need before we just give it the  
4 go-ahead.

5 I think Dr. Berg has raised some concerns about  
6 working up the diagnostic patient but that could certainly  
7 be answered with a much smaller study as opposed to having a  
8 full-scale postmarket screening study.

9 DR. BERG: I would submit that, from the data we  
10 have received, in particular, if the study was **focussed** on  
11 the category 3 and 4 lesions, sort of at the threshold and  
12 established equivalent performance which, I grant you, is  
13 very difficult with readers, but using the same readers to  
14 read the same studies, I think that is where the focus would  
15 be most effective in really answering the sort of questions  
16 that loom in all mammographers minds about the subtle future  
17 analysis that could be different between the two modalities.

18 DR. ROMILLY-HARPER: I tend to agree with both  
19 comments that were just made. I think it is easier to prove  
20 to an individual and, as a physician, it is easier to know  
21 that you are radiating a patient if they are gaining, if it  
22 is a significant gain to that individual and their  
23 diagnosis, but I have a problem with exposing women in a  
24 screening mode who have, really, nothing to gain except for  
25 proving that the instrumentation works.

1 I think we have the data from this study that  
2 shows that it is an effective tool for mammography.

3 DR. HARMS: We are using digital methods quite a  
4 bit in our department. We have digital chest units and  
5 those were readily approved. I can see a difference in the  
6 population as pointed out by the FDA in mammography to other  
7 radiographic techniques.

8 But there are a lot more similarities there than  
9 there are differences and it is a lot closer to that than it  
10 is to the Pap-smear paradigm. So I would like to encourage  
11 more similarity and approval mechanism to other digital  
12 media.

13 DR. GARRA: I have a question about--in looking at  
14 the proposal, what access is available to the Army data to  
15 increase sample sizes? I have heard that it might be  
16 available, that it really isn't available. Can I ask a  
17 question to this point on that, because that is probably  
18 critical if the data is already there. It makes no sense to  
19 repeat it.

20 DR. HENDRICK: The Army data are there to the  
21 extent that there are now 36 cancers and about 7,000 women  
22 have been screened. The 36 cancers are based on an analysis  
23 that was back when there were just about 5,000 women  
24 screened. That information is being written up for  
25 publication right now on an interim analysis of the Army

1 data.

2           The Army data can be made available for further  
3 analysis in terms of the number of cases that would be  
4 needed for a screening population but any further study of  
5 that would be done with new readings, not with the readings  
6 done supported by the Army funds. So the cases could be  
7 made available. All the cancers in a subset of noncancers  
8 could be made available for a further study but all of the  
9 readings would have to be redone.

10           Based on the design the FDA presented and that we,  
11 basically agree with, it would require many readers reading  
12 those cases to eliminate some of the reader variability  
13 issues. So the data could be made available for such a  
14 study that would focus on screening-generated cancers.  
15 Right now, we know of 36. There may be a few more that have  
16 come in since the 5,000 women have been analyzed so we may  
17 be up to low 40s in terms of number of cancers at this  
18 point.

19           DR. GARRA: So, given that scenario, then, we  
20 don't need to irradiate women again. I think we should  
21 explore the possibility--we are talking about basically  
22 money to pay readers. I think the possibility should be  
23 explored of getting that data and doing a reader study to  
24 solidify the numbers that we have sort of large error bars  
25 now on, and then a determination, after that point, as to

1 whether any additional study that needs to be made could be  
2 made.

3 But I think it is premature now, without even  
4 looking at all the data, to try to do this.

5 DR. SCHULTZ: Could I make a brief comment. I  
6 sort of am going back on my promise not to get into the  
7 policy issues, but maybe a couple of small statements might  
8 be helpful. We did believe, and we still believe, that  
9 there are some major questions with regard--as was discussed  
10 in the earlier presentations, not regarding the point  
11 estimates but regarding the width of the confidence  
12 intervals about those numbers.

13 And we agree with some of the comments that were  
14 made that there are questions, not only with the screening  
15 but, also, some questions as far as the diagnostic  
16 populations. We also understand that what was presented  
17 here was essentially a hybrid and gave us a fair amount of  
18 information, obviously information that you have already  
19 told us that you think it demonstrates safety and  
20 effectiveness.

21 So, I think, from that standpoint, we have gotten  
22 a lot of information out of the study that has been  
23 presented here today. But there are some unanswered  
24 questions and we would like to do as much as we can to try  
25 to get those questions answered, not tomorrow, not the day

1 after, but in some reasonable interval in the postmarket  
2 period.

3 With regard to the cost and with regard to how  
4 that data is procured by individual companies, we have  
5 discussed with company, as well as other companies, the fact  
6 that if there are ways that those costs could be defrayed in  
7 a variety of different ways, we would be willing to explore  
8 those options with them.

9 We are also willing to look at ways to cut down on  
10 the number of normal studies that need to be multiple read  
11 which, I think, is also a large part of the additional cost.  
12 There are ways to do these types of studies to get the kind  
13 of information with the kind of data and there are ways to  
14 do those studies in smart ways.

15 I think some of those smart ways, and Dr. Toledano  
16 can help me here and Dr. Wagner--but there are smart ways to  
17 do this to get information that we believe is necessary to  
18 ultimately have a better understanding of how these devices  
19 are going to function.

20 But, again, I think there are different ways,  
21 number one, to do the studies and, number two, pay for them  
22 that would allow these studies to be done over a reasonable  
23 length of time.

24 I hope that answers that question.

25 DR. HARMS: I have another concern and that is

1 that this is rapidly evolving technology with a lot of new  
2 innovation. My familiarity with the PMA is that it is a  
3 relatively rigid process. Is there a mechanism here for  
4 incorporating new innovations that would be beneficial to  
5 patients without locking the companies into some rigid  
6 mechanism?

7 DR. SCHULTZ: I think you are right. Let me not  
8 use the word "rigid" so much as a more involved process. We  
9 recognize that. That is, again, something that we have  
10 heard loud and clear and that we understand. Depending on  
11 the changes that are made, we have a number of different  
12 mechanisms within the PMA process which allow for minor  
13 changes to be made with relatively minor levels of scrutiny  
14 and major changes requiring larger levels of scrutiny.

15 So, for instance, an addition of soft copy to hard  
16 copy which, I think, we would all consider a fairly  
17 substantial change, would require that the sponsor come in  
18 with a supplement which showed the fact that the hard copy  
19 and the soft copy were equivalent.

20 Some of the changes less apt to directly affect  
21 the safety and effectiveness of the product could be made  
22 with less complete, less burdensome, if you will, types of  
23 submissions. We are going to look very hard at that because  
24 we do understand that this technology is not going to be  
25 static. It is going to evolve over time.

1 In fact, most of the technologies that we are  
2 approving today fall into that category. There are very few  
3 technologies that we approve through 510(k) or PMA and, in  
4 fact, the most cutting-edge technologies are the ones that  
5 go through PMA and those are the very technologies that we  
6 know are going to evolve rapidly over time.

7 So I think the new regulations, some of the new  
8 internal changes that we have made, do recognize that and  
9 provide us with a number of different ways of evaluating  
10 these different changes depending on the magnitude of those  
11 changes.

12 DR. SMATHERS: I am troubled by that last  
13 statement about soft copy being a major change because I  
14 think the true benefit to the patient is going to come when  
15 digital radiography comes out with soft copy and all the  
16 flexibility that it offers.

17 I would relate to Dr. Harms' comments in that you  
18 have digital radiography and chest films right now and you  
19 have soft copy there. There have been comparisons of soft  
20 copy and hard copy there. I really don't, in my view, see  
21 that as being a major hurdle to cross in mammography.

22 So I would encourage the FDA to move soft copy  
23 along as fast as possible. My gut feeling is that I really  
24 wouldn't release it until you had soft copy because I think  
25 that is the true benefit of the system. It is marginally

1 the same right now, the way you are going to release it.  
2 Why incur the costs on the medical-care system if you have  
3 something that is just as good but not better?

4 The "better" is going to come in the ability to  
5 manipulate the soft copy and have fewer recalls because you  
6 can do that manipulation.

7 DR. DESTOUET: There is actually existing soft-  
8 copy display of digital images now with stereotactic biopsy  
9 machines so I am not sure why that should be a hurdle at  
10 all. We are already accustomed to using soft-copy display.

11 DR. GARRA: I would like to suggest that I think  
12 that the study that is proposed here is looking backwards  
13 and I agree with Dr. Smathers and Dr. Harms that we need to  
14 look forward. If there is going to be a postmarket approval  
15 study, you might as well go ahead and just do it with soft-  
16 copy and compare it. You will get the hard-copy data anyway  
17 but it will also give you the soft-copy information and you  
18 will save a step, at least.

19 If you are going to incur any costs, then I think  
20 it makes no sense to stay on hard copy. Go to soft copy and  
21 do them both at the same time.

22 DR. SCHULTZ: Does the company want to comment?  
23 If I understood your proposal, the idea of incorporating  
24 soft copy into the postmarket study is already being looked  
25 at.

1           MR. DONNELLY: I think you are right, Dan. The  
2 :onsideration that we have in terms of a postmarket study  
3 ould be--to Dr. Smathers' turn, would be to very quickly  
4 get soft copy included in this PMA, be able to do the PMA as  
5 ve stand today but very quickly do an amendment to include  
6 soft copy as well and for whatever postmarket studies, be it  
7 hose that we have proposed or modifications, be conducted  
8 in a soft-copy environment. We agree with that 100 percent.

9           DR. GARRA: I wouldn't even spend a dollar on  
10 postmarket studies that don't include soft copy. I would  
11 wait until you got it and then just do it all at once and  
12 save the money.

13           DR. DESTOUET: Are there any other comments?

14           DR. GARRA: We have finished with the discussion  
15 and now we are ready to open the second half hour of open  
16 public hearing. You are reminded that the same  
17 identification process--in other words, your name,  
18 affiliation, financial disclosure information and a five-  
19 minute maximum time limit still apply.

20           There is one individual that we know would like to  
21 speak. If there are any other individuals at this time,  
22 would you please raise your hands or please identify  
23 yourself to Bob Doyle.

24           The first speaker is Dr. Earl Steinberg of Covans.

25                           Open Public Hearing

1 DR. STEINBERG: Thank you, Mr. Chairman. As you  
2 said, I am Vice President of Covans Health Economics and  
3 Outcome Services which is a contract research organization.  
4 I also am an adjunct professor of medicine, radiology and  
5 health policy and management at Johns Hopkins University  
6 where I was the Director of Technology Assessment for eight  
7 years.

8 I would like to congratulate the investigators on  
9 what I believe is a creative study design for a very  
10 challenging methodology problem, namely demonstrating the  
11 noninferiority of the comparability of digital and **screen-**  
12 **film** mammography. I also am pleased with the FDA's positive  
13 reaction to the studies that were presented.

14 The issue that I would like to address is what  
15 conclusions can be drawn from these studies regarding the  
16 performance of digital mammography or, for that matter,  
17 screening mammography, in a diagnostic versus a screening  
18 population and what the implications of those conclusions  
19 might be for the issue of whether this is judged to be  
20 substantially equivalent or whether it is judged to be  
21 effective in a PMA sense.

22 Dr. Sacks and other FDA officials have indicated  
23 today their concern that diagnostic performance may be  
24 different in a screening than in a diagnostic population.  
25 For example, digital mammography might perform comparably in

1 a diagnostic population but less well than screen film in a  
2 screening population.

3           This, in fact, was one of several reasons that Dr.  
4 Sacks offered for wanting to have a postmarketing study.  
5 If, as the FDA has suggested, digital and film-screen  
6 mammography may perform differently in these two  
7 populations, then there is not enough statistical power in  
8 these studies that were presented today to assess the  
9 performance of digital mammography in either diagnostic or  
10 in a screening population.

11           The reason for that is that the analysis is based,  
12 as was indicated by Dr. Byrd, on a mixed or a hybrid  
13 population and, hence, the only conclusion that can be drawn  
14 from the data that was presented today is that safety and  
15 digital mammography are, in essence, substantially  
16 equivalent in mammography.

17           We do not have enough data to conclude with any  
18 confidence that digital mammography is non-inferior in  
19 diagnosis or non-inferior in screening as, I believe, would  
20 be required for a PMA.

21           I would like to ask what we know from the  
22 application about the width of the 95 percent confidence  
23 intervals around the deltas for sensitivity, specificity and  
24 the areas under the curve when the two populations are  
25 separated and looked at individually.

1 My suspicion is that they at least double and,  
2 hence, they would not satisfy the criterion in either case.  
3 I, therefore, would urge you to approve this technology but  
4 as being substantially equivalent to screen film without  
5 making any reference to separate performance in diagnosis  
6 and screening separately.

7 DR. GARRA: Thank you. You didn't mention  
8 financial interests. Could you please mention that for the  
9 group?

10 DR. STEINBERG: I apologize. I have been a  
11 consultant for over two years to Fuji.

12 DR. GARRA: Thank you.

13 Dr. Kopans?

14 DR. KOPANS: Dr. Daniel Kopans, again, Director of  
15 the Breast Imaging Division at the Massachusetts General  
16 Hospital, Professor of Radiology at Harvard Medical School.  
17 I should also point out, as you heard today, we provided a  
18 number of the General Electric images and received some  
19 support for that.

20 To those of us, I think, sitting in the audience,  
21 it was pretty clear that General Electric has clearly  
22 established equivalency between digital mammography and  
23 film-screen mammography. I think to those of us who have  
24 used the technology, digital mammography, that was obvious.

25 I am concerned that the FDA has locked itself into

1 a PMA process and I am concerned about the requirement for  
2 postmarket approval studies. I think Dr. Harms has pointed  
3 out some of the important issues which I would just, again,  
4 summarize. I think that the rationale, at least one of the  
5 rationales, that FDA gave this morning for wanting a PMA  
6 approval was based on the cervical Pap smear automated  
7 interpretation system.

8 As Dr. Harms has pointed out, that has absolutely  
9 nothing to do with the digital acquisition of a mammogram.  
10 if you were talking about computerated detection and  
11 diagnosis, then you would have comparability. So the fact  
12 that FDA is using that as a rationale, to me seems  
13 illogical.

14 I think it is also of concern, especially to us  
15 who have used the technology and have seen how well it  
16 performs, that a study that would require double exposure of  
17 individual again, as was pointed out by the panel, would  
18 raise some major ethical concerns.

19 Dr. Sacks pointed out, and he actually cited some  
20 of our work, that getting extra mammograms increases the  
21 yields of cancers. This is nothing new, actually. There  
22 were studies back in the 1980s that show that the more  
23 projections you obtain, the more cancers you find.

24 If you wanted to back a study to show that again,  
25 maybe we should be getting three projections on every

1 individual. That I think is ethically supportable. But to  
2 use that as a rationale for double-exposing women to prove  
3 what is already shown to be equivalent I think is a major  
4 problem and I think doing any of these large studies would  
5 raise ethical concerns.

6           So, in summary, I would again, as I said at the  
7 beginning but, again, having heard now General Electric's  
8 presentation, I would urge the panel--I know FDA doesn't  
9 have to do what the panel suggests, but I would urge the  
10 panel to strongly support approval with a 510(k) mechanism.  
11 I think that, again, equivalency has been clearly shown and  
12 I would like to see us now move ahead to improving this  
13 technology as well as others and not waste scant resources  
14 on just showing that mammography is equivalent to  
15 mammography.

16           DR. GARRA: Thank you.

17           What we are going to do at this point--we don't  
18 have any more people who have asked to speak. We are going  
19 to take a fifteen-minute break at this point and then we  
20 will reconvene at ten minutes of 3:00 and then we will have  
21 final votes and everything.

22           Thank you very much.

23           [Break. 1

24           DR. GARRA: I would like to begin the final  
25 session of this panel meeting. Before we move to the panel

1 recommendations and vote, is there any additional material  
2 the FDA would like to address?

3 DR. CHAKRABARTI: I am Kish Chakrabarti. I am  
4 with the Division of Mammographic Quality and Radiation  
5 Performance, DCRH, FDA. I have one point to clear, that,  
6 under MQSA, FDA required that for any modality, any  
7 mammographic modality, maximum allowed dose per image is  
8 300 millirad. That is under the final regulation.

9 DR. GARRA: Any other comments by the FDA?

10 Now the sponsor, General Electric, has a chance to  
11 make any final comments they would like to make.

12 MR. DONNELLY: Thank you, Dr. Garra.

13 I don't have any more substantive comments. I  
14 want to take the panel. We appreciate the time today and  
15 your thoughtful consideration. Based on the questions,  
16 obviously there was a great deal of review time that went  
17 into preparing for today's session on your part.

18 I also thank you for the insight relative to the  
19 postapproval studies. It is clear this has been a much-  
20 discussed item between ourselves and the FDA in terms of a  
21 meaningful study. I think we all are more or less in  
22 agreement relative to the issue of soft copy and I think  
23 those comments will help us considerably in terms of trying  
24 to go forward to determine an appropriate postmarket  
25 approval study.

1 I also want to thank the FDA. It has been a long  
2 several years in working on trying to seek approval for this  
3 technology to get it into the marketplace. The interest on  
4 G.E.'s behalf has been to try to do this and do this as  
5 quickly as possible based on what we think is the strength  
6 of the clinical studies.

7 While there have been a number of changes and what  
8 not along the way, I would have to say that in the last few  
9 months after the meetings and concurrence to pursue a PMA  
10 path that there has been a lot of cooperation on the part of  
11 the FDA and I think we have worked very closely and  
12 appreciably with them to make sure that we can get the new  
13 technology to the market as soon as possible.

14 So thank you very much.

15 DR. GARRA: Thank you.

16 **Panel Recommendations and Vote**

17 DR. GARRA: We are now ready to move to the  
18 panel's recommendation concerning PMA P990066. The Medical  
19 Device Amendments to the Federal Food, Drug and Cosmetic Act  
20 as amended by the Safe Medical Devices Act of 1990 allows  
21 the Food and Drug Administration to obtain a recommendation  
22 from an expert advisory panel on designated medical-device  
23 premarket approval applications, **PMAs**, that are filed with  
24 the agency.

25 The **PMA** must stand on its own merits and your

1 ecommendation must be supported by safety and effectiveness  
2 ata in the application or applicable publicly available  
3 ublic information.

4 [Slide.]

5 There are several things we consider. Safety is  
6 defined in the Act as reasonable assurance based on valid  
7 scientific evidence that the probable benefits to health  
8 under conditions of intended use outweigh any probable  
9 risks.

10 [Slide. 1

11 The effectiveness is defined as reasonable  
12 assurance that, in a significant proportion of the  
13 population, the use of the device for its intended uses and  
14 conditions of use, when labeled, would provide clinically  
15 significant results.

16 [Slide.]

17 We have several possible options for our vote.  
18 The first is approve with no conditions. The second is  
19 approvable with conditions. The panel may recommend that  
20 the PMA be found approvable subject to specified conditions  
21 such as physician or patient education, labeling changes or  
22 further analysis of existing data. Prior to voting, all of  
23 the conditions should be discussed by the panel.

24 The third choice is not-approvable. The panel may  
25 recommend that the PMA is not-approvable if the data do not

1 provide a reasonable assurance that the device is safe or,  
2 if a reasonable assurance has not been given, that the  
3 device is effective under the conditions of us prescribed,  
4 recommended or suggested in the proposed labeling.

5 At this point, the Chair will entertain any  
6 motions regarding approval or disapproval of this PMA.

7 DR. DESTOUET: Mr. Chairman, I recommend approval  
8 of PMA P990066 without conditions. I recommend that the  
9 manufacturer deploy the soft-copy work station to serve as  
10 an adjunct and/or to replace the hard-copy images for  
11 evaluation of mammography.

12 DR. SMATHERS: I would like to second that.

13 DR. GARRA: Thank you. Dr. Smathers has seconded  
14 that. Did somebody write that down? Bob, could you read  
15 that back to us again, please?

16 MR. DOYLE: Yes. The motion is to approve the PMA  
17 without conditions with a recommendation that the  
18 manufacturer deploy soft-copy work stations to serve as an  
19 adjunct to hard copy.

20 DR. GARRA: This motion has been moved and  
21 seconded. Is there any discussion on this? We should  
22 probably go around the table and everybody sort of has to  
23 give discussion.

24 DR. HARMS: I agree. I feel that further studies  
25 would not be warranted at this time and would be a not-

1       essential use of resources of both the FDA and industry.

2               DR. MALCOLM: I agree with the comments. Clearly,  
3       think it has been demonstrated that at least this  
4       technology, as we know it today, is equal, at least on hard  
5       copy as we see, for the studies as compared to film  
6       mammography. I think there is also additional data that is  
7       out there that, perhaps, was not presented that shows that  
8       we are actually beyond that point and I am not sure if we  
9       need this additional postmarket studies which, I think,  
10      perhaps is not cost effective.

11              DR. GARRA: I, myself, agree with the motion. I  
12      would ask the panel to please consider if we do need to make  
13      any minor suggestions regarding the labeling section of  
14      that. Sometimes, that gets lost in the shuffle, but I also  
15      don't feel that, given the other data that is out there that  
16      is publicly available, so if we could use it in our  
17      determination, that a postmarket study is absolutely  
18      necessary.

19              I would suggest, however, that if one is done that  
20      it definitely include the soft-copy component.

21              DR. BERG: I would agree with your comments,  
22      Brian. I think that there is data already from the Army-  
23      sponsored study that would answer the issues that were  
24      raised by the FDA for postmarket surveillance. I think that  
25      data needs to be made available to the FDA. It is already

1 part of public record, ultimately.

2 DR. ROMILLY-HARPER: I agree with most of the  
3 comments that have already been made.

4 DR. SMATHERS: I concur.

5 DR. TOLEDANO: Ditto.

6 DR. GARRA: Any other further points specifically  
7 regarding the labeling issues or anything that anybody would  
8 like to bring up? Dr. Smathers?

9 DR. SMATHERS: Your comment about an executive  
10 summary in the front of that, I think, is very germane.  
11 This is so long that no one is going to read it. I think a  
12 clear synopsis has to be put together.

13 DR. GARRA: Would you like to amend the motion to  
14 include that?

15 DR. SMATHERS: Yes.

16 DR. GARRA: Do we have a second to that?

17 [Second. ]

18 DR. GARRA: We are amending the conditions section  
19 to say that we would like a change to the labeling.

20 MR. DOYLE: You are approving it with conditions.

21 DR. GARRA: Yes.

22 MR. DOYLE: To include an executive section in the  
23 front of labeling.

24 DR. GARRA: Or something equivalent to that that  
25 emphasizes the difference between this study and a true

1 screening or diagnostic study.

2 DR. SCHULTZ: We are talking about the clinical  
3 section of the labeling? Is that what we are discussing?

4 DR. SMATHERS: Yes.

5 DR. SCHULTZ: Not the summary of safety and  
6 effectiveness. You are talking about the labeling, the way  
7 the clinical data is presented in the labeling, that you  
8 would like it done more succinctly emphasizing the  
9 differences between--or the way that the studies were done?  
10 Is that it? Or study populations?

11 DR. GARRA: I think instead of deleting all the  
12 stuff that is in there, what the idea was was to add one  
13 paragraph that summarized it in a few sentences figuring  
14 that that is--

15 DR. SCHULTZ: Summarizes where the study  
16 populations were drawn from? Is that the major--

17 DR. GARRA: How they differ from a true screening  
18 and a--

19 DR. SCHULTZ: And a true diagnostic population.  
20 Okay.

21 Could I ask for one more clarification with regard  
22 to the hard-copy/soft-copy issue? I am assuming, and maybe  
23 this is not a good thing to assume, but I am assuming that  
24 you don't want to wait for the soft copy to be available to  
25 have this device approved. Is that true? Because the way

1 the recommendation is worded, it is a little confusing as  
2 far as I can tell.

3 Right now, the submission that is before you is  
4 for hard copy. I think the proposal that has been made,  
5 both by the company and by the agency, is that we would work  
6 together to try to achieve a soft-copy approval within a  
7 very, very short period of time following the original  
8 approval.

9 But, currently, we do not have a submission before  
10 us for soft copy so we--

11 DR. GARRA: We are not recommending an approval of  
12 a soft copy. We are recommending that it be deployed for  
13 evaluation.

14 DR. SCHULTZ: That the studies be done to get it  
15 approved as quickly as possible; is that what you are  
16 saying?

17 DR. GARRA: Yes, essentially.

18 DR. HARMS: My opinion is that you would expedite  
19 that integration of soft copy and the final product. We  
20 realize we do not have soft copy to review at this time.

21 DR. SCHULTZ: Okay.

22 DR. GARRA: We just wanted to emphasize the  
23 importance of going to soft copy in that recommendation.

24 DR. SCHULTZ: We hear you loud and clear.

25 MR. DOYLE: The way I see this now, we have

1    approvable with conditions.  There are three conditions and  
2    we have to vote on each one of these conditions separately.  
3    This is how we conduct our business.

4                So first we want to take a vote on approvable with  
5    conditions as a general motion.

6                DR. SMATHERS:  What are your three conditions?

7                DR. GARRA:  Judy?

8                DR. DESTOUET:  Do I have to resubmit the motion?

9                MR. DOYLE:  You have to withdraw the motion.

10               DR. GARRA:  We have to withdraw that motion in  
11    favor of the one with the amendment.

12               DR. DESTOUET:  I withdraw my original motion.

13               MR. DOYLE:  And put a motion forward to approve it  
14    with conditions and we will see if that gets seconded.

15               DR. DESTOUET:  I recommend that we approve the PMA  
16    with conditions.

17               DR. SMATHERS:  I will second that.

18               MR. DOYLE:  All in favor?

19               [Show of hands.]

20               DR. GARRA:  We shouldn't have to do that until we  
21    hear what the conditions are.

22               MR. DOYLE:  No; this is the process.

23               DR. HARMS:  Why can't we approve without  
24    conditions?  We were not privy to this discussion here.

25               DR. GARRA:  The condition was the modification of

at

1 the labeling to include a short summary.

2 MR. DOYLE: And the expediting of the soft copy  
3 and the recommending that the manufacturer deploy soft copy.  
4 I have written down three conditions.

5 DR. GARRA: That's fine. All those in favor of  
6 approval with conditions, please raise your hands.

7 [Show of hands.]

8 MR. DOYLE: It is unanimous. Now, we are going to  
9 take each one of these conditions. I will read them. The  
10 first condition is recommending that the manufacturer deploy  
11 soft-copy work stations to serve as an adjunct to hard copy.

12 DR. GARRA: All those in favor of that suggestion  
13 raise your hands?

14 [Show of hands.]

15 MR. DOYLE: It is unanimous.

16 DR. GARRA: Please read the second one.

17 MR. DOYLE: The second one is, have an executive  
18 section in front of the labeling that emphasizes the  
19 differences between the study population and a true  
20 screening and/or diagnostic population.

21 DR. GARRA: All those in favor raise your hands?

22 [Show of hands.]

23 MR. DOYLE: It is unanimous.

24 DR. GARRA: And the final one?

25 MR. DOYLE: The final one is expedite the approval

1 of the soft-copy modality.

2 DR. GARRA: All those in favor.

3 [Show of hands.]

4 MR. DOYLE: Now we have three. Now we just go  
5 back and approve the motion with those three conditions. So  
6 one more vote.

7 DR. GARRA: We will certainly have this  
8 documented.

9 MR. DOYLE: Does someone want to second that  
10 motion?

11 [Second.]

12 MR. DOYLE: All in favor of approving with those  
13 three conditions that have been approved.

14 [Show of hands.]

15 MR. DOYLE: Unanimous again. Now we would like to  
16 go around and just--

17 DR. GARRA: Let's just quickly go around. We have  
18 already discussed this a little bit. Let's quickly go  
19 around and recap the reasons why each of you voted the way  
20 that you did.

21 DR. HARMS: I believe the device and the data that  
22 is submitted is safe and effective and that it represents a  
23 significant advance for the diagnosis of breast cancer and  
24 should be integrated into clinical practice as well as  
25 possible.

1 DR. MALCOLM: Agree.

2 DR. GARRA: I voted this way because I feel that  
3 these recommendations will best expedite the integration of  
4 digital mammography into clinical practice and puts the  
5 emphasis on moving towards soft copy in an expedited  
6 fashion.

7 DR. DESTOUET: The manufacturer has shown that the  
8 equipment is safe and effective.

9 DR. BERG: I agree and I would add that I think  
10 that there has been the demonstration of substantial  
11 equivalence although I know that is a controversial issue.

12 DR. ROMILLY-HARPER: I agree that the  
13 manufacturers have proven that the device is safe and  
14 effective and this technology will certainly improve the  
15 diagnosis of breast cancer and availability, hopefully,  
16 eventually to women.

17 DR. SMATHERS: I concur with the earlier comments  
18 and, in my parting piece of wisdom to the FDA, would suggest  
19 that, as you look at different detectors that come in, there  
20 will be slight differences. I would ask that you grant  
21 them a bit of latitude, that the net effect of the  
22 differences in the detectors isn't going to be that great  
23 and that, perhaps, they won't have to jump as many hurdles  
24 as General Electric had to.

25 DR. TOLEDANO: I agree with my esteemed colleagues

1 on the panel.

2 DR. GARRA: Mr. Doyle, would you like to make a  
3 final comment?

4 MR. DOYLE: Yes; all I would like to do is thank  
5 the panel, certainly, for coming here to this unscheduled  
6 meeting and I appreciate every one of you getting--100  
7 percent attendance was really fantastic. All I need back  
8 from you, and if you don't have it here today, you can send  
9 it to me, is the orange book. All the rest of the materials  
10 that you were given today, you are welcome to take home.

11 DR. GARRA: Before we adjourn, I would like to  
12 thank the speakers, the members of the panel for their  
13 preparation for this meeting which I think, as meetings go,  
14 is sort of historic. I would also like to extend thanks to  
15 the people from the audience, the public, who commented. I  
16 think your comments are very helpful and will be given  
17 careful consideration.

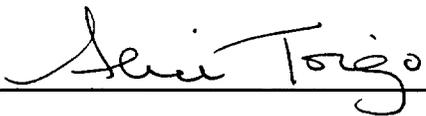
18 I would like to extend special thanks to Judy  
19 Destouet for leading the discussion segment of today's  
20 meeting.

21 If there is no further business, I would like to  
22 adjourn this meeting. Thank you.

23 [Whereupon, at 3:20 p.m., the meeting was  
24 adjourned.]

*C E R T I F I C A T E*

I, ALICE TOIGO, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



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ALICE TOIGO