

UNITED STATES OF AMERICA
 DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
 MEDICAL DEVICES ADVISORY COMMITTEE

+ + +

RADIOLOGICAL DEVICES PANEL

+ + +

April 12, 2012
 8:00 a.m.

Hilton Washington DC North
 620 Perry Parkway
 Gaithersburg, Maryland

PANEL MEMBERS SESSION I:

ROBERT D. ROSENBERG, M.D.	Chair
DOUGLAS M. COLDWELL, M.D., Ph.D.	Non-Voting Member
LORI E. DODD, Ph.D.	Non-Voting Member
YULEI JIANG, Ph.D.	Non-Voting Member
THOMAS J. PAYNE, M.D., Ph.D.	Non-Voting Member
XIAO-HUA "ANDREW" ZHOU, Ph.D.	Non-Voting Member
CRAIG K. ABBEY, Ph.D.	Temporary Non-Voting Member
JAMES S. BABB, Ph.D.	Temporary Non-Voting Member
JOHN DANIEL BOURLAND, Ph.D.	Temporary Non-Voting Member
ROBERT M. FAULK, M.D.	Temporary Non-Voting Member
SUJATA V. GHATE, M.D.	Temporary Non-Voting Member
LEONARD M. GLASSMAN, M.D.	Temporary Non-Voting Member
CAROLYN B. HENDRICKS, M.D.	Temporary Non-Voting Member
DANIEL B. KOPANS, M.D.	Temporary Non-Voting Member
ELIZABETH A. KRUPINSKI, Ph.D.	Temporary Non-Voting Member
ALICIA Y. TOLEDANO, Sc.D.	Temporary Non-Voting Member
MARVIN C. ZISKIN, M.D.	Temporary Non-Voting Member
MADELINE Y. LAWSON, M.A.	Consumer Representative
ELISABETH M. GEORGE, M.S.	Industry Representative
MARLENA VEGA, Ph.D., M.S.W.	Patient Representative
SHANIKA CRAIG, M.H.A., M.B.A.	Designated Federal Officer

Free State Reporting, Inc.
 1378 Cape Saint Claire Road
 Annapolis, MD 21409
 (410) 974-0947

PANEL MEMBERS SESSION II:

ROBERT D. ROSENBERG, M.D.	Chair
DOUGLAS M. COLDWELL, M.D., Ph.D.	Non-Voting Member
LORI E. DODD, Ph.D.	Non-Voting Member
YULEI JIANG, Ph.D.	Non-Voting Member
THOMAS J. PAYNE, M.D., Ph.D.	Non-Voting Member
XIAO-HUA "ANDREW" ZHOU, Ph.D.	Non-Voting Member
JAMES S. BABB, Ph.D.	Temporary Non-Voting Member
JOHN DANIEL BOURLAND, Ph.D.	Temporary Non-Voting Member
IVAN A. BREZOVICH, Ph.D., DABR	Temporary Non-Voting Member
RONALD O. GILCHER, M.D., FACP	Temporary Non-Voting Member
LIANA HARVATH, Ph.D.	Temporary Non-Voting Member
ELIZABETH A. KRUPINSKI, Ph.D.	Temporary Non-Voting Member
C. OLA LANDGREN, M.D., Ph.D.	Temporary Non-Voting Member
SUSAN F. LEITMAN, M.D.	Temporary Non-Voting Member
COL FRANCISCO J. RENTAS, Ph.D., SBB, M.S.	Temporary Non-Voting Member
MADÉLINE Y. LAWSON, M.A.	Consumer Representative
ELISABETH M. GEORGE, M.S.	Industry Representative
MARLENA VEGA, Ph.D., M.S.W.	Patient Representative
LCDR SARA ANDERSON, B.A., B.S.N.	Designated Federal Officer

FDA REPRESENTATIVES:

JANINE MORRIS
Acting Director, Division of Radiological Devices
Office of In Vitro Diagnostic Device Evaluation and Safety

MARJORIE SHULMAN, M.B.A.
Acting Director, Premarket Notification (510(k)) Program

MICHELLE BOLEK
Press contact

FDA PRESENTERS SESSION I:

NANCY G. WERSTO, M.S., DABR
Medical Physicist/Reviewer, Division of Radiological Devices
Office of In Vitro Diagnostics

HUI-LEE WONG, Ph.D., M.Sc.
Epidemiologist, Division of Epidemiology
Office of Surveillance and Biometrics

HELEN J. BARR, M.D.
Director, Division of Mammography Quality and Radiation Programs
Office of Communication, Education, and Radiation

PETITIONER PRESENTER SESSION I:

RUSSELL OVEREND
PWB Health UK, Ltd.

OPEN PUBLIC HEARING SPEAKERS SESSION I:

LEROY HAMILTON, Ph.D.

FDA PRESENTERS SESSION II:

MICHAEL D. O'HARA, Ph.D.
Radiation Biologist, Division of Radiological Devices
Office of In Vitro Diagnostics

HUI-LEE WONG, Ph.D., M.Sc.
Epidemiologist, Division of Epidemiology
Office of Surveillance and Biometrics

RICHARD DAVEY, M.D.
Office of Blood Research and Review
Center for Biologics Evaluation and Research

OPEN PUBLIC HEARING SPEAKERS SESSION II:

M. ALLENE CARR-GREER

SESSION I - INDEX

	PAGE
CALL TO ORDER - Robert D. Rosenberg, M.D.	9
INTRODUCTION OF COMMITTEE	10
CONFLICT OF INTEREST AND TEMPORARY NON-VOTING STATUS STATEMENTS - Shanika Craig, M.H.A., M.B.A.	14
GENERAL ANNOUNCEMENTS - Shanika Craig, M.H.A., M.B.A.	17
RECLASSIFICATION PRESENTATION - Marjorie Shulman, M.B.A.	18
PETITIONER PRESENTATION	
Breastlight Transilluminator - Russell Overend	23
Q&A	35
FDA PRESENTATION	
Overview of Breast Transilluminators - Nancy G. Wersto, M.S., DABR	45
Systematic Literature Review of Breast Transilluminators - Hui-Lee Wong, Ph.D., M.Sc.	48
Breast Light Scanning Clinical Perspective - Helen J. Barr, M.D.	55
Breast Transilluminators Current Regulatory Status - Nancy G. Wersto, M.S., DABR	59
Q&A	61
OPEN PUBLIC HEARING	
Leroy Hamilton, Ph.D.	75
PANEL DELIBERATIONS	79
FDA QUESTIONS TO PANEL	
Question 1	103
Question 2	106
Question 3	108

SESSION I - INDEX

	PAGE
SUMMATION	
Petitioner - Russell Overend	113
ADJOURNMENT - Robert D. Rosenberg, M.D.	113

SESSION II - INDEX

	PAGE
CALL TO ORDER - Robert D. Rosenberg, M.D.	115
INTRODUCTION OF COMMITTEE	116
CONFLICT OF INTEREST AND TEMPORARY NON-VOTING STATUS STATEMENTS - LCDR Sara Anderson, B.A., B.S.N.	120
GENERAL ANNOUNCEMENTS - LCDR Sara Anderson, B.A., B.S.N.	124
RECLASSIFICATION PRESENTATION - Marjorie Shulman, M.B.A.	125
Q&A	130
FDA PRESENTATION	
Overview of Blood Irradiators - Michael D. O'Hara, Ph.D.	131
Systematic Literature Review of Blood Irradiators - Hui-Lee Wong, Ph.D., M.Sc.	135
Blood Irradiators Clinical Perspective - Richard Davey, M.D.	140
Summary - Michael D. O'Hara, Ph.D.	147
Q&A	149
PANEL DELIBERATIONS	155
OPEN PUBLIC HEARING	
M. Allene Carr-Greer	168
PANEL DELIBERATIONS (cont.)	172
FDA QUESTIONS TO PANEL	
Question 1	177
Question 2	182
Question 3	186

SESSION II - INDEX

	PAGE
FINAL COMMENTS	
Consumer Representative - Madeline Y. Lawson, M.A.	198
Industry Representative - Elisabeth George, M.S.	198
ADJOURNMENT	198

SESSION I

(8:10 a.m.)

DR. ROSENBERG: Approximately 8:10, and I would like to call this meeting of the Radiological Devices Panel to order.

I am Dr. Rosenberg, the Chairperson of this Panel. I am a radiologist at the Radiology Associates of Albuquerque and an Emeritus Professor at University of New Mexico. And my specialty, again, is mammography and outcomes research.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in this meeting today has received training in FDA law and regulations.

For today's agenda, the Panel will discuss and make recommendations regarding the 515(i) order issued by the Food and Drug Administration on April 9, 2009 for breast transilluminators, one of the remaining pre-amendment Class III devices. On June [sic] 18, 1995, FDA published a final rule that effectively placed them in Class II based on the recommendation of the Obstetrics and Gynecology Devices Panel, who concluded there was insufficient data demonstrating a reasonable assurance of safety and effectiveness for this type of device. Discussion will include review of current literature to assess the safety and effectiveness of breast transilluminators, consideration of a reclassification petition, and

determination of the appropriate classification for breast transilluminators.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation.

Ms. Morris?

MS. MORRIS: Janine Morris, the Acting Division Director for the Division of Radiological Devices at the Center for Devices and Radiological Health.

DR. GLASSMAN: Len Glassman. I'm a radiologist in private practice in Washington, D.C. I'm also a past chairman of this Panel, Clinical Professor of Radiology at George Washington, and Chief of Breast Imaging at the American Institute for Radiologic Pathology.

DR. BOURLAND: I'm Dan Bourland. I'm a medical physicist with specific expertise in radiation oncology and imaging in that area. I'm a professor at Wake Forest University, Winston-Salem, North Carolina.

DR. ABBEY: I'm Craig Abbey. My area of expertise is observer performance and visual tasks. I'm a research faculty at UC Santa Barbara.

DR. TOLEDANO: My name is Alicia Toledano. I'm a biostatistician. I specialize in evaluating medical imaging, medical diagnostics. And I'm Vice President at Statistics Collaborative in Washington, D.C.

DR. HENDRICKS: Good morning. I'm Carolyn Hendricks. I'm a

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

medical oncologist specializing in breast cancer in Bethesda, Maryland.

DR. ZISKIN: I'm Marvin Ziskin. I'm a Professor of Radiology and Medical Physics at Temple University Medical School in Philadelphia. And my area of expertise is ultrasound and electromagnetic fields, particularly with respect to the safety.

DR. ZHOU: Andrew Zhou, biostatistician, Professor in Biostatistics at University of Washington. My areas of interest is statistical methods in diagnostic medicine.

DR. DODD: Good morning. I'm Lori Dodd. I'm a biostatistician at the National Institute of Allergy and Infectious Diseases. Prior to being at NIAID, I was at the National Cancer Institute for seven years.

DR. COLDWELL: I'm Doug Coldwell. I'm a radiologist and Chief of Interventional Radiology at the University of Louisville, Professor of Radiology and Bioengineering and doing a lot of research in radiation effects as well as cancer therapies.

LCDR ANDERSON: Hi. Lieutenant Commander Anderson of the United States Public Health Service. I'm also Designated Federal Officer for the Food and Drug Administration.

MS. CRAIG: Shanika Craig. I'm the DFO for the first half of this meeting.

DR. BABB: James Babb, Associate Professor of Radiology, New York University School of Medicine. My expertise is in biostatistics as it

pertains to radiologic imaging studies.

DR. PAYNE: I'm Tom Payne. I'm a medical physicist. I was at the University of Minnesota. I then went to a large community hospital. I practiced in radiation oncology, diagnostic medical physics. My special area of expertise is CT scanning and also mammography physics.

DR. FAULK: Good morning. I'm Robert Faulk. I'm a diagnostic radiologist, specializing in breast imaging and located in Omaha, Nebraska. I work in a private practice group, Medical Imaging Consultants.

DR. KOPANS: I'm Dan Kopans, Professor of Radiology at Harvard Medical School and Senior Radiologist in the Breast Imaging Division at the Massachusetts General Hospital. And my area of expertise is breast imaging.

DR. JIANG: Yulei Jiang, Associate Professor of Radiology at University of Chicago. My area of interests mainly are in computer-aided diagnosis of breast cancer and prostate cancer and diagnostic performance evaluation.

DR. KRUPINSKI: Elizabeth Krupinski. I'm a Professor in the Departments of Radiology and Psychology at the University of Arizona. My areas of expertise are in assessment of human observer performance as it relates to medical devices, especially mammographic devices, human factors, and applications to telemedicine.

DR. GHATE: And I'm Sujata Ghate. I'm an Assistant Professor

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

of Radiology at Duke University Medical Center, and my area of expertise is in breast imaging.

DR. VEGA: Good morning. Buenos dias. My name is Marlana Vega. I am a psycho-oncologist. They met me inside for breakfast, and that's how I got invited. No, that's not true.

(Laughter.)

DR. VEGA: I'm a survivor of cancer three times and a third generation. I'm the Executive Director of A Will to Live, Sobrevivir, which Mother Theresa helped me start about 42 years ago when I was a teenager. And I -- not really -- and work primarily in the South Bronx, in Manhattan, and now we have chapters in Antigua, in Puerto Rico, in many places, which works on advocacy for helping people to heal themselves. And I'm very pleased be here with this distinguished Panel. Thank you.

MS. LAWSON: Good morning. I'm Madeline Lawson. I'm the President and CEO of the Institute for the Advancement of Multicultural and Minority Medicine, based in Washington, D.C., with a focus on addressing disparities in health and healthcare. And my expertise is in health communications and advocacy.

MS. GEORGE: And I'm Elisabeth George. I'm here as the Industry Representative. I'm a Vice President of Global Government Affairs, Regulations, and Standards at Philips Healthcare, with the past 10 years focused in the imaging modalities.

DR. ROSENBERG: If you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Ms. Craig, the Designated Federal Officer for the Radiological Devices Panel, will make some introductory remarks.

MS. CRAIG: Good morning. FDA Conflict of Interest Disclosure Statement (Particular Matters Involving Specific Parties) Radiological Devices Panel of the Medical Devices Advisory Committee.

The date of this meeting is April 12th, 2012.

The Food and Drug Administration is convening today's meeting of the Radiological Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry rep, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of the Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 and 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws.

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

Under 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special Government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when it is necessary to afford the Committee essential expertise.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S. Code Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, during Session I, the Panel will discuss and make recommendations regarding the 515(i) order issued by FDA on April 9th, 2009 (74 FR 16214) for breast transilluminators, one of the remaining pre-amendment Class III devices. On July 18th, 1995 (60 FR 36639), FDA published a final rule that misbranded breast transilluminators and effectively placed them into Class III based on the recommendations of

the Obstetrics and Gynecology Devices Panel, which concluded there were no published studies or clinical data demonstrating the safety and effectiveness of this device. The committee discussion will include a review of the present literature to assess the current knowledge of breast transilluminators and determine if sufficient safety and effectiveness data are available to support reclassification of breast transilluminators.

Based on the agenda for today's meeting and all financial interests reported by the Panel members, no conflict of interest waivers have been issued in accordance with 18 U.S. Code Section 208 and 712 of the FD&C Act.

A copy of this statement will be available at the registration table during the meeting and will be included as part of the official transcript.

Elisabeth M. George is serving as an industry rep, acting on behalf of all related industry, and is employed by Philips Healthcare.

We would like to remind members and consultants that if the discussions involve any products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the Panel of any financial relationships that they may have with any firms at issue.

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

Dr. Marlana Vega has been appointed a Temporary Non-Voting representative for the duration of the Radiological Devices Panel Meeting on April 12th, 2012. For the record, Dr. Vega serves as a consultant to the Oncologic Drug Advisory Committee of the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the materials to be considered at this meeting.

The appointment was authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for Special Medical Programs on April 10th, 2012.

Before I turn this meeting back over to Dr. Rosenberg, I would like to make a few general announcements:

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated, at 1378 Cape St. Claire Road, Annapolis, MD, 21409. Telephone is 410-974-0947.

Information on purchasing videos of today's meeting can be found at the FDA meeting registration desk.

The press contact for today's meeting is Michelle Bolek. She's waving at us.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker podium. I request that reporters please wait to speak to the

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Mr. Jim Clark at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and electronic devices at this time.

Thank you very much.

Dr. Rosenberg?

DR. ROSENBERG: We will now hear from Marjorie Shulman, M.B.A., Acting Director, Premarket Notification (510(k)) Program.

I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chairman, Dr. Rosenberg.

(Pause.)

DR. SHULMAN: All right. We'll get this together at some point, right?

Good morning. My name is Marjorie Shulman. I'm Acting Director of the Premarket Notification staff, and I'm going to give a brief overview of classification and reclassification procedures.

So the Act, the Federal Food, Drug and Cosmetic Act, divided

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

the arena of medical devices into either pre-amendment devices or post-amendment devices. And all that meant, it was dependant upon when the devices were introduced into interstate commerce for commercial distribution.

So pre-amendment devices are classified after FDA has either received a recommendation from a device classification panel, such as yourself, published the panel's recommendation for comment along with the proposed regulation classifying the device, and published a final regulation classifying the device.

Reclassification of pre-amendment devices. The Food and Drug Administration may reclassify a device in a proceeding that parallels the initial classification proceeding which took place in the late '70s, early '80s, and is based upon new information respecting a device either on FDA's own initiative or upon the petition of an interested person.

Postamendment devices, those are ones introduced after May 28th, 1976, the date of the medical device amendments, are automatically classified into Class III, and they remain in Class III and require a premarket approval unless and until the device is reclassified either into Class I or II, or FDA issues a substantially equivalent determination, or the device is classified into Class I or II via the evaluation of automatic class redesignation, also known as the de novo review.

A reclassification of a post-amendment device may be initiated

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

either by FDA or industry, and FDA, for good cause, may refer it to a device classification panel, and the Panel should make a recommendation to FDA respecting the approval or denial of the petition.

There are three classes of devices, and a device should be placed in the lowest class whose level of control will provide reasonable assurance of safety and effectiveness: Class I are general controls, Class II are general and special controls, and Class III is premarket approval.

Class I mainly includes devices for which any combination of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. So general controls include such things as prohibition against adulterated or misbranded devices; good manufacturing practices; registration of the manufacturing facility; listing of the device type; record keeping; repair, replacement and refund; and banned devices.

Here are some examples of Class I devices: adhesive bandages, stethoscopes, patient scale, exam light, crutches.

Class II is for devices that cannot be classified into Class I because the general controls by themselves, the ones that were just listed, are insufficient to provide reasonable assurance of the safety and effectiveness of the device, but there is sufficient information to establish special controls to provide such assurance.

So special controls include such things as performance standards, postmarket surveillance, patient registries, development and

dissemination of guidelines, tracking requirements, and recommendations and other appropriate actions.

Some examples of Class II devices: ventilators, ECGs, endoscopes, hemodialysis systems, et cetera.

So how are special controls used? So just as an example, for surgical sutures, FDA has issued a special control guidance to mitigate the risks to health. That includes such things as biocompatibility testing, sterility testing, conformance to the USP monograph, resorption profile testing, and labeling. These special controls, in combination with the general controls, provide reasonable assurance of safety and effectiveness. Companies must provide evidence in their 510(k) submissions of how the special controls were addressed.

Class III devices are for devices which insufficient information exists to determine that the general controls, Class I, and the special controls, Class II, are sufficient to provide reasonable assurance of safety and effectiveness of the device, and the devices are life sustaining and/or life supporting, or are of substantial importance in preventing impairment of human health, or present a potential or unreasonable risk of illness or injury.

So some examples of Class III devices are implantable pacemakers, implantable spinal cord stimulators, IUDs, and extended-wear soft contact lenses.

So what are Class III 510(k) devices? When the panels sat

down in the late '70s, early '80s after the medical device amendments of May 28th, 1976, they placed the devices into Class I, II or III. If a device was placed into Class III, the FDA said over time, we will call for PMAs for these types of devices. So until that time, they will be reviewed as 510(k) devices.

So Class III 510(k) devices, there were approximately 150 or so; I think we're down to the last 20. But no final rule was ever issued, or a final rule was issued, but the rule did not contain a date by which companies were required to submit a PMA. So, therefore, these Class III devices were allowed to proceed to market via the 510(k) route until such time either a call for PMA or a reclassification is finalized.

There's also restricted devices, and it's under the provision of Section 520(e) of the Federal Food, Drug and Cosmetic Act. The FDA is authorized by regulation to restrict the sale, distribution, or use of a device if, because of its potentiality for harmful effect or the collateral measures necessary to its use, FDA determines there cannot otherwise be reasonable assurance of its safety and effectiveness.

So a restricted device can only be sold, distributed, or used either upon the written or oral authorization by a licensed practitioner or under such other conditions specified by the regulation. And if the device is restricted for use by persons with specific training or experience in its use or by persons for use in certain facilities, FDA must determine that such a restriction is required for the safe and effective use of the device.

Devices such as cardiac pacemakers and heart valves require a practitioner's authorization. Another example, though, hearing aids are restricted by a regulation that limits their sales to persons who obtain a medical evaluation of their hearing loss by a physician within six months prior to the sale of the hearing aid. The labeling of hearing aids must provide information on their use and maintenance.

Thank you.

DR. ROSENBERG: Thank you, Ms. Shulman, for your presentation. Does anyone on the Panel have any clarifying questions?

(No response.)

DR. ROSENBERG: Okay. We will now proceed to the Petitioner's presentation. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

MR. OVEREND: Hi, there. My name is Russell Overend, and I'm here representing PWB Health, U.K., Limited, who makes the Breastlight product, as I'll show you shortly. My background is as a physicist, so I'm probably the least qualified person here. But I've been involved in the development and launch of quite a few medical devices over the past few years and as such have been working on this Breastlight product for a couple of companies since about 2007. I do appreciate the opportunity to come

along and present to you guys this morning.

There we go. As I said, the product that is made and sold by PWB Health is the Breastlight. I brought a couple of products along that should give you a better idea about the product. It's a fairly simple-to-use product. It's intended to be used at home. And two buttons: bottom button switches on and off; the top button adjusts the brightness. And it really only comes on to full power when it's in full contact with the skin. You can see that. So it'll give you an idea of how the product's used. If you want to have a look at it, I'll just --

(Pause.)

MR. OVEREND: As you can see from the photos on the screen, the product is intended to be used in the dark, and it allows the user to see some of the internal structure of the breast either by looking down at the breast when they have it in front of them or in front of a mirror, which is what we recommend in the indications for use.

For most women, what they'll see is just what you see in the screen there. They'll see the veins and blood vessels, arteries within the breast. But it does allow the user to see quite a lot of fine detail within the breast, and really the projector and the images here don't do justice to it.

All right. So let's see. The Breastlight itself is sold as a home-use aid to breast awareness or breast self-examination as an additional part of your normal breast awareness routine. It works on a very different

principle to a mammography and ultrasound. Mammography and ultrasound obviously work on the principle of absorption of x-rays or sound waves or a reflection of sound waves generated by the density differences within the breast.

The Breastlight itself works on the principle of light absorption by the hemoglobin in the blood. So the red light that we use at 617 nm, it passes quite well through normal breast tissue, and it's transmitted, it's scattered within the breast. But it's strongly absorbed by hemoglobin within the blood. So that's why most women who use the Breastlight will simply see the blood vessels within the breast.

Let's see. The product was developed initially with a radiologist. He was a professor of medical physics at Aberdeen University in Scotland. And I started working with him, we started working with him in 2007.

And the product was launched in July 2008, and it's currently sold in the U.K., where I come from, various European countries, Middle East, Africa, China, and others. We're talking to distributors and regulators in both Australia and Japan at the moment. And we hope to be successful there. And in all other countries that we sell it, it's classed as a Class I medical device.

It's designed to be a low-cost product so that it can be afforded to be used at home. It's obviously not currently for sale in the USA,

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

but if it was, my guess is it would be retailed for under \$100. And it is very clearly indicated as a non-diagnostic product. It's designed to be simple to use at home. And in our opinion and the opinion of the other countries that have reviewed it, it is a safe and effective product.

In the four or so years that the product has been launched, there's been no adverse reports from users as part of our postmarketing surveillance responsibilities. I checked just before I left the U.K., and to date, we've sold 28,000 of these, so we're building up quite a healthy dataset of case studies. And you may have seen in the box there's a prompt to have users register any experiences that they've had at the PWB website. And again, as I say, we're building up some useful kind of case studies there and comments.

We have completed three studies as part of our postmarketing surveillance of this product, and I guess that's what you guys are interested in seeing today. The conclusion that we draw from these studies is that the Breastlight encourages a greater proportion of women to check their breasts on a more regular basis, and it provides additional reassurance to women who are anxious about checking their breasts.

The key thing is that many women are unsure or unaware about how to check the breasts. And the Breastlight, if used in addition to the normal breast self-examination regimen, provides some additional reassurance. And I have to say that -- and I guess there may be some

skeptics about -- they raise the question of fears of false reassurance or over-reliance on the Breastlight, and in the data that we've seen from users, we haven't seen any evidence of that.

Okay. We had some initial dialogue with the FDA. I think it was back in 2007, 2008, which was when we were first made aware of the Class III situation that we find ourselves in at the moment. Despite that, the FDA also highlighted some potential risks for electrical shock risk, for optical radiation risk, and for the potential for missed or delayed diagnosis or unnecessary anxiety from false positive.

We had already anticipated these three and other potential risks as part of our requirements under ISO 14971. I really feel we have mitigated these risks for electric shock. The device complies with ISO 60601, which requires it to be electrically safe. It is a low-power, low-voltage device, and it's been fully tested to EMC, ESD, complies with the Low Voltage Directive.

For optical radiation risk, as I said, it's 617 nm wavelength output. Although it's quite bright, it is eye safe, and the level of output is such that it's classified as a Class I LED. You all have seen from the product the additional, which is now patented, feature of the product is that it has a capacitive switch so that it only comes on to full power when it's in contact with the skin, and actually saw that it doesn't dazzle the user when they're using it, allowing the user to see more of the detail within the breast

structure. That also has the effect of reducing the likelihood of exposure to the eye.

So the main remaining question is the potential for missed or delayed diagnosis or false positives. We deliberately designed instructions for use, a DVD and packaging, to be appropriate for that misuse and, you know, feel free to have a look at the IFU there. And we have completed three studies that quantify the benefit of the Breastlight and then indicate that there was no evidence of faulty assurance or unnecessary anxiety with the product.

So the first study that we did was back in 2007, 2008. It was carried out by an independent market research company. We were looking for volunteers to try the product, so we put an ad in a women's institute magazine and a nursing and practice magazine. So it was a self-selected group, if you like.

But we provided them with a Breastlight, and there were proposed indications for use on DVD at the time. We gave them a questionnaire and asked them to complete the questionnaire partially before and then after using the Breastlight. And the results were then collected from the 1,087 users.

And the things that we found was that the IFU and the DVD that we provided with the product do convey an appropriate level of caution with the interpretation of the results, which was quite reassuring because

we had put a lot of effort into that. And we did see a 33% increase in breast self-examination frequency as a result of the use of the Breastlight. And out of the 1,087 users, 4% of people thought that they saw something, and most of them consulted a doctor or a nurse. Of them, three went on to have a mammogram, and one user out of the 1,087 had detected a previously undiagnosed non-palpable breast cancer. I believe the size of it when it was detected was 12 mm, or 1/2 an inch.

The main thing we found was that there was an increased confidence in self-checking at home. Eighty percent of the women were more convicted in self-checking when using the Breastlight.

So we had some follow-ups from that that we rolled into the product. We updated the DVD and showed the product being used by women. We included some more information in both the DVD and the IFU of what to look for.

And we had the data reviewed by a consultant surgeon at University College London, a Mr. Jayant Vaidya. He, I'll have to say, was initially a skeptic about the product. He was quoted -- I should say he was misquoted in an adverse newspaper article, and we thought we'd follow up with the guy. And when we actually sat him down and showed him the product, took him through the data we had, he was quite impressed with it. And he had published and presented some papers on the device and its usefulness, so that turned around quite nicely.

So that was the first study. The second study is maybe a bit more of what you're used to seeing. After we launched the product, and we had a lot of questions from doctors and from retailers, and they really wanted to know how effective the product was in detecting cancer. I have to say, honestly, we were reluctant to undertake such a clinical trial not just because the product was -- not just because it was expensive doing the trial, but because we clearly sell the product as a non-diagnostic device. So to undertake a trial where we were using a non-diagnostic device and comparing it to other diagnostic devices didn't sit well with us. It kind of undermined our claim that it was a non-diagnostic device.

However, as these things happen, one of the major retailers in the U.K., Boots, insisted that we do such a trial before they would stock the product, so we did the trial. And this trial was run in the U.K. in a National Health Service hospital in the north of England, in Sunderland.

I have to say, the ethics committee approval for this was not straightforward. We wanted to run the trial the way that the product is intended to be used, which is really by women themselves, untrained, at home. But clearly the sample size to do that in undiagnosed cases in the general population would be too large and too long. So we agreed to do a study in a referral clinic with an enriched dataset, women who had previously had seen something, felt something and were referred on, but were still undiagnosed at that point. Even then, the ethics committee

wouldn't allow us to run the trial with a woman using the product herself and felt that that was too stressful for women in that situation in that type of referral clinic, and I have to say we agree with that.

So the product was used by an untrained nurse, a nurse untrained in the Breastlight. And if a woman consented to participate in the trial, the nurse would carry out an examination, make up her mind about whether it was, you know, was cancer present or not, indicate the position of it, seal the answers away, and then the women would then go on to standard care thereafter.

The results from that was that the Breastlight performs reasonably well against final histological and cytological findings. From the 300 patients that took part, there were 18 confirmed cases of malignant tumors. Of them, 12 were detected with the Breastlight, giving a sensitivity of 67%. And I have to say that compares with 16 out of the 18 were found by x-ray mammography. So clearly not an alternative to mammography, but still beneficial, we feel, in the product.

The results of that were published in a Milan Breast Cancer Conference, and the results reinforce our view that the Breastlight is obviously not an alternative to actual mammography, but it's still a very useful addition to a woman's breast self-examination routine.

And the third study that we did -- if you remember, we still didn't have a lot of data on the intended use of the product, so we wanted

to do a study that followed how a woman who had the product used the product over a period of time. And that was really in response to some U.K. health professionals that were concerned about the potential for false reassurance or anxiety or unnecessary anxiety when using a product like this.

So that was carried out by Edinburgh University. It was ethics committee-approved. And Breastlight users were chosen from within the university itself, so it was a mixture of staff and students. And there was a good spread of ages in there. And the users were asked to keep a diary over six months of use of the product, and a questionnaire was issued before and after.

And the key findings from that small trial was that the Breastlight was found by 50% of people who used it to be a valuable addition to their existing breast health routine. It increased their confidence when self-checking, and it helped them be more breast aware. There was no evidence that the Breastlight caused significant distress amongst the patients, and the women reported an increase of 44% in undertaking a breast health routine when they're using the Breastlight.

So to sum up, really, what we've found is that the benefits of the Breastlight does increase the confidence in women who use the product in carrying out breast self-examination. And we do see an increase in breast self-examination frequency, and we think that's because the women are

more confident. Women are less likely to seek -- sorry -- excuse me -- women are more likely to seek a medical opinion when using the Breastlight rather than wait and see what happens. And we have a lot of anecdotes of women who find a lump and do nothing about it. And if they find a lump and they see something with the Breastlight, something changes, then they're going to do something about it, which we think is a good thing.

Doctors who have used the product with patients report that Breastlight may have particularly applicability for women with naturally lumpy or fibrous breasts, and because there's no blood with the kind of fibrous tissue, then the Breastlight, the red light shines right through so nothing is seen. Our data would suggest that there are about 20% of the general population would consider themselves to have naturally lumpy breasts, and a lot of these people do not carry out a regular breast self-examination because there's always lumps there. Some of them have so many lumps, they can't tell what -- if it's a new one or not. So that's particularly useful for women with naturally lumpy breasts.

The doctors also indicated to us that it may be also suitable for checking for interval cancers. In the U.K., women over 50 are called for a screening mammogram every three years. I know it's different in the U.S. But for checking between your regularly scheduled mammograms, then if you've got the all clear from your last mammogram, you use the Breastlight and you see a change, then it prompts most women to then go and get -- go

and see their doctor.

A lot of feedback that we get is that it's particularly useful for women with a higher anxiety towards breast cancer, perhaps due to a family history or having a previous sufferer of the disease. The product really does encourage women to be more breast aware and to carry out a better self-examination. It also provides more information to the women, and we find that -- or it's reported to us that when a woman does present herself to a GP, she is -- feel like more educated about what's going on with her own breast health and she can have a more opened and informed discussion with her doctor.

Okay. So our recommendations to the Committee, really, in our opinion, the benefits of the Breastlight outweigh the perceived risk. We feel that with appropriate safeguards in place, and we very strongly try to do that with a good instructions for use and DVD and packaging of the product, that with appropriate safeguards in place, the Breastlight should be made available in the U.S., as in other countries, as an aid to breast self-examination. And we kind of petition the Committee to consider its reclassification as a Class I medical device with general controls and -- based on the definition that Marjorie outlined earlier.

So thanks for that, and I just want to -- any questions?

DR. ROSENBERG: I would like to thank the Petitioner, Mr. Overend of PWB Health, for his presentation.

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

Now, does anyone on the Panel have a brief clarifying question for the Petitioner? And please remember that the Panel may also ask Petitioner questions during the Panel deliberations this morning. We have about 10 minutes, or so, for this.

DR. ROSENBERG: Krupinski?

DR. KRUPINSKI: Yeah, Elizabeth Krupinski. My question is regarding your next to the last slide, regarding the three benefits that you listed. So those, just for clarification, those are based on that last study with 53 participants, and it was essentially at the beginning, they gave a self report of use confidence and likelihood of seeking medical advice, they used it for six months, and then they basically again reported from that six-month period their use, their confidence, and their likelihood of seeking advice, correct?

MR. OVEREND: Yeah. Russell Overend. Yes.

DR. KRUPINSKI: Okay.

MR. OVEREND: That's exactly right, yeah.

DR. KRUPINSKI: Okay.

DR. TOLEDANO: So this is Dr. Toledano. I'd like you to go back to slide 3 for a moment. And you mentioned that the device is currently sold in the U.K., Europe, Middle East, Africa, China, and others, and that it is safe and effective? What would you like to tell me about Canada?

MR. OVEREND: Right. What I'd like to tell you about Canada

was the product was originally sold as a Class I medical device in Canada, and we had a distributor in Canada who went away from the marketing controls that we had in place and made an unauthorized change to the claims about the product. As soon as we thwarted that, we had the claims withdrawn, we made changes, et cetera, we were in full cooperation with Health Canada, and Health Canada reclassified the product as a Class II medical device and had the product withdrawn because we couldn't at that time provide the necessary -- we didn't have ISO 13485, to be honest. So we couldn't meet the requirements of Health Canada at that time.

So in Canada, the product was essentially downgraded from -- upgraded, if you like, sorry, from a Class I to a Class II as a result of the distributor making unauthorized changes to the marketing of the product.

DR. TOLEDANO: So the recall was voluntary?

MR. OVEREND: The recall -- we worked with Health Canada, and we realized we didn't have a choice but to recall it. But our intention is to go back to Canada once we have 13485, and just at the moment, we don't have ISO 13485, so we're unable to sell the product in Canada.

DR. KOPANS: Dan Kopans. Do you have any fundamental data on the actual transmission of light? It's my understanding that this kind of light actually doesn't transmit directly through the breast; it's all scattered and diffused. And for that reason, my question is do you have any actual science as to how small a lesion you can see at what depth in the breast?

MR. OVEREND: Okay. Russell Overend again. We haven't done basic science on it. We haven't done kind of lab tests, or anything like that. And what we do -- and I agree with you that there's a lot of scattering that goes on, and a lot of, in addition to the absorption and kind of a reflection, if you like, of light as well. And the best way I can answer is that we've seen -- we've had reports of cancers being detected with the product down to 7 mm. And the one case that was cited that was 12 mm in the first trial, and it was about 3 cm under the surface.

So we've got anecdotal -- not anecdotal -- we've got -- we're building up a kind of case history of cancers that have been detected. And, you know, the basic science would say that the deeper the cancer is, the less likelihood it is to be detected, but overall, the data that we've seen is that, on average, about 2/3 of the cancers that are present and undiagnosed are detected with the product.

DR. GLASSMAN: Len Glassman. Could you describe the training that your subjects got? Did it include physical examination of the breast or just the device? And if so, did you test to see whether the physical examination training was actually the differentiating factor in your success rather than the device?

MR. OVEREND: Hi, Russell Overend again. We didn't do any training for the user of product. We provided the product as we would to any customer. So we provided them with the IFU, the indications for use;

we provided them with a DVD. We didn't physically take them into a room and train them on how to use it because that mimics how the product is used in the general population. So to answer your question, there isn't any data on for the Breastlight found -- you know, found something or whether they found it by palpation or seeing a surface change. Training didn't cover that.

DR. ROSENBERG: Dr. Bourland?

DR. BOURLAND: Yes, Dan Bourland. I had a question relative to the statement here about "may have particular applicability to naturally lumpy or fibrous breasts." But at the same time, then, what would abnormal be compared to?

MR. OVEREND: I guess the statements there for fibrous breasts is that, as I understand it, fibrous breasts occur in some women naturally and are not necessarily anything to worry about. So the positive point to that from the Breastlight point of view is that if there's no blood associated with the product -- sorry -- with the fibrous tissue, then the light will pass right through it. So it's an additional reassurance that there's been no change in that fibrous lump.

DR. ROSENBERG: Dr. Zhou?

DR. ZHOU: Andrew Zhou. So one of the risks associated with this device, probably the false positive or false negative. So in your third study, you mentioned that there was no evidence that use of Breastlight

caused significant distress. How did you get the results? Did you have a questionnaire asking to say if you have a false positive -- so how -- where does this data come from?

MR. OVEREND: Yeah. Russell Overend again. Yes. There was quite a thorough questionnaire that went out with the product in these tests, and it's very heavily -- the questionnaire was very heavily biased towards asking questions about how women felt about the product, because that's really its intended use. So when women did see something and they went to the doctor, the questionnaire was there to capture how they felt about it either by checking a box or by writing comments. And they were collected in the data.

DR. ZHOU: How did you get the conclusion there that it does not cause significant distress? Did you ask, like, about whether the woman felt distressed when they maybe get the wrong results from the Breastlight? Did you ask that question to the patient?

MR. OVEREND: That was part of the questionnaire. This was purely a questionnaire study. There was no follow-up one on one with particular respondents. It was purely a questionnaire study.

DR. ROSENBERG: Dr. Dodd?

DR. DODD: So as a follow-up to that, in the third study, did you keep track of how many findings these women had?

MR. OVEREND: There were no findings in the third study. It

was a sample of, I think, 57 women. They didn't find any breast cancers.

DR. DODD: But I mean any false positive findings? You know, you said that some of them went to their clinician if they found --

MR. OVEREND: No, there wasn't in the third study. That was in the first study, the 1,087.

DR. DODD: Okay. So you're saying of the 53 patients in the third study, they didn't have any findings of any kind --

MR. OVEREND: They didn't see anything untoward. They weren't prompted to go and see a doctor or a nurse, and for that sample size, that's roughly what we would expect anyway.

DR. DODD: Okay. So we wouldn't have then been able to measure any signs of distress because they weren't able -- the sample size wasn't powered to --

MR. OVEREND: The things of distress that I thought I was answering earlier were in the larger sample size with the first study and where we had some women go on for some follow-up and consultations with their doctor.

DR. DODD: Okay. But the key findings states that there was no evidence that using the Breastlight caused significant distress amongst the participants.

MR. OVEREND: That's right.

DR. DODD: And you wouldn't expect distress unless something

was actually seen with the Breastlight. So I'm just concerned that the sample size was too small if there were no findings at all in this cohort.

MR. OVEREND: I guess you could have distress with using -- some people may think they would have distress with using the product and, naturally, because they're not sure as to what they're going to see until they use it, that level of distress wasn't there. Obviously, for that study there wasn't the follow-up number of cases that we could then ask about whether they were distressed in something they see -- they saw.

DR. DODD: And then just to follow up on the second study, so the screening was performed by an untrained nurse; is that correct?

MR. OVEREND: Yeah. The way it worked was that when a woman was called to the clinic, she was asked if she wanted to participate in this trial, and an untrained nurse then carried out the assessment with the Breastlight. The results were then separated, and the woman went into standard care, and the result was then collected at the end.

DR. DODD: Okay. And the nurse was instructed to do solely the Breastlight and not do any breast exam after?

MR. OVEREND: Yes. And it was a series of nurses over the time.

DR. DODD: Okay.

MR. OVEREND: Okay?

DR. COLDWELL: This is Coldwell. It seems that the key

findings and probably the basis for the use of this is what you have put in here as increased confidence in their own self-checking abilities?

MR. OVEREND: Yeah.

DR. COLDWELL: Did you have any measure of how well they were trained in self-checking? Did they go through any kind of training for self-checking before they utilized this to make sure that they all started out at the same level?

MR. OVEREND: Let's see. What we're trying to do is what happens in the general population. And the questionnaire was quite heavily focused on what were their attitudes and behaviors before using the Breastlight. So we've actually got quite a lot of data that suggests that before using the Breastlight, women were -- there was a spread from the ones who never self-checked to the ones who do it regularly and are confident. And so we've simply got questionnaire answers on their attitudes, their behavior, their frequency of checking before using the Breastlight. So there wasn't any observation of users to check their effectiveness in checking. It was purely the self-assessment of and their honesty in how often they check, how confident they are in checking, and how thorough they feel they are in checking.

DR. ROSENBERG: Yeah. Quick question, safety. This is a consumer device. And child safety, would this be safe for a child to insert in their mouth or put on their eye.

MR. OVEREND: Yup, it would.

DR. ROSENBERG: With full power?

MR. OVEREND: With full power, yeah. And we had it tested by an independent lab on light output at full power. And I guess the only danger is that you could put it against your eye and --

DR. ROSENBERG: No, that was the question. Would that be dangerous?

MR. OVEREND: It wouldn't. I've attested to that.

DR. ROSENBERG: Okay.

MR. OVEREND: I've actually done it myself as well.

DR. ROSENBERG: We have, I guess, two more questions; then we'll be done.

Dr. Toledano? Yeah, the consumer -- Ms. Lawson?

DR. TOLEDANO: Okay. So it's Dr. Toledano again. When I opened up the brochure in your box, it says right on the top that this device will help you notice changes in your breasts over time. We've heard lots of different studies with lots of different ideas for what you might claim. So what does the device do?

MR. OVEREND: Russell Overend again. What the device does -- and the way that women tell us that they use it is that -- and what it was intended for is to help you look for changes, okay? So it's not a one-time check. Maybe I didn't make that clear. This is a product that, you

know, you're going to use every month for, you know, a couple of years. And what women tell us is that -- and once they use it regularly, they get used to seeing the shape of the blood vessels within their breasts. Some of them call it their road map, if you like. It's a bit like that, some roads. And over time, it's bit like the patterns in the, you know, the palm of your hands. You know, you get to know what's there. So after a couple of uses, you get used to that, and women are encouraged to look for changes. If a shadow develops in a certain area, then they're encouraged to report that and look for a change, okay.

DR. ROSENBERG: Ms. Lawson?

MS. LAWSON: Madeline Lawson. I was interested in the educational background and the representation of the breast users, the ethnic representation, number of minorities, African-American, Latinos, Asian-American women, the ethnic representation.

MR. OVEREND: Let's see. They were largely -- these tests were all done in the U.K., and the U.K. is mainly white women. So I don't have the actual data on that. But if your question is about skin color, we know that we provided samples to a charity in Ghana because we wanted to test that, and the product was able to be used successfully and by a charity called MammoCare in Ghana. But I'm afraid I don't have the data that you're -- and it would be different in the U.K. because the demographics are very different.

DR. ROSENBERG: Quick question, and then we'll go to the FDA.

DR. ABBEY: Craig Abbey. Is there any specific language about pregnancy when the breast may be undergoing changes anyways?

MR. OVEREND: Yup. There is a comment in the -- one of the adverse comments in the brochure that you shouldn't use the product while lactating, so that's specifically covered there.

DR. ROSENBERG: Thank you. We will now hear from the FDA.

MS. WERSTO: Good morning. My name is Nancy Wersto. I'm a medical physicist and reviewer in the Division of Radiological Devices in OIVD.

We're here today to discuss the classification of breast transilluminators. So I will start off the presentation, give you a little bit of information on the background, I think most of which you've already heard, a little bit on the regulatory history. Then Dr. Hui-Lee Wong will provide you with a literature review from 1991 to the present. Dr. Helen Barr will present a clinical perspective of these devices. And then I'll come back with the current regulatory status of breast transilluminators. And, lastly, we have a few questions we would like you to discuss during the discussion session.

Okay. So light scanners or breast transilluminators are also known as light scanners, diaphanosopes, or optical breast imagers. They

are electrically powered devices. And they emit low intensity visible light or near-infrared radiation with wavelengths in the range of 700 to 1050 nm.

The device is pressed against the breast to illuminate mammary tissue, and this is typically performed in a darkened environment. The basic operating principles, as we've already heard, is that light is preferentially absorbed by hemoglobin in the blood.

Okay. Now, these are two examples of breast transilluminators. The device on the left is a much larger system. The breast undergoes some light compression, and then posteriorly, there is an array of light-emitting diodes. And the image is picked up by a CCD camera, and then there is additional onboard software processing. And the device on the right now you are quite familiar with. It is a handheld breast transilluminator.

All right. So breast transilluminators belong to that group of devices that Ms. Shulman previously described as a pre-amendments device. This merely means that they were in commercial distribution prior to May 28th, 1976, when the Medical Device Amendments were enacted. On January 11th, 1991, the Obstetrics and Gynecology Devices Panel met to discuss a number of pre-amendments devices. And one of those devices were breast transilluminators. Subsequent to that meeting, the FDA issued a final rule in 1995 classifying breast transilluminators as Class III. So we're here today to discuss the citizen's petition which was received for reclassification and now to complete the classification process.

All right. As Ms. Shulman previously mentioned, medical devices are placed into either Class I, Class II, or Class III. So those devices for which general controls provide a sufficient assurance of -- a reasonable assurance of safety and effectiveness, these are placed in Class I. And stethoscopes are an example of a Class I device.

For those devices that, well, that our general controls are not sufficient but special controls may be developed are placed in Class II. And most of our imaging and therapy devices, CT, MR, full-field digital mammography, ultrasound, and linear accelerators, these are all Class II devices.

Now, when a device cannot -- the risk of a device cannot be -- have a sufficient reasonable assurance of safety and effectiveness through general controls alone, and there is inadequate information for the special controls to be developed, these devices are placed in Class III. And breast tomosynthesis is an example of a Class III device.

So, currently, regulation for breast transilluminators may be found in Part 21 of the Code of Federal Regulations, Section 892.1990. So as you can see, the regulation takes into account the indications for use of the device along with its technology. And the enactment date specifically for breast transilluminators requiring either a premarket approval, PMA, or a product development protocol, or PDP, has not been established.

Okay. Now I will turn the presentation over to Dr. Hui-Lee

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

Wong, who will provide you with a review of the literature.

DR. WONG: Good morning. My name is Hui-Lee Wong. I'm an epidemiologist at Office of Surveillance and Biometrics, Division of Epidemiology. I'll be presenting the systematic literature review of safety and effectiveness of breast transilluminators.

We will begin with a brief background and methods followed by the main findings on safety and effectiveness of breast transilluminators and followed by a discussion of strengths and limitations of the literature review, and lastly, our conclusions.

Following the receipt of the petition, FDA conducted a new systematic literature review on breast transilluminators. We sought to answer these following questions:

What is the evidence for effectiveness of breast transilluminators for the detection of cancer, other conditions, diseases, or abnormalities?

What are the reported adverse events associated with the use of breast transilluminators for the detection of cancer, other conditions, diseases, or abnormalities?

We searched the PubMed database using these following search terms listed here on the slide. We used broad search terms in order to capture all the relevant articles and data for breast transilluminators. We limited the search to English publications. The FDA Executive Summary

included publications starting from 1995. We have since revised the literature review to include articles starting from 1991, that is, since the 1991 FDA Obstetrics and Gynecological Devices Advisory Panel. In this presentation, we have included an additional three articles from 1991 to 1995.

The inclusion criteria for the literature review are articles or publications that evaluated devices that uses the wavelength of 700 to 1050 nm transmitted to the breasts for diagnoses of cancer, other conditions, diseases, or abnormalities. We further limited it to randomized controlled trials, observational studies, systematic literature reviews, and meta-analyses.

Our PubMed search initially yielded 353 records. Articles and full text, as necessary, were reviewed. Of this, 342 articles and records did not meet our inclusion criteria and were excluded for these following reasons: non-clinical study; and not relevant to breast transilluminator devices per indication, and this is because of our wide search terms; not specific to breast transillumination; non-human study; and combination devices/approaches, and these include ultrasound-guided optical devices or magnetic resonance imaging-guided and optical devices.

Eleven articles were eligible for full epidemiological review. One additional record was identified through cross-referencing. Therefore, 12 articles were included in this review. Of these 12 articles, two

publications were essentially reporting the same clinical data but reported on different aspects of technical aspects of the device. Therefore, 11 independent articles will be presented and summarized in this presentation.

Of the 11 articles, none were randomized controlled trials, nine were cross-sectional study, and two were retrospective study. The study populations were from the United States, Sweden, Germany, France, and United Kingdom, with sample size ranging from 18 to 610 subjects. The initial review covered imaging modalities that included handheld transilluminator, optical mammography, and these include time domain or continuous wave, and optical tomography with or without contrast agents.

We will first present the evidence in our literature review for the effectiveness of breast transilluminators for the detection of cancer, other conditions, diseases, or abnormalities. In our literature review, around nine studies reported on breast cancer, one reported on benign cyst, and one reported both on cancer and women without cancer.

We will discuss the effectiveness, aspects of the effectiveness in the order listed here on the slide. Specifically for performance measures, we will present the findings in the mode it was actually evaluated, in this case, standalone, where the optical breast imager was evaluated independently, or adjunctive use, where the device was evaluated in conjunction with other tests.

For comparator, eight studies used histopathology-confirmed

biopsies as the comparator. And this is considered to be the gold standard for breast cancer classification. Of these eight studies, seven were from European populations. Information in the publications were not sufficient for us to determine in terms of comparability to the United States breast cancer classifications. Two studies compared with x-ray mammography, and one study compared with magnetic resonance imaging. For the latter three, the performance measures would be percent agreement, positive or negative, as opposed to sensitivity and specificity had histology as reference been used.

Here on the slide you see the summary of the performance measures in our literature review here at the first bullet. As you can see, majority of the studies evaluated the sensitivity for breast cancer. There is limited data for women without breast cancer.

In terms of scale reporting, all of these studies used the scale of dichotomous, that is, cancer or no cancer, malignant versus benign. None of them had the finer skills of category, for example, the five skills of category used for rating x-ray mammography by the Breast Imaging Reporting and Data System ratings, or BI-RADS. None of these were on a scale of probability, or neither any of them were on actionable items, for example, no action versus full-op or biopsy.

So moving on to the standalone use of optical breast imaging devices. In the first table here, you see studies that used histology as the

reference. Oh, yes, before we go on, for this slide and for subsequent slides, for studies that do not report the measures of uncertainty -- point estimates, FDA constructed 95% confidence interval based on binomial proportions and were available as reported point estimates and sample size. And these will be indicated by an asterisk.

So back to the slide. In the first row, this study reported the following performance measures in the Swedish light scanning multi-registry study and also reported the positive predictive value in this population. In the second row, Jarlman and colleagues reported sensitivity for 243 breast cancer using -- with dense breasts, and they reported that light scanning mainly failed in detecting small invasive cancer and lobular and ductal carcinoma in situ carcinoma.

For screening populations, Braddick in 1991 performed retrospective analysis of a screening program in Scotland that used clinical examination and light scanner, where they retrospectively looked for records of screen positive woman and followed up by defining the outcome of cancer using cancer registries and hospital notes and reported these following performance measures.

We are still on the standalone use. However, instead of histology, Jarlman in 1992 presented these positive -- this percent agreement using extra mammography as a comparator. And for every undercover analysis for standalone use, Poplack in 2007 evaluated a new

infrared tomography device and presented this area under the curve of 0.7 between -- they differentiated between BI-RADS 4 and 5 versus BI-RADS 1.

Schneider in 2001 evaluated a three-dimensional dynamical optical mammography with intravenous injection of a bolus, which is the indocyanine green, ICG. And using ROC analysis of this bolus, basically, they looked at protrusion parameters to define a cutoff point between malignant and benign and reported the sensitivity, specificity, and performance measures listed down here.

We now present findings for adjunctive use of optical breast images. In this case, all five studies here, the breast was first scanned by x-ray mammography to identify and localize the lesions. Then optical imaging were performed.

The table here lists the four studies where the reference is histology. In this case, the approach of actually using lesion localization with x-ray mammography to interpret the optical images may lead to different performance measures as compared to the standalone mode, which, for example, it may limit false positives that may be reflected in higher specificity and also ROC curves.

Poellinger in 2008 performed area under the curve analysis for a computer tomography laser mammography. And in this case, they were evaluating to see whether their device can actually add on to the diagnostic capacity of x-ray mammography. They reported a mean AUC difference of

0.07 for the device itself versus device and x-ray mammography.

So for all the performance measures that we just reported just now, a number of factors can actually affect them. One of them is reader variability or reproducibility. There was limited data in our literature review on reader variability. One study estimated the intra- and inter-observer agreement for a computer tomography laser mammography between two readers that were blinded and independent.

The other factors that may affect the performance can be lesion size and lesion depth. While six studies in our literature review summarized the sizes of the lesions summarized here in this slide, none of them provided formal analysis of the performance of the device by this lesion. There is also limited data on performance of these optical breast imagers for lesions less than 10 mm or 1 cm, that is, the range usually found for screening women without any symptoms.

There were no reports in our literature review of formal analysis by age, body mass index, race, menopausal status, and breast density.

We will now present the reported adverse events in the literature associated with the use of breast transilluminators for detection of cancer, other conditions, diseases, or abnormalities. In our literature review, none of our studies reported whether or not any of the adverse events had occurred.

So strength of our literature review is that histopathology was the choice of comparator for the majority of the studies, and this is considered to be the gold standard for detection of breast abnormalities. However, there were no randomized controlled trials or prospective studies in our literature review. And reporting in our literature review were limited -- were insufficient for us to determine whether the optical imaging was performed before or after biopsy, whether it was performed with the knowledge of the histopathology findings or whether the location of the lesions detected by the optical imaging devices correspond with the images detected by the comparator.

Test performance. Information of test performance for women without cancer or benign cancer is limited. Likewise, reader availability information is also limited.

In conclusion, additional studies to address the safety and effectiveness of breast transilluminators are needed.

This concludes the presentation for the literature review. Now Dr. Helen Barr will present the clinical perspective. Thank you.

DR. BARR: Hello. My name is Dr. Helen Barr. I'm the Director of the Division of Mammography Quality and Radiation Programs in CDRH. That's the division that runs and administers the MQSA Program. I also practiced clinical breast imaging for many years prior to coming to the FDA.

Excuse my voice. In fact, let me get a cup.

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

(Pause.)

DR. BARR: I'm sorry. I'm getting over a bout of pneumonia, which has proved to be a formidable opponent.

Briefly I'll talk about the concept behind breast light scanning, some limitations of the technology itself, a summary of early breast light scanning research that still seems applicable today, a little bit about a current clinical breast workup, and what a breast diagnostic device needs to be. The concept behind the transillumination was that light in the red and near-infrared range is absorbed by hemoglobin and that absorption of the light would be different in benign and malignant tissue and, therefore, it could be distinguished one from the other.

Some natural limitations of this are that hemoglobin absorbs light whether it's in a lesion, a vessel, or whether it's free in tissue, which can lead to false positive. Some indirect signs were identified early on as possibly being useful, such as increased vascularity and abrupt vessel caliber change, but with this technology, especially without flow parameters, they turned out not to be reliable indicators of malignancy. And then there was also the penumbra effect with light in that you need all portions of the breast close to the skin to ameliorate the structural shadows obscuring smaller lesions.

In the last 1980s, Dr. Carl D'Orsi, who was at this Panel yesterday, got a grant from NIH to study this technology. And the

conclusions that he drew were that the sensitivity was not high enough to detect lesions under 1 cm in size, so therefore, this should not be a screening device; that the specificity was too low - it should not be used alone for diagnosis because it couldn't reliably distinguish between benign and malignant lesions; and they didn't come up with any known adjunctive uses.

Now, this is a crazy slide, and I know there's, you know, a million variations on the clinical breast workup. But what this example is designed to do is say that here you have lots of different things. You see screening mammography, you see diagnostic mammography, diagnostic ultrasound, possible MRI, needle biopsy, et cetera. What you don't see is breast transillumination, which hasn't been proven to be useful in the clinical breast workup that we currently use in the United States.

I was asked to talk a little bit about what a useful diagnostic breast imaging device would look like. It would have high specificity. It would be able to distinguish benign from malignant. It would have to have at least reasonable sensitivity, and especially in breast imaging, we certainly need to see lesions less than 1 cm to get breast cancer at its earliest, most treatable stages. It would need to be useable across a range of patient populations, people with dense breasts, large breasts, or the limitations of its use would need to be spelled out. It would need to have low operator variability or high reproducibility. And it would need to detect signs that

reliably indicate the presence or absence of disease. And I talked about diagnostic devices that currently, as you saw in the C.F.R., it says diagnosis. But for screening, you could, you know, easily turn this around for screening, where it would need to have a high sensitivity, et cetera.

The characteristics of breast light scanners are that they have a low sensitivity for lesions under 1 cm in size. They have low specificity. They have high operator variability and low reproducibility. And interpretation can be based on unreliable signs.

In the 1991 Obstetrics and Gynecology Panel, they identified three major risks associated with breast light scanning, and I posed the question of whether these are still true today, if there's anything that's changed since that time. They identified misdiagnosis or the failure of the device to differentiate between benign and malignant lesions, delayed diagnosis, false negative results can lead to delay in timely diagnosis and delayed treatment, allowing an undetected condition to worsen and increase morbidity and mortality.

And, finally, I wanted to talk a little bit about the additional clinical information that the Petitioner provided and sort of our take. The first source, with the 1087 users, was a market research survey. It wasn't found in peer-reviewed literature. And the data is on product use and not safety and effectiveness. The second source, the 300-patient source, again, not found in peer-reviewed literature. It was an observational study in

women who were already reporting symptoms. And the third source, again, not found in peer-reviewed literature, and it was data from a questionnaire; the validity of that instrument isn't known to us.

Thank you.

MS. WERSTO: Okay. Nancy Wersto again, and I will follow up with a few comments on the current regulatory status of these devices, the FDA. Subsequent to that 1991 Obstetrics and Gynecology Devices Panel, FDA had published both a proposed rule and a final rule in 1995, which effectively placed breast transilluminators in Class III and also created that regulation that we saw earlier in Section 892.1990. The final rule also required either a PMA or a PDP to be submitted. Now, Section 515(b) of the Food Drug & Cosmetic Act requires the FDA to call for PMAs by specifying a specific date in the Federal Register. And this is a rulemaking process that requires both notice and comment.

Now, Section 515(i) of the Food, Drug & Cosmetic Act requires us to set a schedule to call for PMAs. And so in response to that, the FDA published a proposed rule on August 25th, 2010, which again placed breast transilluminators in Class III. And its intent now was to establish that effective date requiring either PMA or PDP. It also provided an opportunity for public comment.

Well, in response to that opportunity for public comment, we did receive the citizen's petition on September 9th, 2010. And the Petitioner

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

reported that, as you heard earlier, in countries outside of the United States, breast transilluminators are considered Class I devices. However, we recognize that there are differences in the regulatory requirements between CE Mark and FDA clearance. The Petitioner also states that the risks associated with breast transilluminators are adequately mitigated.

And they have described their device as a "nondiagnostic product." And the Petitioner provided some evidence of safety and effectiveness from three sources containing additional clinical information, which Helen had reviewed. Ultimately, the Petitioner requested that the FDA consider placing breast transilluminators as a nondiagnostic device in Class I.

Okay. So today in your discussion session, there are a few things we would like you to do. We would like you to review the risks of these devices and identify any new risks or risks which may have been overlooked. We would like you to consider the appropriate mitigations for these risks and to evaluate the merits of the citizen's petition.

In order to do that, you will need to determine whether there is sufficient valid scientific evidence to demonstrate a reasonable assurance of safety and effectiveness of breast transilluminators. And, ultimately, we would like you to come to consensus on the appropriate classification based on the evidence you've heard today.

Thank you very much for your attention. This concludes our

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

presentation.

DR. ROSENBERG: I would like to thank the FDA for their presentation.

Does anyone on the Panel have a brief clarifying question for the FDA? Please remember we may also ask FDA questions during deliberations later.

Dr. Kopans?

DR. KOPANS: And I'd like to make sort of one comment question and the other a direct question. I would hope that the FDA, particularly when it comes to breast devices, breast cancer detection devices, be more careful using the word detection versus actually demonstrate. Unless it's a blinded study -- in the review, we heard unless it's a blinded study, I would suggest that a device that shows a lesion whose presence is already known is not detecting it but actually just demonstrating it. And I think that's a very important distinction.

The other question I have is the FDA summarized several studies. I think a number of them certainly used laser light for transilluminator, and I would suggest, but I'd like to hear FDA's opinion, that laser transillumination is probably different than diffuse light transillumination, which is the device under discussion. Does the FDA have any position on that?

DR. WONG: Thank you for your comments. Hui-Lee Wong. I

do -- well, for the first comment, I do agree with that. It should be demonstrate versus detection. For the second one, actually, the way we included the literature, the publications, is that they're all in the order of 700 to 1050. So if their methods actually say that the device uses this particular wavelength, then it was included.

Thanks.

DR. KRUPINSKI: Elizabeth Krupinski. Follow-up question on that, on the literature review. Out of the 11 studies, how many were handheld? And just to verify what you just said, that your study looked at 700 nm and above, and their device is 617 nm. So does their device fall in your literature review? And then did any of the studies you looked at look at the benefits that they claimed, which is in increased patient compliance or breast examination, increased reporting and increased use and so on?

DR. WONG: Hui-Lee Wong. So I think that's three questions there. So the first question is whether there are any handheld transilluminators. There is one, and that's the Cheng in 2003, if you can pull up my additional backup slides here. But it's actually adjunctive mode. So they first actually used x-ray mammography. None of them, we do not have any actually in standalone. So let's see.

DR. KRUPINSKI: That's okay. That answers the question.

DR. WONG: That answer questions? And your second question is would the Petitioner's device in be in our literature review.

Because our inclusion criteria follows what the regulation was, which is 700 nm to 1050, had they had any peer review literature, our literature review would probably not include that.

And you had a third question? Sorry.

DR. KRUPINSKI: Did any of the studies that you did, especially the handheld one, look at the potential types of benefits that the Petitioner is claiming for their device?

DR. WONG: No, we did not have any of those with any validated instruments. Most of the studies were -- I think they were optimizing the device. So a lot of times, we have to construct the sensitivity and specificity ourselves.

Thank you.

DR. HENDRICKS: Yeah, Carolyn Hendricks. I just need clarity, I think, for the information that I've heard this morning about whether we are addressing either a diagnostic or a non-diagnostic tool, because the information from the Petitioner appears to hinge on the whole issue of breast self-awareness, but all the information from the FDA relates to this device in the detection of breast cancer. And to me, there seems to be a significant disconnect, and I need better clarity on that as a charge to us as a panelist.

DR. ROSENBERG: FDA, please?

MS. MORRIS: Yes. So the subject of today's meeting is specific

to what we see in the regulation for the reclassification. And if we could have the slides pulled back up quick enough -- otherwise I can read it out of the regulations. It should be under -- yes, 21 C.F.R. 892.1990, transilluminator for breast evaluation. The transilluminator, also known as the diaphanoscope or light scanner, is an electrically powered device that uses low intensity emissions of visible light and near-infrared radiation, approximately 700 to 1050 nm, transmitted through breasts to visualize translucent tissue for the diagnosis of cancer, other conditions, diseases, or abnormalities.

Anything outside of that classification is not the topic of today's discussion, but there are other pathways in which products that could have a different indication for use go to market. But today we're focusing on this classification and whether or not devices with that indication for use and technological characteristics, whether or not there is safety and effectiveness information to support the appropriate classification.

DR. ROSENBERG: Thank you. Toledano and then --

DR. TOLEDANO: Thanks. It's Dr. Toledano, and I have two quick questions of clarification for the FDA. So the first question of clarification: If a device has these properties right there on the slide, is it forced to have an indication for detecting cancer, other conditions, diseases, or abnormalities, because there are other clinically meaningful indications.

But so often, FDA has the reputation of forcing manufacturers to seek a detection or a diagnosis indication. So I'd like to know from you if the manufacturers will be forced into this indication. That's my first question.

DR. ROSENBERG: Ms. Morris?

MS. MORRIS: Forced is a strong word. There are devices that may not meet this exact definition described in the C.F.R. that could get onto the market through our normal regulatory pathway. So, for instance, a device would come on the market, it doesn't fit this definition, but they could say that they are substantially equivalent to this or something else, depending upon whether or not this is determined to be a Class I or a Class II. And if we find that it's not substantially equivalent, the alternative is that they would by default become a Class III device or they can request an automatic reclassification under what we call the de novo process, and we can evaluate the safety and effectiveness data.

And if we determine that you can establish special controls, then we could reclassify it into a Class II or a Class I. We could also determine whether or not it could be exempt. But for today's topic, again, we're focusing on those products -- it's a product class -- that fit within the technological characteristics for that indication for use. And that's what we want to focus on. But that doesn't provide a barrier of other products with a different type of indication for use to get on the market through the normal regulatory pathway.

DR. TOLEDANO: Okay. So then to follow up on that, if this gentleman -- and then we can get back to our regular Panel -- but if this gentleman whose device emits under 700 and has a different IFU, if he takes transilluminator out of his name, is he no longer subject to this regulation?

MS. MORRIS: The way I see it right now, the way this product is being described, it doesn't fit this regulation, but there are other alternatives in which he can pursue market.

DR. ROSENBERG: Dr. Ziskin, did you have a question?

Dr. Kopans?

DR. KOPANS: Yeah. I think I'd like to have either some clarification from the FDA or just acceptance of what I have to say -- Dan Kopans.

In the Executive Summary, which we were given, and I'm not sure if it was mentioned again today, the suggestion is made that the light passes "easily" directly through the breast. In fact, that's not the case. Even coherent laser light, only 1/10 of 1% will pass through a cubic centimeter of breast tissue. So none of this light is passing directly through the breast. I think there are also other statements suggesting that you can see blood vessels in the breast. Again, I would challenge that unless someone can present data to the contrary. The only blood vessels that you see are blood vessels in or immediately underneath the skin, which are backlit by the scattered and diffuse light that is causing the breast to glow.

So I think we need to be careful about light will get through the breast, but it takes a very torturous path, and there's essentially no resolution at anything, you know, really beneath the skin that tells you that you're seeing anything really inside the breast. And I would just as an example, and maybe this will come up again later, just using the device in, admittedly, not a darkened room, you can't actually see the bones in the palm of your hand with the light behind it. And your hand -- in my experience, breasts that are compressed, there are some breasts that are less than 2 cm but not very many in compression. Most are thicker than that, so the amount of light that actually is getting directly through is miniscule.

DR. ROSENBERG: Dr. Faulk?

DR. FAULK: Robert Faulk. Question probably mostly for the FDA here. I guess I need definite clarification in terms of evaluation of effectiveness of the device, because what you're saying is that the device should be evaluated in terms of effectiveness for its ability to diagnose breast cancer. But I think what I was hearing earlier from the Sponsor in response to a direct panelist question was that the intended usage was "look for changes in the breast." So it seemed that what the Sponsor is requesting for intended use is actually different than what we're supposed to evaluate effectiveness for intended use by the FDA.

DR. ROSENBERG: Ms. Morris?

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

MS. MORRIS: Thank you. Yes. I realize that there is some confusion with this. The fact that there is a petition, we need to provide the opportunity for the Petitioner to address the Panel to consider it. It was the Petitioner's choice of words of how to label their device, and perhaps there is not the understanding that the subject is whether or not the device for its indication for use is safe and effective for that use. The pre-amendments device, when they determine Class III, was for the diagnosis of cancer and other abnormalities.

So that's why I'm trying to keep it focused on what the original intent of the classification was for. Other indications for use, again, to put it in very abstract terms, would be considered a different device because it has a different indication for use that would alter the intended therapeutic or diagnostic effect. So certainly that can be a medical device, it can be reviewed by the Agency, and it can be evaluated for that. But, again, the purpose of today's meeting is the classification of transilluminators for that wavelength description for the indication written in the regulations.

Does that help?

DR. FAULK: Yes.

DR. ROSENBERG: Yeah, Ms. George?

MS. GEORGE: This is Elisabeth George. I just want to have a clarifying question on the actual regulation, the way it's written, because two things I read in here; one, it says "approximately 700 to 1050." It

doesn't say "700 to 1050" so -- and it's in brackets. So to me, that means that that's giving you a conception of range, where I think is where the FDA is coming from where this device could possibly fall into it.

And then when I read the last part of the sentence, you could read that to visualize translucent tissue abnormalities. It doesn't say for the diagnosis of abnormalities, the way I would read that. It says for the diagnosis of cancer.

DR. ROSENBERG: Ms. Morris?

MS. MORRIS: Yes. So that does provide the flexibility to consider the product, and we can take in advisement the Panel's recommendation if we want to consider the product within a range, of course, yes, I agree that approximate gives flexibility to open it up; it doesn't have to be restricted to that. And then if there is a desire to consider only the presence of abnormalities, we would take that under advisement. I was trying to make sure that we focused on the classification that was already listed in the C.F.R. and not go too far astray from that original classification.

DR. ROSENBERG: Dr. Jiang?

DR. JIANG: Yulei Jiang. Can I make a suggestion that we heard the indication for use different from what we're discussing, but we never saw the indication for use. Can maybe the Petitioner or FDA pull that up sometime so we can be clear on that?

DR. ROSENBERG: FDA, please?

MS. MORRIS: So I do not have the specific indication for use for the product that was described earlier, but perhaps the Petitioner could provide that for us.

DR. ROSENBERG: Yeah. Quick, please?

MR. OVEREND: Okay. Russell Overend again. Let me try and find it on here.

Can you find it for me?

(Pause.)

MR. OVEREND: There we go. Put it up on the screen. The intended use of the product is as home-use aid to breast awareness, breast self-examination, as an additional part of your normal breast awareness routine.

DR. ROSENBERG: Thank you.

MR. OVEREND: Okay.

DR. ROSENBERG: Dr. Zhou?

DR. ZHOU: I think I have two questions. First, I think we want to be careful that we're not actually evaluating this particular product. That's not our Panel's function here. We are evaluating the whole class. So maybe he has a different indication for use; maybe other one has an indication. I don't think we are here to actually evaluate that particular product. So that's first question.

Second is I just want to get a clarification from FDA that for

the handheld product, when you do the literature review, are those used by patient or used by doctors or nurses or healthcare providers?

DR. ROSENBERG: Please?

DR. WONG: Hui-Lee Wong. So for the handheld product that is Cheng and colleagues in 2003, let's see, it's a handheld transilluminator; it's used by patients, it's a P-scan handheld.

DR. ROSENBERG: Further questions, clarifications?

Yes, Ms. George?

MS. GEORGE: Question on that handheld device that's used by the patients. Earlier you mentioned that there were no adverse event reports, and if the focus of one of the concerns was misdiagnosis, I'm wondering what a patient would even consider or know to communicate as an adverse event with the device because they wouldn't -- false positive or false negative, they would never even think to communicate that. So I'm wondering what types of adverse events would have even been considered to be reported.

DR. WONG: This is Hui-Lee Wong. I will answer that and then refer that to the clinical reviewer also. So in the literature review, there were no reports of it. And as you said, they did not measure any endpoints at all. What we would like to see, for example, is to then extrapolate from the performance measures and look in terms of false positives versus false negatives. But that is not reported.

MS. GEORGE: But would the physician who identified that the patient had a cancerous event even know that the patient had utilized that device themselves?

DR. WONG: So overall, the reporting conduct of the studies in the literature review were very limited. They tend to be -- as I say, they tend to be more optimization of the device. And quite a number of the performance measures we actually constructed ourselves from the data itself, so --

DR. ROSENBERG: Last question, Dr. Kopans?

DR. KOPANS: Yeah. I'm just curious. Did the FDA -- I mean one of the claims for this particular product is improving breast self-awareness. I happen to think that's a good idea, but based on the science, there are two randomized control trials of breast self-examination that have not shown a statistically significant decrease in deaths in women who were theoretically trained in breast self-examination. And to my knowledge, unless the FDA has found it, there are really no studies that confirm that breast self-awareness actually reduces deaths. Is that the FDA's findings as well?

DR. BARR: Helen Barr, FDA. Yes, I agree with that.

DR. ROSENBERG: Thank you. All right. Let's take a --

DR. DODD: I have one --

DR. ROSENBERG: Dr. Dodd?

DR. DODD: This is with regard to the Cheng study, 2003. I believe that was the one that you were just referencing. Am I wrong, the P-scan?

DR. WONG: Hui-Lee Wong. Yes.

DR. DODD: Okay. I'm just reading the pilot clinical trial, and here, just to clarify, it says that the radiology technician at MGH who knew the locations of the suspected malignant areas found by the mammograms conducted the P-scan examinations. So my reading of that is that it wasn't done by the patients. Am I --

DR. WONG: Oh, yes, yes, sorry. That is correct. Because they actually have another one that is guided by ultrasound. Yes, that's correct.

DR. DODD: Okay.

DR. WONG: Sorry about that.

DR. DODD: And, again, that wasn't a detection task because they already knew the location?

DR. WONG: Right.

DR. ROSENBERG: Okay. It is now 10:05. We will take a 10-minute break; 10 minutes please.

(Off the record at 10:05 a.m.)

(On the record at 10:16 a.m.)

DR. ROSENBERG: All right. It's now 10:16, Open Public Hearing. We will now proceed with the Open Public Hearing portion of the

meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Ms. Craig will now read the Open Public Hearing disclosure process statement.

MS. CRAIG: Both the Food and Drug Administration and public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Dr. Rosenberg?

DR. ROSENBERG: Okay. There has been a request to speak by the following: I don't have any names listed -- Leroy Hamilton? Yes. Okay.

I'm sorry.

Each speaker will be given approximately five minutes to address the Panel. Once you have been asked to approach the podium, please be sure to state your name, company, and any affiliation you may have with the entities presenting today.

Thank you.

DR. HAMILTON: My name is Leroy Hamilton. I have no connection with any of the participants, the companies involved with this meeting. I'm here as a private citizen concerned about the regulation of medical devices by the FDA.

This morning Ms. Shulman gave you a nice presentation about classification. She did not mention something that I find quite important, and that is the classification questionnaire. When I read the -- when I applied to speak at this meeting, I had no idea that a reclassification was being considered, so my talk is particularly relevant under these circumstances. And this slide presentation is running against my will. I'm going to start it over or we'll get -- we need this --

UNIDENTIFIED SPEAKER: There you go.

DR. HAMILTON: I have recorded my narration, so I'm going to let this slide show take the job. So sound, please.

UNIDENTIFIED SPEAKER: It's there. You just have to go through your slides until it gets to your sound.

DR. HAMILTON: The sound starts on the first slide. The sound starts on the first slide.

(Recording) It's important that you have a clear understanding of what constitutes life supporting or life sustaining --

(Live) Now, I would like to start the slide show over again so --

(Recording) Your understanding of the second phrase is equally important. The third phrase requires a good understanding of the device and how it is used. If none of the three conditions in the second part of the definition is satisfied, the device does not qualify for Class III.

Now, let's turn to the classification questionnaire. In 1976, we used a very early version of this form. There have been at least five versions since 1997. This slide identifies the current version which expires next month.

Now, consider the hypothetical device with the characteristics shown on this slide. These ensure that the device does not qualify for Class III according to the definition we just discussed. We only need to answer the first six questions to get the classification:

One: Is the device life supporting or life sustaining? No.

Two: Is the device for a use which is of substantial importance in preventing impairment of human health?

Three: Does the device present a potential and reasonable risk of illness or injury?

Four: Did you answer yes to any of the above three questions? No.

Question Five: Is there sufficient information to determine that general controls will be sufficient? No.

Question Six: Is there sufficient information to establish special controls? No.

As you can see, the questionnaire places the device in Class III even though it does not satisfy the definition of (audio malfunction). There's a simple conclusion that the Form 3429 has a serious flaw.

If the Panel agrees with my analysis, the Panel could refuse to use Form 3429 until the problem is resolved. The Panel could advise CDRH of the need to revise Form 3429 to conform to the definition of Class III.

Why didn't I take this issue to the FDA? Well, I tried to. The ombudsman refused to meet with me or even answer questions. He answered -- he ordered CDRH employees not to reply to communications from me. He suggested that I present the issue during the Open Public Session at the Panel meeting. That's why I'm here.

If the Panel agrees that my analysis is correct, you can begin to appreciate there are important implications to be considered. For example, some of the 428 devices in Class III may have been over (audio malfunction).

Are there any questions?

(Live) So are there any questions?

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

DR. ROSENBERG: Are there any questions from the Panel?

(No response.)

DR. HAMILTON: I think it's regrettable that my presentation was not intact. You missed some of the important steps in discussion of the definition of Class III. And the issue I want the Panel to understand is that the classification questionnaire, which you may or may not be using currently, I don't know, but that questionnaire has a serious flaw in it, as I've described in this presentation. My time was limited. I couldn't give more of the story. But I'm happy to -- I'll be here all day. And if there are questions later during the Open Public Hearing this afternoon, I will be available to answer questions at that time.

Thank you for your attention.

DR. ROSENBERG: Thank you, Mr. Hamilton.

Does anyone else wish to address the Panel at this time? If so, please come forward.

(No response.)

DR. ROSENBERG: Seeing none, does the Panel have any questions for the Open Public Hearing speakers?

DR. TOLEDANO: So it's Dr. Toledano, and I just wanted to say thank you for putting together your presentation and making the effort to come out and communicate your findings in public.

DR. HAMILTON: I want to thank you for asking your question

or making a comment. This is not my first attempt to get the story at a panel meeting. This is my third attempt. The first one, I was overruled by a CDRH employee who overruled a panel chairman who had given me permission to speak. At the second meeting, I had a slide show which I was working on at the last minute and ran long, so I didn't get to the punch line.

This one we find has another glitch. It seems the gremlins are well perched on my shoulder. But thank you.

DR. ROSENBERG: All right. Thank you, Panel. I pronounce this portion of the Open Public Hearing to be officially closed, and we will proceed with today's agenda, Panel deliberations.

We will return to the Panel deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak to identify themselves each time. This helps the transcriptionist identify the speakers. We will open up the floor to questions for both Petitioner and/or the FDA.

Do any Panel members have a question or comment for the Sponsor or FDA?

Dr. Glassman?

DR. GLASSMAN: Len Glassman. I have a question for the Petitioner. In your first study of 1087 patients, one of the key findings was 1 out of 1,087 detected previously undiagnosed non-palpable breast cancer.

How many additional cancers were detected that were palpable or suspected in that group?

MR. OVEREND: There were no other. That was the only one that was detected.

DR. GLASSMAN: And I noticed from your data, if I'm interpreting it correctly, that approximately half of your patients were 50 or over, which would make them eligible in the U.K. for screening mammography. And yet it states here that only three out of five or six hundred, say 500, had a mammogram. Is that an accurate number?

MR. OVEREND: Probably. I think in the U.K., it's once you're over 50, you get called for a mammogram every three years, and that makes -- that doesn't start on your 50th birthday. So it could be on your 53rd birthday, if you like.

DR. GLASSMAN: And --

MR. OVEREND: And you're more or less right, yeah.

DR. GLASSMAN: Okay. So I guess this is a comment rather than a question, but then I'm concerned about what increased confidence is doing for the diagnosis and detection of breast cancer. But thank you.

DR. ROSENBERG: Dr. Faulk and then Dr. Abbey?

DR. FAULK: Robert Faulk, question for the Sponsor. As I understand it, your real intended use for this product is really looking for a change over time, is your intended use; is that correct??

MR. OVEREND: Russell Overend again. Yes, that is correct, and --

DR. FAULK: Okay. If that is your intended use for the product and we are to judge the efficacy -- if we were judging the efficacy of that, what data do you have to present to us that gives us any indication of the effectiveness of your study in looking for a change? So how do we know whether your device can actually "look for a change"?

MR. OVEREND: Russell Overend again. That is the trial that we would like to have carried out, but the ethics committee wouldn't have allowed us to carry out that trial. And so we're unfortunately limited to the trial that we've got. And I think what we're trying to do is generate enough data over time to answer questions like that but from various angles within the restrictions that the ethics committee would have placed upon us.

DR. FAULK: Okay. So if I'm correct, then, at this time there is no data to really indicate the effectiveness of this device for detecting a change in the breast. And therefore, I guess by default, there's no data to give us an idea of the effectiveness of if there is a change, what is the significance of the change?

MR. OVEREND: I think that's probably right. But I also say that, given the restrictions that the ethics committee put on us in doing such a trial, it's unlikely that that data, as you described it, would ever become available through a test like that.

DR. ROSENBERG: Dr. Abbey?

DR. ABBEY: So I guess this is a question for the FDA. If we were to recommend reclassification to Class I, it strikes me that a device could come in much like the device yesterday except working on optical technology instead and not have any sort of a panel meeting where they displayed any sort of ROC curves or anything because it would be a Class I correct in that assessment, that if we reclassify it to a Class I device, then they skip all the basically scientific studies, et cetera, for a device that would not necessarily be intended for population of -- the population of women, but a device that's intended for diagnosticians, per se?

DR. ROSENBERG: Ms. Morris?

MS. MORRIS: If I understand your question, if the Panel would recommend the device that's the topic of this discussion as a Class I, then it would be subject to general controls. And one of those controls, unless determined to be exempt, would be a premarket notification, 510(k), in which we would determine whether or not it's substantially equivalent to the original device. If we found that it was not substantially equivalent, then it would become a Class III.

DR. ROSENBERG: Dr. Hendricks?

DR. HENDRICKS: Question for the FDA. Just clarification on the issue raised in the Open Public Comment section, please.

MS. MORRIS: I'm sorry. I'm not quite --

DR. HENDRICKS: Well, as I understand it, in the Open Public Comment section, significant concerns were raised about some inconsistencies in the definition of a Class III device. I just wanted clarification on behalf of all the panelists.

MS. MORRIS: Okay. So I'm not familiar with the concern regarding the classification questionnaire, but for the sake of this discussion, we are actually not using the classification questionnaire that's being referred to in the Open Public Hearing. Does that answer your question?

DR. TOLEDANO: Thank you. So it's Dr. Toledano. I have two questions about the topic of today's meeting. The first is what such devices are currently approved and for sale in the U.S. from, you know, before the 1976. And the second is are any such devices currently under review by FDA?

DR. ROSENBERG: Ms. Morris?

MS. MORRIS: I'm sorry. Could you repeat that for me?

DR. TOLEDANO: Yes. So today we're talking about -- oh, sorry, it's Dr. Toledano again -- transilluminators for breast evaluation coming under the 21 C.F.R. Section 892.1990. What such devices, how many of these devices are currently approved and being sold in the United States?

MS. MORRIS: Thank you. Janine Morris. Currently, since this classification, we have not received any premarket notifications for this device in which they have been cleared. So they are not -- there should be

no devices that are out on the market currently that are legally marketed.

DR. TOLEDANO: Thank you.

DR. ROSENBERG: Dr. Kopans?

DR. KOPANS: Dan Kopans. Yes. I'm curious, from the Petitioner, why would an ethics committee not allow you to do a study with a safe and fairly harmless device?

MR. OVEREND: Russell Overend. They were concerned for the potential of distress to the patient in finding something that they didn't know what it was. So they didn't want to cause undue distress to the patient.

DR. KOPANS: But presumably -- Dr. Kopans again -- presumably the patient would be asked to volunteer, ask to participate, and that would be her decision, it would seem to me.

MR. OVEREND: We tried that argument, but the ethics committee at the time just decided that they -- the distress to the patient was not something they could allow.

DR. ROSENBERG: Ms. Vega?

DR. VEGA: Hi, Marlena Vega, Dr. Vega. I want you to know that I'm one of the few Latinos that enjoy haggis before we ask. Okay. And that's my colleague over there as well, eh?

That said, I'm afraid that I have some very strong consternation about -- as a psycho-oncologist, okay, with patients that I see,

okay, who are, shall we say, rather very obsessive and anxious and have family histories, myself included, and who really, really, really are looking for almost to grab onto anything, in a way, I can see them taking your breast light and on a daily basis and then almost an hourly basis running around, and oh!

The problem then would be that they would then call one of these wonderful radiologists and say, listen, I have to see -- I have to come into the office; I have to because I see something. And unfortunately the people that might benefit, which might be some of the minority populations who really don't have the -- are not necessarily at all going to be able financially or culturally to adhere to some of -- so I'm just wondering if in the future, perhaps, if you have the tenacity, and obviously you do, to keep coming back over the -- that you might consider, as one of my colleagues had suggested, that there are really culturally diverse responses, and they do exist in England as well.

Okay. The other piece is that there has to be some kind of a profile that comes about that can perhaps, in fact -- a psychological profile, whatever kind of thing, that would in fact help women, okay, to determine just the amount of usage and the possibility of the positive of it rather than, you know, doing this constantly or whatever.

So I'm really talking as a patient advocate about I think that it's wonderful, and I agree with Dr. Kopans, that advocacy and interest and

touching one's own breast -- I'm the originator of the Macarena, okay, so that we do the self exam, and I do it all over. So touching, becoming familiar, owning one's own body, okay, rather than having somebody else who is a relative look at it, who drives the truck occasionally and then says, oh, that lump is going to go away after your period, which I really think that if you could, in fact, think more about the patients that you want to serve, it might be very productive.

Thank you.

DR. ROSENBERG: Okay. Dr. Zhou.

DR. ZHOU: Andrew Zhou. I just want to make sure we got all your point -- you got -- because based on the information we have, the data, I did not see -- I do not see why you think your device can be classified as a Class I device. Can you summarize some new evidence you have not showed us or that's all, all you show us so far?

MR. OVEREND: Russell Overend here again. That's the main evidence that we've got. We have a kind of case history of case studies that people volunteer to us, but they've not been clinically -- they've not been peer reviewed or consolidated in any way. So the data that we've got is what I've shown you today.

Can I reply to your comments of earlier? I don't know if that's --

DR. ROSENBERG: Briefly, yeah, please.

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

MR. OVEREND: Okay. Thanks. A couple of things. We think that a lot of women do like the product; they initially start off concerned about it, but what they're looking for is more reassurance. I don't know if you noticed the helpline -- sorry -- in the IFU, there was a nurse helpline. And largely, most of the people who carry out a breast self-examination with the Breastlight will do it at night when it's dark, and you know, we had nurses on call to answer their questions and try to reassure them. So I think we've been as responsible as we can.

And we have advocated sharing Breastlights between groups. We have trialed kind of loan of Breastlights in order to be kind of socially responsible and provide them to different groups. But I would say that -- maybe this a point for consideration. If you were concerned about the misuse of the Breastlight, then one of the options open to you is to -- whether it's under a Class II or a Class I would be to put in place some controls that perhaps allowed the Breastlight initially to be sold under the supervision of a doctor, and we'd be quite happy with that because that -- I think what we're finding is that over time, people become a lot more relaxed about it. The doctors get to know it. And if it was under a doctor's control, then that might be an easier first step to accepting the Breastlight in the U.S. market.

DR. VEGA: I could actually see you having focus groups and actually support groups if, in fact, you know, to extend this, where it was

sort of discussed, taught, and whatever if, in fact, that's the reality that occurs.

DR. ROSENBERG: And I think the discussion is a general one on light scanning and not exclusively on this sample. But it's important.

Dr. Bourland, did you have a question? I think I've --

DR. BOURLAND: Yes. Thank you. Dan Bourland. Follow-up question for the Petitioner to Dr. Faulk, actually, relative to monitoring of change.

So to monitor change, there must be a baseline. So are there instructions for women in terms of, okay, you're now obtaining the baseline, they don't quite know whether it's normal or abnormal, and then -- but there is something. And then I think the image receptor in this case is the eye, which involves the brain and memory. So how do we know how that works over time relative to memory of is this the same or is this different or not? Because other devices, for instance, have an image receptor which then captures the image.

And then I'm also curious, relative to this, is one so-to-speak viewpoint, the eye here, transillumination from below, does that change relative to the angle of the device? And for instance, how would one see going the other direction?

MR. OVEREND: Okay. There's a few questions --

DR. BOURLAND: So I'm sorry. That was maybe three

questions.

MR. OVEREND: Few questions.

DR. ROSENBERG: You can answer it briefly, but I think we're deviating from kind of the focus here, which is not this particular device, but it's conceptually about light scanning devices and the scientific evidence we need.

DR. BOURLAND: Okay. Thank you.

MR. OVEREND: Okay. I'll be as brief as I can. We rely on the brain to memorize it. And to answer your question, we do encourage the women to move the source of the light around different parts of the breast, and yes you do see the -- it's almost like the shadow of the blood vessels move as well. So it does depend on where you shine the light, but that also affects -- allows you to have a more effective check, if you like. So I've forgotten what the rest of your questions were. But hopefully that answers them. But basically you rely on the person to remember what they've seen. And as I said before, women describe it as the road map of their breast. Over time, they remember what the pattern looks like for them.

DR. BOURLAND: Okay. Thank you.

DR. GHATE: Hi, I'm Sujata Ghate. Just a question. You mentioned reassurance several times; in other words, women would be reassured if it's negative. But do we really have many true negative data? I mean, have these women been followed long term to see if a cancer has

developed in the areas that show up as negative?

MR. OVEREND: Sorry, Russell Overend. We didn't do follow-up studies with the ones -- on these three trials, but there was data as part of them on the kind of negative sensitivity. I can't remember off the top of my head, but I think of the 282 negative cancers, I think there was about 260 of them were correctly identified as negative by the Breastlight, which we were quite pleased with that one because that's better than the false positive rates that we see in other screening techniques.

DR. ROSENBERG: Dr. Krupinski, did you have a question?

DR. KRUPINSKI: Yeah, follow-up to what you just said. You just said that they were negative for cancer. Does that mean they were finding benign lesions, or were they just truly normals? There's a difference.

MR. OVEREND: I think they were just truly normals. I think, but I -- I have sent out the full findings of that to Shanika, so hopefully she's distributed that to you. We can look it up if required.

DR. ROSENBERG: Dr. Ziskin and then Dr. Glassman.

DR. ZISKIN: I have a question for the FDA, and it has to do with safety, essentially. All of the breast illuminators were grouped into as a single device as far as concerns. Yet the only thing in common is the 700 to 1050 nm wavelength. But as far as safety goes, the intensity of the beam would be very important, the beam width, and ultimately, it's the temperature elevation that would be most important because that's the real

concern here, for damage to the eye, particularly for a device that's going to be used in the home where it can be used inappropriately, for prolonged exposures, and so on. So that if you're going to have anything but a Class III for everything, you'd have to say, well, okay, up to a certain limit, it could be a Class I or a Class II, but other than that, you would have to make some distinction based upon what is the expected output and temperature elevation that could occur.

MS. MORRIS: Janine Morris, FDA. So I'm hoping that I'll address your question, but ask again if I don't. But part of your Panel deliberations is to talk about the different classifications. And you heard earlier about Class II classification talks about special controls. And if you found that there was a particular product with certain specifications that would mitigate those risks that you describe, then that's what we consider special controls. So certainly those would be addressed as a Class III. But as you know, many of the Class II devices have many of those risks that you describe, but they're adequately mitigated by these special controls we have.

DR. ROSENBERG: Dr. Glassman and then Ms. George.

DR. GLASSMAN: Since we're into the Panel deliberation part, couple of comments of a general nature. First, I agree completely with Dr. Kopans about light being scattered by the breast, and if you only look from the top, you only see the immediate superficial things under the skin

because everything else is scattered.

Also, light of any wavelength that would possibly be used for transillumination is stopped by any solid tissue in the breast. And the more dense the tissue, the more likely you will get a black spot. It's not just hemoglobin. And if you look microscopically at breast cancers, there's -- at least in the low and intermediate grades, which are very common breast cancer, they're much more likely to have fibrous tissue than they are multiple large vessels that might have an effect.

So I think the scientific underpinnings of hemoglobin absorption are somewhat shaky. I think the class of transilluminators in general, there is little, if any, credible, high-quality scientific data that they are effective. And in the absence of their being effective, there is a negative safety implication of delay in diagnosis. So from what we've heard today from my standpoint, they're not effective, and therefore, they haven't been proven to be safe, and therefore, Class III is the best they get.

DR. ROSENBERG: Thank you.

Ms. George and then Ms. Toledano.

MS. GEORGE: Just to answer some of the questions I think that were asked about the safety aspects, whether it's a Class I, II, or III, one of the things that manufacturers would have to do in the sale of our products into the United States would be either to prove through our submission on our own through safety analysis as to why it is safe or through

the use of many of the international standards. The Petitioner mentioned the 60601, which is the electromechanical ones. There's associated performance standards. There's the AAMI HE75, which is the human factors and usability, which we would have to prove. The FDA is frequently asking manufacturers for proof on efficacy and usability to ensure that it's capable of being used by the population that it is being asked to use it. And then the ISO 14971, which is the risk management, which is throughout the whole process and life cycle of the product, to understand those risks.

So whether it's Class II or Class III, those things would all be things that the manufacturer, upon their submission, that the FDA would be expecting to see fully and effectively delineated and described either through actual data submission or through a certification that they had, in fact, done those assessments.

DR. ROSENBERG: Yeah, Kopans?

DR. KOPANS: And Dan Kopans. I'd just like to second the comments that were made earlier. It seems to me that there's no predicate device that has been shown to be effective. Well, I guess maybe it's a question to the FDA. Assuming this is thought of now as a new device, because there's no predicate device to do a 510(k), for example, does that automatically make it a PMA, or is there a way that a totally new device that has no precursor, if you will, that's been approved? How does that work?

DR. ROSENBERG: Thank you, Dr. Kopans.

Ms. Morris?

MS. MORRIS: Janine Morris. I'm not entirely sure I understand your question, but if we would assume that these were not pre-amendments, that there wasn't a transilluminator prior to 1976 in commercial distribution, at any time, a product can come in to be determined for classification. Our classification is the 510(k) process. We would determine whether or not it was substantially equivalent to a predicate. Almost anything can be a predicate that is under the regulations. The key is, is it substantially equivalent to that predicate. And if we couldn't find that it was substantially equivalent in terms of its intended use and technological characteristics, then we would find it to be a Class III.

DR. ROSENBERG: Follow-up, sure.

DR. KOPANS: Follow-up to that question, then. Dan Kopans. Again, I don't know exactly how the FDA approval originally came up for light scanning, diaphanography, whatever you want to call it, but my understanding of the science is that there is no effectiveness for these devices. So it was approved under the previous guidelines, whatever they were. So given that assumption, does that mean that a predicate device that wasn't effective in the first place is still a predicate device and you can be equally as ineffective? Is that what I'm hearing?

(Laughter.)

DR. ROSENBERG: Ms. Morris?

MS. MORRIS: Janine Morris. Technically, that can be true, but let me go back to the history of this device. So during the classification periods of the late '70s and early '80s in which we had classification panels to determine, of all those devices that are out on the market, that they were legally marketed, meaning that they went through commercial distribution, interstate commerce, we determined what the relative risks were for all these products. These were not originally part of that classification, but later on it was determined -- perhaps this was the scenario:

Someone said, well, I have this transilluminator, and it was commercially marketed prior to 1976, and here is the evidence of that. And we said, okay, it does appear like you have pre-amendment status. And then that either puts it into an unclassified category or we would hold a panel meeting to determine its classification. And that took place for these devices in 1991, in which the Panel said that this is, in fact, a Class III device, based on the evidence, because they didn't think that it was effective.

So it's a pre-amendments Class III, but FDA did not call for PMAs, meaning that in the Federal Register, our obligation is to say at this date, all companies who want to market transilluminators for this indication for use must submit a PMA. This is the completion of that process.

DR. ROSENBERG: Dr. Toledano?

DR. TOLEDANO: So it's Dr. Toledano. So I'm going to follow up on Dr. Kopans and Ms. Morris.

So if a company can figure out a predicate, they can come in through the 510(k), and then you can say it's NSE and then a de novo becomes Class III. Or we can tell you please put out a notice that they're all Class III, and then you put the call for PMAs at some date and it becomes a Class III. Do I have our options?

MS. MORRIS: Janine Morris, FDA. I think that we have, like, apples and oranges here. Today we're talking about a Class III pre-amendments device. Anything post-amendments has to go through a classification process, which is our 510(k) process in which we would determine -- we can take an example of, you know, x-ray detector and say, well, what is the predicate. And we would determine -- you could have an x-ray detector that is quite different from the ones that are currently on the market. And for one reason or another, due to the intended use or the new technological characteristic, we might find that x-ray detector to be non-substantially equivalent, Class III. They have the option to request automatic reclassification under de novo in which we would then evaluate safety and effectiveness data.

But today we're talking about a Class III pre-amendments. It's already been determined to be a Class III. We're opening it up because of the Petitioner to do we want to reconsider that since we haven't talked about this since 1991. What do we know since 1991? Do we remain in Class III, or do we want to reconsider that original decision?

DR. TOLEDANO: Thank you.

DR. ROSENBERG: So, in essence, is there new scientific evidence to change the 1991 panel decision? Does that summarize what you just said?

MS. MORRIS: Janine Morris. Yes.

DR. ROSENBERG: Dr. Glassman?

DR. GLASSMAN: Len Glassman. Let me make sure I understand this because I'm a little bit confused, and maybe other people are, too. If we leave these transilluminators as a Class III and somebody comes in with a new device that falls under this category, they do a 510(k), the FDA in this hypothetical situation says, no, this is a Class III, they're not approved as a Class III? They have to apply using Class III standards? There's no automatic approval? Just want to make sure we all understand that.

DR. TOLEDANO: So why would they use a 510(k)?

MS. MORRIS: Janine Morris, FDA. So technically, the 510(k) premarket notification process is our classification process for everything post-amendments. So let's go through the hypothetical scenario that based on the Panel's advice, that we keep the devices that are described under the classification as a Class III, a different company comes with a transilluminator, maybe different characteristics, maybe a different intended use. They might come in and say, well, we're not -- they don't use the Class III device as a predicate because if they did, then they automatically are a

Class III, and they would have to submit a PMA, and we would send them a letter telling them that.

But perhaps there is another device that is legally marketed for something different, it's generally maybe similar technological characteristics -- maybe it illuminates light but it might have a different intended use -- and it was determined to be a Class II device, they could say, well, we're substantially equivalent to that. And then we go through our decision making to decide whether or not we agree. We may still say no, your indication for use leads to a new intended use, and you're also a Class III, different from the original pre-amendments Class III determination.

DR. KRUPINSKI: Elizabeth Krupinski for the FDA. So the pre-amendment predication and definition that we're operating on here today is that it's a diagnostic device, correct? I mean, that's what's in the definition and that's what we're considering? It as a diagnostic device, correct?

MS. MORRIS: Janine Morris, FDA. That's how I read the definition as well, yes.

DR. ROSENBERG: Further questions or we can go -- yes, Dr. Jiang?

DR. JIANG: I guess I have a question for FDA, and then I'll make a comment.

So it sounds like this process would have taken place with or without the Petitioner's petition, but we're here today because he

petitioned?

But then the comment, it seems to me there's a sense that the Petitioner's point are not particularly relevant to what we're discussing here because his device is not a diagnostic device, but we're talking about a diagnostic device here.

DR. ROSENBERG: FDA?

MS. MORRIS: Yes. But that's what's being revealed today at this Panel meeting. But the point that a petition was submitted to the Agency, we need to do due diligence and present this to the Panel for reconsideration so that all opportunities to discuss the facts of this classification can be determined and settled, and we can proceed with the final classification of the device that is defined under the regulation.

DR. ROSENBERG: Dr. Kopans?

DR. KOPANS: Yeah. Dan Kopans. That last question raises another question in my mind. I've already mentioned the issues at least the way those of us in breast imaging think about detection versus diagnosis. Is there a definition -- I'm sure there is somewhere -- as to what a diagnostic device means? Does that just mean a device that's used to assess human beings, or what does diagnostic actually mean to FDA?

DR. ROSENBERG: Ms. Morris?

MS. MORRIS: Janine Morris, FDA. I can't explicitly answer that. Let me defer to anyone else here from FDA, but I don't think there is

anything in the regulations that defines that for us.

DR. KOPANS: If I can just -- to come back -- I'm awaiting the answer, but again, I think the FDA probably uses diagnostic in a much broader application than some of us who use it in a very specific way.

DR. ROSENBERG: Please.

DR. BARR: Helen Barr, FDA. Yes, I would agree with that. It does have a broader definition. But generally it's for use in somebody who has a symptom or a sign rather than an asymptomatic population.

DR. ZHOU: Can I say a few words about that? I mean, it sounds like we distinguish between diagnostic versus predictions, a disease diagnosis and prediction of the disease. I think if you talk about prediction, which is occur in the future, the diagnosis probably not occur in the future but in the present. So that's my understanding.

DR. DODD: Lori Dodd. This does say the diagnosis of cancer, other conditions, diseases, or abnormalities. So we might tend to think of a diagnosis of an abnormality as a screening or detection task rather than a diagnosis task. So I would read it as being more general as well.

DR. ROSENBERG: Okay. Then are we ready to go to answer the FDA questions?

(No response.)

DR. ROSENBERG: Further clarifications?

(No response.)

DR. ROSENBERG: Okay. At this time, let us focus our discussion on the FDA questions. Copies of the questions are in your folders. I want to remind the Panel that this is a deliberation period among the Panel members only. Our task at hand is to answer the FDA questions based on the data in the Panel packs, the presentations we've heard this morning, and the expertise around the table.

With this said, I would ask that each Panel member identify him or herself each time he or she speaks to facilitate transcription.

Please show the first question.

MS. MORRIS: Excuse me. Janine Morris with the FDA. I just want a point of clarification. We had a few additional slides that talked about safety and effectiveness. These were definitions of safety and effectiveness found in our regulations. They were reviewed yesterday; also, the definition of valid scientific evidence. But not all the Panel members here today were here yesterday. Would you like us to review those definitions prior to going to the questions?

DR. ROSENBERG: Yeah, please.

MS. WERSTO: Okay. Nancy Wersto again. Assurance of safety can be found in 21 C.F.R. Section 860.7(d)(1). There is a reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by

adequate directions and warnings against unsafe use, outweigh any probable risks.

Okay. Assurance of effectiveness, 21 C.F.R. Section 860.7(e)(1). There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

All right. Valid scientific evidence, which is found in Section 806.7(c)(2): Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

DR. ROSENBERG: Just I'm assuming in your statements, these FDA regulations and guidelines, that significant is not the way it's used in statistics, in other words, statistically significant. And I say that because

certainly in this medical literature, the journals especially frown upon the use of the word significant unless it's with regard to statistical significant. So I'm assuming that you're using it as the common language use as opposed to biostatistics?

MS. MORRIS: Janine Morris, FDA. That's correct. It allows flexibility for that definition.

DR. ZHOU: Can I follow up on that? But if you are not statistically significant, can you still claim to be significant?

(Laughter.)

DR. ROSENBERG: Ms. Morris?

MS. MORRIS: Janine Morris, FDA. In the scope of the regs, yes.

DR. ZHOU: That's kind of dangerous.

DR. ROSENBERG: The regs are not written by biostatisticians.

(Laughter.)

MS. WERSTO: Nancy Wersto.

Question 1: The key risks to health of breast transilluminators identified by the Obstetrics and Gynecology Devices Panel include missed diagnosis, delayed diagnosis, delayed treatment, electrical shock, and optical radiation. Please identify any additional risks to health that should be addressed with respect to breast transilluminators for the diagnosis of cancer, other conditions, diseases, or abnormalities.

DR. ROSENBERG: Dr. Kopans?

DR. KOPANS: Yeah. I would probably add in there unnecessary interventions. We don't know that this has happened, but I'm assuming, as with most devices, that something will be seen that will necessitate additional evaluation.

DR. ROSENBERG: In other words, additional imaging?

DR. KOPANS: Additional imaging, needle biopsies. I mean, there's all kinds of different things.

And in the FDA regulation that we just heard, the probable benefits have to outweigh the possible harms. And I haven't heard any demonstration yet of a benefit except breast self-awareness, which, again, from a science --

DR. ROSENBERG: I think we're just dealing with the risks right now.

DR. KOPANS: Oh, okay. I'm sorry.

DR. ROSENBERG: Yeah.

Dr. Dodd and then Dr. Hendricks.

DR. DODD: Yeah. Lori Dodd. Just wanted to expand on that and maybe call it overdetection, because overdetection would imply the psychological aspects as well as whatever other follow-up comes after that.

DR. ROSENBERG: What's that, please?

Oh, would we include anxiety as a result of false positives?

DR. PAYNE: I was just going to comment on that, in terms of user anxiety, because it's part maybe of delayed diagnosis, but it's a different component.

DR. ROSENBERG: Dr. Abbey?

DR. ABBEY: So I think distress or anxiety is really conditional upon whether the Petitioner's device falls in this category or not because it doesn't sound like it's a diagnostic device, so I don't think we're talking --

DR. ROSENBERG: Yeah, we're talking hypothetically about this class as a diagnostic tool.

DR. ABBEY: Right. So are handheld devices such as this in this case?

DR. ROSENBERG: Ms. Morris?

MS. MORRIS: They could be. So it's a broad definition of a transillumination for an indication that we've stated.

DR. ROSENBERG: Please.

DR. BOURLAND: Dan Bourland. The optical radiation is -- I think it's a noun, but in any case, the risk might include heating. Whether that should be specifically listed or eye injury or something like --

DR. ROSENBERG: Thermal injury?

DR. BOURLAND: I don't know how specific that needs to be named, but potentially.

DR. ROSENBERG: Other risks?

(No response.)

DR. ROSENBERG: Okay.

Ms. Morris -- Dr. Jiang?

DR. JIANG: I don't know -- maybe the additional financial burden is a risk.

DR. ROSENBERG: Financial? I don't know -- no. Actually, we don't deal with finances in these deliberations.

Okay. So I think we're time to summarize Question 1.

Ms. Morris, with regard to Question 1, the Panel generally believes that these are the primary risks, and there may be some other, as noted, minor additional risks to patients. Strike minor. Thank you. Risks. Strike minor.

MS. MORRIS: Thank you. You've addressed Question 1.

DR. ROSENBERG: Thank you, Ms. Morris.

Okay. Question 2, please?

MS. WERSTO: Okay. Question 2:

Class I medical devices are those for which general controls are sufficient to provide a reasonable assurance of safety and effectiveness. Please discuss whether you believe general controls alone adequately mitigate the risks associated with breast transilluminators for the diagnosis of cancer, other conditions, diseases, or abnormalities.

DR. ROSENBERG: Dr. Glassman?

DR. GLASSMAN: Len Glassman. I would answer that no. And

the reason is that this is an extremely broad definition of devices, some of which, if ever approved, would be in the hands of trained medical practitioners; others may be in the hands of people in their homes with small children running around. So until such time as we would know the characteristics of a specific piece of equipment, the answer should be no.

DR. ROSENBERG: Ms. Hendricks?

DR. HENDRICKS: Carolyn Hendricks. Just again, this is the third time this has come up in this discussion this morning. Is the highlighted areas, is it diagnosis of cancer, diagnosis of other conditions, diagnosis of disease, and diagnosis of other abnormalities? Have we resolved at the Panel level that this is a diagnostic tool for the diagnosis of those four categories?

DR. ROSENBERG: Ms. Morris?

MS. MORRIS: So my personal interpretation of the regulation is the diagnosis of each of those. If the Panel believes that it could be interpreted differently, we can discuss it, but that's currently how we're interpreting it.

DR. ROSENBERG: Is everybody in agreement, then, with Dr. Glassman?

(No response.)

DR. ROSENBERG: Ms. Morris, with regard to Question 2, the Panel generally believes that Class I medical device controls are not

sufficient to ensure safety and effectiveness.

MS. MORRIS: Thank you for answering Question 2.

DR. ROSENBERG: FDA, please, Question 3?

MS. WERSTO: All right. Question 3:

Class II medical devices are those for which special controls in addition to general controls are necessary to provide a reasonable assurance of safety and effectiveness. Is there sufficient information to establish special controls for breast transilluminators?

DR. ROSENBERG: Dr. Hendricks?

DR. HENDRICKS: I think we'd have to conclude no, as the Panel I think has not heard any evidence in support of the effectiveness of these devices.

DR. ROSENBERG: Dr. Glassman?

DR. GLASSMAN: Len Glassman. I concur with Dr. Hendricks.

DR. ROSENBERG: Ms. Morris, with regard to Question 3, the Panel generally believes that Class II special controls would not be sufficient to ensure safety and effectiveness.

MS. MORRIS: Thank you.

DR. ROSENBERG: Next question?

MS. WERSTO: Class II medical devices -- oh, you know, I'm sorry. This goes on for a second frame here:

Would the addition of special controls to general controls

mitigate the risks, and what should the special controls include?

DR. ROSENBERG: Dr. Glassman?

DR. GLASSMAN: To take the last one, I don't think we can define special controls until we know the characteristics of the piece of equipment that's being considered. Again, comments just referable to what I said before.

DR. ROSENBERG: So I can add to the prior statement that it's too general a class to at this point establish what special controls would be necessary.

MS. MORRIS: Okay. Thank you.

DR. ZHOU: This is Andrew Zhou. If we already consider this Class III, why would you want to consider the special controls for Class II?

MS. MORRIS: Janine Morris. I'll just clarify. Unfortunately we didn't read the entire question. Question 3 talks about special controls and sufficient information; then asks if we would consider special controls, what would they be. So this was a continuation of our previous question. So taking the question in total, if you have a different point of view, please state it for the record.

DR. ROSENBERG: Dr. Ziskin?

DR. ZISKIN: Well, if there was a control that would limit the output of the optical radiation to a point in which you would not have a significant increase in temperature, I would be satisfied for that particular

aspect of it.

MS. MORRIS: Janine Morris with the FDA. Just keep in mind that the classification is based on technological characteristics as well as the indications for use that determine its intended use.

DR. ROSENBERG: Yeah --

DR. COLDWELL: Coldwell --

DR. ROSENBERG: Coldwell --

DR. COLDWELL: I still haven't heard any scientific studies to validate the efficacy of this, so I would continue with -- even though it may be technologically safe if those thermal controls were placed, I still haven't seen enough evidence to convince me it's a worthwhile piece of equipment.

DR. HENDRICKS: Carolyn Hendricks. This is going back to Dr. Kopans' comment. Should we be considering the -- if there is no evidence of effectiveness, do we need to comment then on the risks, if there is no demonstration of effectiveness in this class?

DR. ROSENBERG: Ms. Morris?

MS. MORRIS: Yes, Janine Morris. No. This is only if you were going to consider it as a Class II device, then we would like you to expand on what you think the special controls should be.

DR. ROSENBERG: This hypothetically is a new device we're presented whose characteristics we don't know, yeah.

Okay. Are we now up to -- does that conclude Question 3?

Thank you.

Question 4, please?

MS. MORRIS: Okay. So this is Janine Morris with the FDA. We can go to the question that's in the book, but we felt that it wasn't necessary if you felt that it was not a Class I and if you felt it was not a Class II, it would default into Class III, and that's what we're trying to determine. So if, for the record, the Panel could confirm that you believe that this device under the classification should remain in Class III, that would be helpful.

DR. ROSENBERG: So the question to the Panel is, is there -- is the Panel comfortable with the device remaining as a Class III device? Any comments or discussion?

Dr. Glass -- we can just go around.

DR. GLASSMAN: I'm comfortable with Class III, Len Glassman.

DR. BOURLAND: Dan Bourland. I'm comfortable with Class III primarily based on the lack of evidence relative to effectiveness.

DR. ABBEY: Craig Abbey. I'm comfortable with Class III.

DR. TOLEDANO: Alicia Toledano. I'm comfortable with Class III, but I don't understand why we wouldn't then discuss the requirements for a design of a pivotal trial under Class III, but it's totally up to you guys.

DR. HENDRICKS: Carolyn Hendricks. I'm comfortable with the designation of Class III.

DR. ZISKIN: Yes, for Class III. As long as diagnosis is in the

Class III category, then it has to be, I agree.

DR. ZHOU: Andrew Zhou, so based on the evidence we have seen today, I agree they have to remain on the Class III.

DR. DODD: Lori Dodd. I agree it should remain under Class III.

DR. COLDWELL: Coldwell. I agree, Class III.

DR. BABB: James Babb. I'm comfortable only with the designation as Class III.

DR. PAYNE: Tom Payne. I concur with Class III, and I base that primarily on the comment made by Dr. Bourland, and that is I think in order to use the device, it does have to have some scientific evidence of efficacy. Thank you.

DR. FAULK: Robert Faulk. I believe this device fits best into Class III.

DR. KOPANS: Dan Kopans. I agree with Class III.

DR. JIANG: Yulei Jiang. I agree with Class III.

DR. KRUPINSKI: Elizabeth Krupinski. I agree with Class III.

DR. GHATE: Sujata Ghate. I, too, agree with Class III.

DR. VEGA: I get to agree? Hey, go with Class III, segura. All right. Class III for sure.

(Laughter.)

MS. LAWSON: Madeline Lawson. I agree with Class III.

MS. GEORGE: And this may surprise you, but I, too, agree with

Class III based on the definition in the C.F.R. 892.1990, because of the lack of effectiveness data as well as the lack of data to address the identified risks.

DR. ROSENBERG: Ms. Morris, I think we have a consensus.

MS. MORRIS: Thank you. Just for the record, we were not voting, per se, but we have a consensus. Thank you.

DR. ROSENBERG: Okay. At this time, the Panel will hear summations, comments, or clarifications from FDA and the Petitioner, and you have three minutes each.

MS. MORRIS: Janine Morris with FDA. We have no summation at this time.

DR. ROSENBERG: Mr. Overend?

MR. OVEREND: Thank you. Russell Overend. Obviously, I'm a bit disappointed with that, but I understand the regulations that you got to work within. I wouldn't mind a follow-up conversation if that's possible with the FDA after this to see what avenues we can explore as a non-diagnostic device. But I appreciate your time today in considering it and look forward to future discussions with the FDA.

Thank you.

DR. ROSENBERG: Thank you. Thank you very much. Does anybody have any additional comments? If not, we will return from -- go to lunch in our room and return at 1.

I would like to say thank you to the Panel members, and this

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

session is now adjourned. As I said, we'll return at 1:00.

(Whereupon, Session I was adjourned.)

SESSION II

(1:15 p.m.)

DR. ROSENBERG: It's approximately 1:15, and I would like to call this meeting of the Radiological Devices Panel to order.

I am Dr. Rosenberg, the Chairperson of this Panel. I am a radiologist/mammographer at the Radiology Associates of Albuquerque and Professor Emeritus at University of New Mexico. And my area of expertise is mammography, breast imaging, and outcomes research.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA law and regulations.

For today's agenda, the Panel will discuss and make recommendations regarding the 515(i) order issued by the Food and Drug Administration on April 9, 2009 -- oops --

(Off the record.)

(On the record.)

DR. ROSENBERG: During Session II, the Panel will discuss and make recommendations regarding the classification of blood irradiators. Blood irradiators have been found to be substantially equivalent to predicate devices marketed in interstate commerce prior to May 28th, 1976 and are subject to general controls provisions of the Food and Drug and

Cosmetic Act. These devices have never been formally classified. There is an agreement between the Center for Devices and Radiologic Health, CDRH, and the Center for Biologics Evaluation and Research, CBER, that outlines which FDA center will regulate these devices.

CDRH regulates irradiators intended for use in the immunologically active cells in blood and other tissues, and CBER regulates irradiators intended for use in the in-process inactivation of HIV viruses or other pathogens. The Committee discussion will focus on whether these devices should be classified in Class I, II, or III.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation.

Ms. Morris?

MS. MORRIS: Janine Morris, the Food and Drug Administration.

DR. BOURLAND: I'm Dan Bourland. I'm a medical physicist in radiation oncology and at Wake Forest University.

DR. BREZOVICH: Hi, I'm Dr. Ivan Brezovich. My area of expertise is medical physics for therapy of cancer. I work at the University of Alabama at Birmingham. I'm a full professor.

DR. HARVATH: Liana Harvath. I'm formally of the federal government, 33 years as a research immunologist. My area of expertise is in

leukocyte biology.

DR. LEITMAN: Susan Leitman. I am a senior staff member of the Department of Transfusion Medicine at the National Institutes of Health in Bethesda, and my interest is in irradiation of blood products, blood collection, donor safety, and aphaeresis safety.

DR. RENTAS: Frank Rentas. I currently serve as the Director of the Armed Services Blood Program. I'm a colonel in the United States Army. And my area of expertise is blood banking and transfusion medicine.

DR. ZHOU: Andrew Zhou, Professor in Department of Biostatistics at University of Washington. My research area is statistical methods in diagnostic medicine.

DR. DODD: Hello. I'm Lori Dodd. I'm a biostatistician at the National Institute of Allergy and Infectious Diseases. Prior to joining NIAID, I was at the National Cancer Institute for seven years.

DR. COLDWELL: Hello, I'm Doug Coldwell. I'm a Professor of Radiology and Bioengineering, and head of Interventional Radiology at the University of Louisville. And my area of research is in radiation dosimetry as well as a whole lot of other things.

(Laughter.)

LCDR ANDERSON: Hi, I'm Lieutenant Commander Anderson of the United States Public Health Service. I'm also Designated Federal Officer for the FDA.

DR. BABB: James Babb, Associate Professor of Radiology, New York University School of Medicine. My expertise is biostatistics.

DR. PAYNE: I'm Tom Payne. I'm a medical physicist. I was at the University of Minnesota for a duration of about 10 years. I then went to a large community hospital. I did radiation therapy at that hospital. I have also worked in CT scanning and mammography physics. I'm currently a consultant medical physicist.

DR. GILCHER: I'm Ron Gilcher. I'm the CEO and Medical Director Emeritus of the Oklahoma Blood Institute. My areas of expertise are internal medicine, hematology, and transfusion medicine. Currently, I'm in private consulting business.

Thank you.

DR. LANDGREN: I'm Ola Landgren. I'm a hematologist by training. I'm a senior investigator at the NCI Intramural Program in Bethesda, and I'm the head of the Multiple Myeloma Program at the NCI.

MS. CRAIG: Shanika Craig. I'm the DFO that'll be helping out silently during this meeting.

(Laughter.)

DR. JIANG: Yulei Jiang, Associate Professor of Radiology at University of Chicago. I'm a medical physicist. My area of interest -- computer-aided diagnosis of breast cancer and prostate cancer and also evaluation of diagnostic performance.

DR. VEGA: Hi, I'm the comic relief.

(Laughter.)

DR. VEGA: Buenos tardes. Good afternoon, everybody. I have a rare blood type, but not why I'm here. I am a psycho-oncologist. I started an organization almost 43 years ago in my youth for women who had cancers and who had no insurance. I'm a three-time survivor of cancer and third-generation survivor. I'm the only survivor, actually, in my family.

My real, real, real expertise is in survivorship. I've been here for two and a half days. I don't even know my name anymore. I'm in the wrong panel -- no, no, no. And actually I'm delighted to be with this Panel, and it keeps changing, which is lovely because I'm metamorphosing along with it. But we are consistent, the three of us here, Moe, Joe, you know, we're with the three stooges --

(Laughter.)

DR. VEGA: And so I welcome the new audience and certainly say hello to the Panel. Thank you.

MS. LAWSON: Hi, I'm Madeline Lawson. I'm President and CEO of the Institute for the Advancement of Multicultural and Minority Medicine that's based in Washington, D.C., with a focus on addressing disparities in health and healthcare. My expertise, among other things, is health communication and advocacy. And I'm a Consumer Representative to this Panel.

MS. GEORGE: And last but not least, the Industry Representative. I'm Elisabeth George with Philips Healthcare, Vice President of Global Government Affairs, Regulations, and Standards, with about 10 years of experience in the imaging modalities. And prior to that, actually, seven years experience in blood washing, blood separating, and rapid infusion equipment.

DR. ROSENBERG: Thank you, thank you. If you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Okay. Lieutenant Commander Anderson, the Designated Federal Officer for the Radiological Devices Panel, will make some introductory remarks.

LCDR ANDERSON: The Food and Drug Administration, FDA, is convening today's meeting of the Radiological Device Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the

Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

During Session II, the Panel will discuss and make recommendations regarding the classifications of blood irradiators. Blood

irradiators have been found to be substantially equivalent to predicate devices marketed in interstate commerce prior to May 28th, 1976 and are subject to the general controls provisions of the Federal Food and Drug and Cosmetic Act. These devices have never been formally classified. There is an agreement between the Center of Devices and Radiological Health and the Center for Biologics Evaluation and Research, CBER, that outlines which FDA center will regulate these devices. CDRH regulates irradiators intended for use in the immunologically active cells in blood and other tissues, and CBER regulates irradiators intended for use in the in-process inactivation of HIV viruses and other pathogens. The Committee discussions will focus on whether these devices should be classified in Class I, II, or III.

Based on the agenda for today's meeting and all financial interests reported by the Panel members, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208 and Section 712 of the FD&C Act.

A copy of this statement will be available at the registration table during the meeting and will be included as part of the official transcript.

Elisabeth M. George is serving as the industry representative, acting on behalf of all related industry, and is employed by Philips Healthcare.

We would like to remind members and consultants that if the

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

discussion involves any products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the Panel of any financial relationships that they may have with any firms at issue.

For the duration of the Radiological Device Panel Meeting on April 12th, 2012, Ronald Gilcher, Liana Harvath, and Susan Leitman from the Blood Products Advisory Committee in the Center of Biological Evaluation and Research, CBER, have been appointed as Temporary Voting members -- I'm sorry -- Temporary Non-Voting members.

For the record, Dr. Vega is from the Oncologic Drug Advisory Committee in the Center for Drug Evaluation and Research and will be serving as a non-voting Patient Representative for this session.

These individuals are special Government employee who has undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

Dr. Francisco Rentas is a regular Government employee from CBER and has been appointed as a Temporary Non-Voting member who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

This appointment was authorized by Jill Hartzler Warner, J.D.,

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

Acting Associate Commissioner for Special Medical Programs on April 10, 2012.

Before I turn the meeting back to Dr. Rosenberg, I would like to make a few general announcements:

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated, 1378 Cape St. Claire Road, Annapolis, MD, 21409. Telephone is 410-974-0947.

Information on purchasing videos of today's meeting can be found at the FDA meeting registration desk.

The press contact for today's meeting is Michelle Bolek. She's waving.

And I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speakers' podium. I request that reporters please wait to speak to the FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Mr. James Clark at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

Thank you very much.

Dr. Rosenberg?

DR. ROSENBERG: Thank you. We will now hear from Marjorie Shulman, M.B.A., Acting Director, Premarket Notification (510(k)) Program.

I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair, Dr. Rosenberg.

Thank you.

MS. SHULMAN: Thank you. Good afternoon. For the people who heard this this morning, feel free to take a brief nap.

(Laughter.)

MS. SHULMAN: I'm Marjorie Shulman. I'm Acting Director of the Premarket Notification 510(k) staff, and we're going to talk about reclassification and classification procedures.

Basically, the Federal Food, Drug and Cosmetic Act divided the devices into two groups. It was either pre-amendment devices or post-amendment devices; pre-amendment devices were ones that were on the market prior to May 28th, 1976 and post-amendments were ones that were introduced to the market after that.

So the classification of pre-amendment devices, they were classified after FDA received a recommendation from a device classification panel, published the Panel's recommendation for comment along with the

proposed regulation classifying the device, and then published a final regulation classifying the device.

For reclassification of a pre-amendment device, FDA may reclassify it in a proceeding that paralleled the initial classification proceeding and based upon new information respecting a device either on FDA's own initiative or upon the petition of an interested person.

For classification of post-amendment devices, post-amendment devices are automatically classified into Class III, and they remain in Class III and require premarket approval unless and until the device is reclassified into I or II, FDA issues a substantially equivalent determination, or the device is classified into I or II via the evaluation of automatic class redesignation, also known as the de novo review.

For reclassification of a post-amendment device, it can be initiated either by FDA or industry, and the FDA, for good cause shown, may refer the petition to a device classification panel and then Panel would make a recommendation to FDA respecting the approval or denial of the petition.

So there's three classes of medical devices, Class I, II, and III. And a device should be placed in the lowest class whose level of control would provide reasonable assurance of safety and effectiveness; Class I is general controls, Class II is general and special controls, and Class III is premarket approval.

Class I mainly includes devices for which any combination of

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

general controls are sufficient to provide reasonable assurance of the safety and effectiveness of devices. General controls include, for example, prohibition against adulterated or misbranded devices; good manufacturing practices; registration of the manufacturing facility; listing of the devices that are manufactured there; record keeping; repair, replacement, refund; and banned devices.

Some examples of Class I devices: adhesive bandages, stethoscopes, patient scales, exam lights, crutches.

Class II are for devices that cannot be classified into Class I because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness, but there is sufficient information to establish special controls to provide such assurance.

Special controls include, for example, performance standards, postmarket surveillance, patient registries, development and dissemination of guidance/guidelines, tracking requirements, and recommendations and other appropriate actions.

Some examples of Class II devices are ventilators, ECG machines, endoscope, hemodialysis, et cetera.

So how are special controls used? As an example, for surgical sutures, FDA issued a special controls guidance to mitigate the risks to health. It included such things as biocompatibility testing, sterility testing, conformance to the USP monograph, resorption profile testing, and labeling

that included some warnings, precautions, and adverse reactions. These special controls, in combination with the general controls, provide reasonable assurance of safety and effectiveness. So companies must provide evidence in their 510(k) submission of how the special controls were addressed.

Class III is for devices for which insufficient information exists to determine that the general controls and the special controls are sufficient to provide reasonable assurance of safety and effectiveness of the device and the devices are life sustaining and/or life supporting, of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury.

So some examples of Class III devices are implantable pacemakers, implantable spinal cord stimulators, IUDs, and extended-wear soft contact lenses.

What are Class III 510(k) devices? These are devices that were on the market prior to May 28th, 1976, but FDA did not issue a classification -- no, I'm sorry. I've confused myself. Class III 510(k) devices are pre-amendment devices where we did issue a classification, classifying it into Class III, but we have not yet called for a PMA or a PDP to come in. So, therefore, these Class III devices are allowed to proceed to market via the 510(k) route until either a call for PMA or a reclassification is finalized.

There's also restricted devices under the provision of Section

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

520(e) of the Federal Food, Drug and Cosmetic Act. The FDA is authorized by regulation to restrict the sale, distribution, or use of a device if, because of its potentiality for harmful effect or the collateral measures necessary to its use, FDA determines there cannot otherwise be reasonable assurance of safety and effectiveness.

A restricted device can only be sold, distributed, or used either upon the written or oral authorization by a licensed practitioner or under such other conditions specified by regulation. And if the device is restricted for use by persons with specific training or experience in its use or by persons for use in certain facilities, FDA must determine that such a restriction is required for the safe and effective use of the device.

So, for example, devices such as cardiac pacemakers and heart valves require a practitioner's authorization. Hearing aids are restricted by a regulation that limits their sales to persons who obtain a medical evaluation of their hearing loss by a physician within six months prior to the sale of the hearing aid. The labeling of hearing aids must provide information on their use and maintenance. That is it.

Thank you.

DR. ROSENBERG: Thank you. Now, we have 10 minutes of question and answer of the Panel to FDA to -- if there are any questions concerning that talk on device classification.

Those of us who were here earlier probably are clear, but yes,

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

yeah, Ms. Leitman?

DR. LEITMAN: It's such an obvious question. Why 35 years later is this coming up? Why didn't it come up 30 years ago?

DR. ROSENBERG: Ms. Morris, can you answer that, or who? Ms. Shulman. Thank you. Pass the hot potato.

MS. SHULMAN: Yeah. We were busy -- no.

(Laughter.)

MS. SHULMAN: Because for the classification of unclassified devices, they do go through the 510(k) route, so we did have programs in place to regulate these devices. It's very expensive and time consuming to hold a panel meeting, and the only way to classify an unclassified device is to bring it back to a panel and classify it that way. And it was a matter of time and money. And it wasn't that they were ignored. They did go through the 510(k) process. They just haven't been officially classified.

DR. ROSENBERG: All right. Yes?

DR. HARVATH: Just a question for clarification -- Liana Harvath. The present discussion will focus on the blood irradiator as the device itself, and many of us are familiar with it in the use for irradiating blood. And so I just wanted to make clear for my own understanding that we are looking at the device itself for that specific purpose, and we are not discussing the blood component in terms of graft versus host disease associated with transfusion. Is that a correct understanding?

MS. SHULMAN: That is a correct understanding.

DR. ROSENBERG: Ms. Morris, is that correct?

MS. MORRIS: Yes, that's correct.

DR. ROSENBERG: Thank you.

DR. HARVATH: Thank you.

DR. ROSENBERG: Okay. Thank you.

I think we are at a time for the FDA presentation.

DR. O'HARA: Good afternoon. My name is Michael O'Hara. I'm a radiation biologist, and I'm a member of the Division of Radiological Devices.

Let me make sure I get the -- today I'm going to give you a little background on blood irradiators, some regulatory history. Dr. Hui-Lee Wong is going to discuss the literature review. Dr. Richard Davey from CBER is going to discuss a clinical review. We'll give a little summary and then have Panel discussion.

So when viable T-lymphocytes are transfused in blood or blood products engraft and when they engraft and multiply in tissues of a recipient, they can react against the tissues of the recipient. This is called transfusion-associated graft versus host disease, or TA-GVHD.

While TA-GVHD is a rare complication of transfusion, in patients who develop it, it's fatal in the majority of patients. The use of ionizing radiation to prevent TA-GVHD is an established practice for

immunosuppressed patients, fetuses, very premature newborns, as well as in patients who may have a likelihood of having one HLA haplotype in common with a donor. And it's estimated that over two -- that there are over two million units of irradiated blood transfused each year.

The regulatory history for these devices. As you already heard, the purpose of this meeting is to determine the appropriate regulatory classification for the medical devices known as blood irradiators. Blood irradiators are currently unclassified devices because they weren't identified during the classification process conducted in the '70s and early '80s. Blood irradiators were determined to be pre-amendment devices since they were in commercial distribution prior to May 28th, 1976, when the Medical Device Amendments became effective.

Once these devices were determined to have pre-amendment status, subsequent devices were evaluated under the 510(k) premarket notification, and they were found substantially equivalent to those devices. Over 30 years, we've found 12 devices to be substantially equivalent for blood irradiation to prevent graft versus host disease.

So the general device description for these devices. The definition for the device description, there are basically two types -- I'm sorry. I was getting ahead of myself. There are basically two types of blood irradiators currently being regulated by CDRH. There's the isotope-containing blood irradiators, and there's the x-ray tube-containing blood

irradiators. Both types are capable of delivering 25 Gy of ionizing radiation to containers filled with blood or blood products.

The isotope-containing blood irradiators -- sorry for the busyness of the slide, but I was just trying to summarize it as completely as I could. Most of the isotope-containing blood irradiators either contain one or in some cases two radioactive sources. They can either be cobalt-60 or, more prevalent, cesium-137. And these things are housed in a lead-shielded container. They usually have a method to put the radioisotope source in a line of sight with the sample to be irradiated either through shutters or through an elevator mechanism, or in some cases, they have kind of a record player that moves the source into position.

Exposure times are determined electrically by electrically powered timers. Sample chambers can vary in dimensions. Safety interlocks are used to prevent accidental exposures. And all of these components are reviewed currently during our premarket review. And we're specifically looking at many of the safety features on these types of devices.

There can also be ports for computer connection -- data download or determine exposure times. The dose rates at 30 cm from any surface for these services do not exceed 2 mR/hour, and that's a Nuclear Regulatory Commission/Agreement State regulation. And, again, during our premarket review, we look for these things.

The x-ray tube containing blood irradiators. They're capable of

emitting -- some are capable of emitting x-rays in a 360 degree environment. Some use carousels to uniformly expose samples to ionizing radiation. They can include methods to cool the x-ray tube, filter the x-ray tube. And, again, there's timers and safety interlocks on these devices. And, again, CDRH, it's one of the things that CDRH looks very closely at. And these devices cannot exceed an exposure of .5 mR in one hour at any .5 cm outside the external surface. And this is to comply with the regulations set out in 21 C.F.R. 1020.4 for cabinet x-ray systems.

So the indications for use for these devices. The definition. It is a description of the disease/condition the device will diagnose, treat, prevent, cure, mitigate, and it includes a description of the patient population for which the device is intended. For blood irradiators, they're fairly consistent across the 12 devices. The blood irradiators, they are used to irradiate blood and blood products to prevent graft versus host disease.

So what are some of the relevant important agreements and guidance documents? Well, isotopes such as cesium-137 and cobalt-60 and their safe use are under the regulatory authority of the Nuclear Regulatory Commission. Blood irradiators as medical devices are among a few medical devices that are jointly regulated by the Center for Biologics Evaluation and Research and CDRH. And on October 31st, 1991, a working relationship was signed between CBER and CDRH which specified who would regulate what component of these devices and other devices.

There's an important guidance document. It's entitled "Recommendations Regarding License Amendments and Procedures for Gamma Irradiation of Blood Products." And it was published by CBER on July 22nd, 1993. And it spells out recommendations on manufacturing, quality control procedures, labeling, and other aspects of production and use. And it also calls for the dose or radiation that the central axis of the blood bag can be irradiated to, which is 25 Gy.

And now I would like to turn the podium over to Dr. Hui-Lee Wong, who is going to talk about the systematic literature review.

DR. WONG: Good afternoon. My name is Hui-Lee Wong. I'm an epidemiologist at the Office of Surveillance and Biometrics, Division of Epidemiology. I'll be presenting the systematic literature review of the safety and effectiveness of blood irradiators.

We'll first begin with a brief description of the background and methods, followed by the main findings on safety and effectiveness of blood irradiators for treatment of blood products to prevent transfusion-associated graft versus host disease, followed by discussion of study design and methodological issues, and finally our conclusions.

The objectives of our review are: What are the reported adverse events associated with the use of blood irradiators for the prevention of transfusion-associated graft versus host disease? What is the evidence for effectiveness of blood irradiators used for the prevention of

transfusion-associated graft versus host disease?

We searched department database through February 2010 using the following search terms listed here on this slide. Our search was limited to English publications, and there were no limits on the publication date. We further limited our searches to randomized controlled trials, observational studies, case reports, systematic literature review and meta-analysis, and in vitro or laboratory studies.

Our initial yield of department search was 125. First pass exclusion of this 125 records led to an exclusion of 89 records because they were not relevant, not specific, not in English, non-systematic review, non-human studies, and no safety or effectiveness outcome. Of these, 16 were eligible for full-text epidemiological review. An additional 21 articles were excluded because they were not relevant, not specific to device, non-systematic review, and there were no safety or effectiveness outcome. A total of 15 articles or publications are included in this review and will be presented today.

So of these 15 papers, one was a randomized controlled trial, two case reports, two national surveys, five in vitro dosimetry studies, and five on blood cellular effects. They were published between 1975 and -- 1976 -- sorry -- and 2005 and were performed in the United States and abroad.

We will now present the evidence for reported adverse events

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

in the literature associated with the use of blood irradiators for the prevention of transfusion-associated graft versus host disease.

The 1993 FDA recommendation for blood irradiation in transfused blood products is 25 Gy at the blood product isocenter and at least 15 Gy at any point within a canister. In our literature review, when a blood irradiator was used at the FDA recommended dose of 25 Gy, we did not identify any adverse reports in the literature, nor were there any articles reporting device malfunction or safety concerns for irradiator operators, now, in instances when the irradiation dose was above 25 Gy.

In the 1994 United Kingdom survey, 12 centers used a dose below 25 Gy, and they reported 1 out of 12,000 of these patients developed transfusion-associated graft versus host disease. Another case report documented patient's death after receiving a transfused blood irradiated to 15 Gy. We do note that transfusion-associated graft versus host disease may be underreported due to clinical -- they may overlap with other symptoms.

We will now present the evidence for the effectiveness of blood irradiators used for the prevention of transfusion-associated graft versus host disease in the literature.

Our literature search did not identify any studies that directly assessed an FDA-cleared blood irradiator and its effectiveness in regards to preventing transfusion-associated graft versus host disease. We did identify one randomized controlled trial. In this case, they were looking at endpoints

of the viability and function of other blood components, in this case, platelets. They did not use FDA-cleared blood irradiator. Rather, they used improvised device at 15 Gy. What it did was it compared 12 Israeli cardiac surgical patients transfused with irradiated whole blood and with 12 -- and 12 that were transfused with non-irradiated blood, and reported no significant difference between these two groups for postoperative hemostasis or bleeding and platelet aggregation capacity. This is at preoperative surgical determination and postoperative.

In terms of dosimetry, a 1989 national survey of blood banks reported variation in blood irradiation protocols, and this included variation in dosimetry. For in vitro study, one study reported reasonable dosimetry variation in blood bags and syringes from isocenter of various blood irradiation containers. Another study quantified this variation at around 6% across sample. And another study also reported that the amount of incidental radiation is modest during the period of time the drawer is opened and closed, and they brought in algorithm to correct that.

For the effective dose for T-lymphocyte inhibition, one study reported that 30 Gy was sufficient to inhibit all mitogen response in mixed lymphocyte cultures. They however did report a small response to a T-lymphocyte suppressor pathway concanavalin at 25 Gy.

For studies that looked at the viability and function of other blood products, two studies measured in vitro biological changes to blood

following irradiation, and this included changes in the metabolic signaling and cellular properties. However, they did not report any known clinical effects.

So one of the strengths of our literature review is the inclusion of national surveys that concluded large cohorts. However, our literature review did not identify a study which directly assessed the effectiveness of the use of an FDA-cleared blood irradiation device to prevent transfusion-associated graft versus host disease. And it contains limited clinical data on the effectiveness or safety of blood irradiators. However, such a study, where we directly compared between irradiated blood products and non-irradiated products may not be feasible, given the widespread blood irradiation practices in this country and the variability of the outcome.

We also found variation in clinical and laboratory practices when it comes to dosimetry, storage, and instrumentation. The inconsistencies between these studies pose a challenge in summarizing literature.

In conclusion, if used at the FDA recommended dose, safety concerns for blood irradiators are minimal in the literature, and with irradiated blood products, development of transfusion-associated graft versus host disease is rare in the literature.

Thank you. Now Dr. Richard Davey will present the clinical perspective.

DR. DAVEY: Thank you very much. I'm Richard Davey from the Office of Blood at CBER. And I'd like to give you a very brief overview of some of the clinical aspects of blood irradiation in transfusion-associated graft versus host disease. I just want to say I think your Panel has some clear experts in this area that are going to be major contributors to the discussion; Dr. Harvath, Dr. Leitman, Dr. Rentas, Dr. Gilcher are all well-established experts in this area.

Just a little bit of background for those of you that are not actively involved in transfusion medicine. We transfuse about 14 million red cell units a year out of perhaps 16 million that are collected. And about 2 million units of platelets are also transfused. And as you've heard earlier, about 2 million units of blood products are irradiated every year, according to our best estimate.

Just to give you a little bit of an idea of how TA-GVHD relates to other blood product adverse events, I have this slide from some studies done in England, the Serious Hazards of Transfusion Program in England, between 1996 and 2001. I think it's pretty relevant to the United States also. And I think you can see that in terms of hazards of transfusion, by far the biggest problem is incorrect blood being transfused. TA-GVHD, if you can see the little sliver at the top of that pie chart, is a small problem, and it's getting smaller as irradiation is becoming more widely used.

So in terms of reported cases of TA-GVHD, there were three --

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

and we've heard a nice literature review from the previous speaker -- there were three reviews in the early '90s that identified 87 well-defined cases of TA-GVHD. We think those reviews identified many other cases that may well have been TA-GVHD but were not entirely, completely classified. It's a difficult diagnosis to make because many of these patients, as you know, are very seriously ill, in ICUs, and have complicating clinical presentations.

In addition, my second bullet, the TA-GVHD, as you'll see in a subsequent slide, may appear days to even weeks after the implicated transfusion. So unless the clinician is acutely aware of this problem and this issue, he or she may not tie the complication of the graft versus host disease through the transfusion that may have occurred a week, two weeks, or even three weeks prior. So we think that given the reported cases that you've heard from the previous speaker and that I'll outline, those cases are probably underreported. We feel there's probably more of this complication occurring, but it's not being completely recognized.

However, my final bullet, I think the good news is now that irradiation of blood products is widely accepted for the clinical indications that I'll outline in a couple of slides, the indication or the reported cases of TA-GVHD is really quite small. Like I mentioned, there were 87 cases reported in the literature in the early '90s. In the last seven years, we've only had three fatal cases reported to FDA, and those are all in patients that received non-irradiated products. Filling in that gap between early '90s and

2005, not on this slide, I identified 21 fatal cases of TA-GVHD reported to FDA over that period from, say, the early '90s and that 2005. So the number of cases are small, but the clinical consequences of this complication are severe.

Just very briefly, let's review the clinical presentation of a patient with TA-GVHD. As I mentioned, the symptoms usually develop well after the implicated transfusion, 7 to 10 days, typically, but there's a bigger range, 3 to 30 days. The signs and symptoms really mimic GVHD you might see after a bone marrow transplantation, with a rash, fever, GI problems, elevated LFTs. But there is one important difference. With TA-GVHD, the marrow really gets affected in a very major way. You get profound marrow aplasia. And that's the element that results in this problem being so uniformly fatal, with mortality exceeding at least 90%, as best we can tell. Treatment is really not effective. If you develop this problem, it's not a good thing.

There are a number of clinical uses and indications for irradiation to prevent TA-GVHD. I've listed some of the most prevalent ones; this is not an inclusive list. But you can see that patients with any kind of immune deficiency or patients with certain specified malignancies really require irradiated blood products. You need to irradiate granulocyte transfusions, which were often given to immunocompromised patients. You want the granulocytes to work but not the lymphocytes.

The last two at the bottom have been alluded to by previous speakers also. We want to irradiate any product where there might be a HLA haplotype identity between the donor and the recipient. So that includes any transfusions from blood relatives or specifically donors that are selected to be compatible; platelet donors, for instance, you want to get an HLA compatibility.

Radiation is recommended for premature infants who are weighing under 1,200 g and certain patients with other hematologic malignancies. I think many transfusion services irradiate these routinely just to make sure that there is no patient that goes unprotected.

You don't want to irradiate stem cells or bone marrow for transplantation. That's a bad thing. You want the stem cells to survive in a graft. You don't want to kill them with radiation. That's happened unfortunately.

We've talked a bit about the effect of radiation on lymphocytes. The good news is lymphocytes are very sensitive to irradiation. We've heard some data presented a moment ago. This one table shows that at 5 Gy, according to this particular summary table, there is really no proliferation in the MLC; 15 Gy inhibits mitotic activity; and 25 Gy completely abrogates cell growth. So even at very low doses, lymphocytes do become inactivated, which is the good news.

On the other side of the coin, however, the lymphocytes are

not the only blood element that are affected by irradiation. Red cells also are damaged to some extent by the doses of radiation that are used. On this particular table, if you can follow it, goes through four studies, going from right to left, where blood was irradiated at 21 days, 28 days -- or I'm sorry -- irradiated and then stored for 21 days, 28 days, 35 days, or 42 days, different studies.

And if you look at the bottom row, where it says 24-hour red cell recovery, you can see in each of these four studies, the irradiated products survive less well than the non-irradiated controls. And if you get to 42 days, which is the recommended storage time for red cells in the refrigerator these days, the irradiated products, on a study done by Dr. Leitman and myself, were only 68.5%, which falls under the recommended 75% survival that was in effect at least when that study was conducted.

So based on this series of studies, the recommended storage for red cells that are irradiated is 28 days from the time of storage, or 42 days, whatever comes first. So it's only -- if you irradiate on day 1, the storage time for red cells is only 28 days, not 42 days.

Here is a picture of a few of the irradiators that are in use. The two devices on the right side of the slides are gamma irradiators. I'm not sure whether they're cobalt or cesium. These are very heavy instruments. They weigh probably two tons or more with all the lead

shielding. So you really have to get the floor of your facility specially constructed so they don't crush down on the folks on the floor below.

And it has to be very rigidly controlled. The NRC now, as has been mentioned, is very attentive to these devices. And over the last few years especially since 9/11, these devices now are very heavily controlled in terms of walled-off special rooms with 24 surveillance; anyone using the irradiator has to be security-cleared, fingerprinted, et cetera. It's kind of a big deal.

And I think because of that, some facilities have moved to the X irradiator, which one example is on your left, to avoid Nuclear Regulatory kind of issues that come up. The X irradiators all have their issues; they needed special -- a lot of plumbing, they get very hot, the tubes wear out. So each set of devices have their own particular issues to deal with.

These devices, again, as have been mentioned before, need to be validated. You need to make sure that they're delivering the proper dose of radiation. And this is a typical irradiation isodose graph for self-contained blood irradiator with a pencil source of cesium, shall we say, where the canister rotates around, exposing the blood product to the cesium source as it rotates.

And you can see in this particular study that, as you might expect, the periphery of the canister, which rotates closest to the pencil in the middle section on the vertical axis, gets the highest dose; the top and

bottom gets the lowest dose; the middle, we want to get 100% of the dose. 100% should be 25 Gy targeted to the center portion of the container and, as you've heard, no less than 15 Gy at any other point.

So the instruments have to be validated periodically to make sure they're achieving the desired radiation. You have to make sure that your half-life of the material is taken into account every time you validate these -- you know, the radioisotope instruments throughout material that decays; cesium decays slowly, 30-year half-life; cobalt a little more rapidly, a 6-year half-life. But that has to be entered into your calculations.

Another thing to keep -- that's of interest is that many if not most blood centers or blood transfusion services make sure that each unit is identified as being irradiated if that unit needs to go to a patient requiring an irradiated unit. So this is one device that can actually be attached to each unit that it's been irradiated. It's kind of a sticker. And you can see very kind of cleverly, if it's irradiated, the "not" section, the N-O-T, gets blacked out. If you get 25 Gy to that particular device, then that gets blacked out. So the indicator says it's irradiated. That's a great QC method. And I think most hospitals use this or a similar device to make sure that the product is actually getting the recommended dose.

So it is a very high-level overview. Again, just by way of review, TA-GVHD is rare but a very devastating complication of transfusion. Irradiation of blood components for appropriate patients does prevent this

adverse event. I think it's -- there is really zero -- if you irradiate, you're not going to get this problem. I think the problem that exists is human error, maybe the hospital misses a diagnosis or the wrong unit goes to the wrong patient. That's the problem we have to make sure is mitigated, not the fact that an irradiated unit is going to cause a problem.

Irradiators have to be validated to assure that the device delivers the appropriate dose. And QC with maybe those strips, we recommend or we feel clinically, should be performed in all irradiated units to assure they have received the required radiation dose.

So with that, thank you very much.

DR. O'HARA: So in summary, the safety summary, for blood irradiators, they've had few published problems over a long period of time, as evidenced from the review by Dr. Hui-Lee Wong. An interesting publication was by K. Tadokoro. And they actually had a nice international flair to how they reported their problems with these irradiators. And they reported very, very few and very minor problems in their publication.

And what are some of the controls that produced the safe use of blood irradiators? General controls, premarket review, the current CBER guidance document has been very important in producing these controls, as well as the regulations for cabinet x-ray systems in 21 C.F.R. 1020.4.

What about the effectiveness? It's an established technology to prevent graft versus host disease in transfused patients. It's been used

for over 35 years, with few negative reported consequences. The number of irradiated units has remained constant at least over the last five or six years to about 2 million units a year.

The controls that produced effectiveness, effective use of blood irradiators? Again, premarket review, radiation safety procedures at hospitals and institutions that use these, dosimetry, and the dosimetry is also outlined in the CBER guidance document, and the safety regulations that are outlined in 21 C.F.R. 1020.4.

So today what we're asking you to do is to review the risks that we've presented and identify any new risks that you may know of. Consider appropriate risk mitigation. Determine whether valid scientific evidence demonstrates the safety and effectiveness of these blood irradiators. And come to consensus on the appropriate classification based on the evidence that you've heard today and that you know.

Thank you.

DR. ROSENBERG: I would like to thank the FDA speakers, Drs. O'Hara, Davey and Wong, for their presentations.

Now is the time -- we have about 10 minutes. Does anybody on the Panel have brief clarifying questions for the FDA? Please remember that the Panel may also ask questions of the FDA during the Panel deliberation session later this afternoon.

Dr. Payne?

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

DR. PAYNE: Tom Payne, medical physicist. Just out of curiosity, we're talking about blood irradiators here, but what about food irradiators? Doesn't the FDA have something to say about food irradiators, which are very similar devices?

DR. O'HARA: Michael O'Hara. I think the Center for -- the Food Center handles that. We don't. At least in my experience, we haven't had a food irradiator come --

UNIDENTIFIED SPEAKER: (Off microphone.)

DR. ROSENBERG: Yeah, Dr. Zhou and Rentas and Dodd.

DR. ZHOU: My question might be short. So what is the gold standard for identified TA-GVHD? What is the gold standard for diagnosis of the TA-GVHD? So you talk about the clinical symptoms, but what is the gold standard?

DR. LEITMAN: The diagnosis of TA-GVHD hits you in the face like a bomb.

DR. ZHOU: So there's no error associated with the clinical diagnosis?

DR. DAVEY: Well, there are errors in terms of patients who are often very sick, and they have very similar clinical disorders in an ICU. So it may be complicating for a clinician to make the right diagnosis. But as Dr. Leitman says, if you -- these people, the bottom falls out on them. They get very sick very fast. Their marrow just shuts down and they die.

DR. LEITMAN: There is a gold standard. If you can find that the patient's tissue HLA type is consistent with family members or you have a prior type and demonstrate there are circulating HLA haplotypes circulating in the blood stream different from the tissue type and consistent with the blood donor type -- and that's been done several times and published -- that's a gold standard.

DR. ROSENBERG: Thank you, Dr. Leitman.

DR. ZHOU: Is that commonly used in practice, in clinical practice, you use the standard you just mentioned?

DR. ROSENBERG: FDA, please?

DR. LEITMAN: Is it in common use? I'd say that, you know, in academic centers. When one tries to do that in the community, I doubt you would do that.

DR. DAVEY: I would agree with Dr. Leitman. There is no FDA standard. But I think that what is done clinically is if you suspect the diagnosis, in order to be sure, do what Dr. Leitman suggests, see if they're circulating lymphocytes from the donor that has the same HLA type as the donor lymphocytes themselves in the recipient. Then you're pretty much certain that that's the diagnosis.

DR. ROSENBERG: Dr. Gilcher?

DR. GILCHER: Yeah. I agree with Dr. Leitman. And I think that it hits you like a bomb in the face, and you have to have a high degree of

suspicion. But in one particular case that I was observed -- or that I was involved with back at the University of Oklahoma, the patient should have received irradiated blood and did not. And the herald sign was the development of aplasia in the marrow. And then an attempt was made to do a transplant. When the patient was tissue-typed, he didn't match anyone. And somebody said, wow, we better look at the units. Then they came to us. And, in fact, we found that he had received a unit of non-irradiated blood and grafting had occurred. So we were able to trace it back. But it was the development of aplasia -- this was a Hodgkin's disease patient -- the development of unexpected bone marrow aplasia was really the herald sign.

DR. ROSENBERG: Dr. --

DR. RENTAS: Frank Rentas here. You know, it is clear to me that the regulatory guidelines that the FDA and other regulatory agencies have had for the last 20, 30 years, whatever it is, provide the safety and effectiveness that is needed. My question to the FDA is would you consider those guidelines Level I or Class I guidelines, general controls, or Class II guidelines, general plus special controls? And if you do say Class II, what specific special controls are you talking about?

DR. ROSENBERG: FDA?

DR. O'HARA: This is Michael O'Hara. The CBER guidance document we consider a Class II guidance document.

DR. RENTAS: What specific special controls are we talking about that resulted in that classification?

DR. O'HARA: Again, Michael O'Hara. And that is a special controls guidance document. That's what we would consider controls for this along with the -- for the cabinet x-rays, the cabinet x-ray information in C.F.R. -- what is it -- thanks, 20.4.

DR. DODD: Lori Dodd. Reviewing the data that was presented by the FDA, it appears as if it's been demonstrated to be safe. But in terms of level of effectiveness, I don't see the effectiveness data here. So I'm curious, could the FDA summarize what effectiveness data -- did I miss something? Because my interpretation of what's been presented is there really isn't any valid scientific data demonstrating the effectiveness for the prevention of this TA-GVHD. Now, that's not to say that, you know, that -- I mean, it seems -- it appears it's been demonstrated to be used safely. And maybe based on basic scientific principles of killing of the T-lymphocytes, that's sufficient to make that leap. But are we concluding effectiveness based on that? Or what are we -- how are we reaching the conclusion of effectiveness?

DR. ROSENBERG: Ms. Morris?

MS. MORRIS: Yes. So let me revisit. This is a slightly different scenario than we discussed this morning, as there may not be a great deal of literature out in the public domain that conclusively shows this. So part of

the reason of having the Panel is bringing the experts on board to say, in lieu of the fact that there isn't this demonstratable amount of literature on safety and effectiveness, that doesn't mean that in its absence there isn't a demonstration of effectiveness by the fact that low incidence -- of occurrence of graft versus host disease is not prevalent in our population.

So we have to think about when we're going through a classification, we're looking at general controls and special controls. And if we would determine they are currently marketed, legally marketed products on the market right now for this use, and if we would take them off the market and call for PMAs, we have to consider that as well as making a decision of whether or not they are a Class I or a Class II.

So that's part of the purpose of this meeting, is to bring the experts on board to weigh in on if it's not apparently obvious, then with their experience and scientific knowledge, have that part of the discussion.

Does that help?

DR. DODD: Yeah. That helps. And I guess I'll just follow-up that during the Panel deliberations, I hope I can hear from people on the Panel about specifically this question.

DR. BREZOVICH: Ivan Brezovich. I have one question to the FDA. Apparently, there are already lots of controls in place now which are comparable to Class II controls. So if it were Class II control device, what additional controls would come in to improve safety?

MS. MORRIS: Janine Morris, FDA. So those controls -- actually, the ones that were described can be considered the special controls. So if you believe that the controls that are already in place are adequate and help assure the safety and effectiveness, then those would be the special controls we're talking about to allow it to stay in a Class II or to be in a Class II classification.

DR. ZHOU: I'd like to follow up with Dr. Dodd's question. I would like to see the data even though we might rely on the experts to establish effectiveness -- they do have study, right, I think, based on the epidemiology review by the FDA? So the question is what the parameter they used in those study to measure effectiveness of this device? Are there any parameters?

DR. LEITMAN: Could I -- this is Dr. Leitman. So there's an enormous wealth of basic science investigation showing that the mean lethal dose for circulating maternal lymphocytes is about 200 cGy. And you irradiate with 2500 cGy. And the reason you're in tenfold excess is because of the irregular shape of a blood component as it sits in a canister, turning, exposed to a fix source. It's actually not the greatest way to deliver a homogenous dose. And we accept that. So we're in great excess of the mean lethal dose to circulating lymphocytes.

So that doesn't answer your question, though, of what's the demonstrated efficacy. You could never do a clinical trial. It would be

incredibly unethical. But there is a fascinating study from Europe about 15 years ago, maybe 20 years ago, when it was not appreciated the risk of transfusion-associated graft versus host disease with autologous transplant was the same as with allogeneic transplant. This was a consortium of European transplant centers. And 25% of the first 20 or 30 or so patients who received an autologous transplant died of lethal graft versus host disease from non-irradiated blood components. And it didn't -- when they realized what was going on, all subsequent patients -- it wasn't a randomized trial; it was a retrospective review prospective change. And when they irradiated products, no graft versus host disease, transfusion-associated GVHD was not seen again.

I also want to mention there is about five, six case reports of irradiated products associated with TA-GVHD. Those were all in the era before FDA required -- before the guidance, before 1993, before FDA required that an indicator be placed on a blood unit to indicate that irradiation had been performed. And I feel those are all that the operator thought they irradiated but forgot to hit go, got distracted. So you couldn't be assured that the product was actually irradiated in any of those cases.

DR. ROSENBERG: Yeah. Let me break in. I think we're going into the Panel deliberations, which is just perfect. So let us for the record consider that we're now in the Panel deliberations. We will go back to other aspects. So --

UNIDENTIFIED SPEAKER: (Off microphone.) So we're doing Panel deliberations?

DR. ROSENBERG: So let's -- yeah. What's that? Yeah. So are you done, Dr. Leitman?

DR. LEITMAN: I am.

DR. ROSENBERG: Okay. Excellent. Okay. Yeah, we can just actually go around.

DR. BOURLAND: Okay. Dan Bourland here. I had a question actually about the guidance document. And does it apply to both x-ray units as well as gamma irradiators, or is it at least being applied in that manner?

DR. O'HARA: Michael O'Hara. It does apply officially to gamma irradiators, but it doesn't mention the x-ray irradiators. But I think the intent is the same for both of them.

DR. BOURLAND: And a follow-up to that -- I mean, I've read through it some, but in terms of details, for instance, is there a minimum dose rate that's specified in that document or that manufacturers otherwise follow?

DR. O'HARA: Michael O'Hara. I don't remember if it specifies dose rate.

DR. LEITMAN: It specifies a dose but not a dose rate.

DR. BOURLAND: Right. That's what I'm asking just based on --

DR. ROSENBERG: Yeah. I need everybody's name so we -- for

the record. Thanks.

DR. BOURLAND: Okay. Thank you.

DR. ROSENBERG: Please.

DR. BREZOVICH: Yeah, Ivan Brezovich. Are those CBER guidelines, are they mandatory, or are they more or less voluntary?

DR. O'HARA: Michael O'Hara. I believe they're mandatory for blood irradiator -- or blood companies that ship blood over interstate lines. And I believe -- about half a dozen people in the room could correct me, but I think that's about 80% of the blood that's irradiated in the United States.

MS. MORRIS: Janine Morris, FDA. I just want to clarify. The majority of guidance documents are not necessarily mandatory. It would be a guideline specified in the Code of Federal Regulations if it was mandatory. But these guidances are often used as a means of identifying what the appropriate specifications are to ensure a reasonable assurance of safety and effectiveness.

DR. LEITMAN: Leitman. At the time a blood center is inspected by the FDA, if it irradiates blood products, its standard operating policies really have to conform to the guidance, and the inspector looks for conformance and you're cited if you don't conform. So although it's not law, it looks very bad to get an FDA citation on your inspection.

DR. ROSENBERG: Dr. Brezovich? Oh -- yeah.

DR. BREZOVICH: If those guidelines are not absolutely

mandatory, would they become mandatory if the blood irradiators now were suddenly considered a Class II device? Would that make the difference?

MS. MORRIS: Janine Morris, FDA. So when you make a determination of Class II with special controls, when you specify a special control, it will then be more or less mandatory.

DR. ROSENBERG: Dr. Bourland?

DR. BOURLAND: Dan Bourland. I had one other follow-up to the guidance document relative to homogeneity, which had been mentioned down here, dose homogeneity. So 25 Gy with a minimum of 15 Gy. So actually, in various literature that was presented, it said something like a 6% deviation. I think that's on actual measurements. But, in fact, there could be a 40% variance in dose within the, so to speak, the irradiation chamber; is that correct?

DR. O'HARA: Michael O'Hara. I don't know if it's up to 40%. I have no idea. But that's why they have the indicator that goes with the blood bags.

DR. BOURLAND: Um-hum.

DR. ROSENBERG: Can anybody on the Panel address that question?

DR. LEITMAN: This is Dr. Leitman. So I've been looking at dosimeter radiator reports performed using multiple techniques, including TLD chips, MOSFETs, and radiation-sensitive film for about 25 years now.

And many of those techniques characterize the absorbed dose throughout the irradiation chamber. And it varies over a twofold range. If you said the mid-plane of 2500, you'll get a range from about 1,500 to 3,000 to 3,500.

DR. RENTAS: Frank Rentas. If I could just add, I think the best level of effectiveness, what we have -- and this is not a sexy subject because we've been doing this for so many years. There's just not a lot of research out there on this -- is the fact that I cannot find a single case out there of someone that followed the regulatory guidelines and irradiated a blood product the way they were supposed to, I cannot find a single case of transfusion-associated GVHD out there.

DR. ROSENBERG: Dr. Payne?

DR. PAYNE: Just some comments. As a medical physicist, and my colleagues have made some comments, but -- and this is just focused on the device. This is pretty clear to me. It looks like Class II. It smells like it, looks like it, I think it is, in terms of -- and the reason I say that is that's a linear accelerator for treatment -- this is kind of the linear accelerator equivalent for blood products. I mean, it radiates this; you put something in it, and then you irradiate it. And I think it would be -- I think Dr. Bourland touched on something -- I think it would be nice in the specifications to talk about homogeneity of dose. It sounds to me like it could be plus or minus 50%. I mean, it could be maybe greater than that, but that might be a place to start.

And then I think -- I used to know a little bit about radiobiology, but I've sort of let it go. And that is the dose rate, in terms of the dose that you're looking at, for those of us who've been in therapy, this is 2500 cGy. And so, you know, something like a dose rate of 50 cGy per, I don't know, minute, something like that. I don't know if we need it that -- well, I guess maybe -- I don't know. Maybe it's got to be 10 cGy a minute, or something. But I guess a dose rate comment wouldn't be inappropriate. But now I'll defer to the experts.

DR. ROSENBERG: Dr. Gilcher, Jiang, and Zhou.

DR. GILCHER: 25 Gy is the minimum, and one can go above that. In our system, we had an irradiator and two of our hospitals had irradiators. And the one hospital that dealt with the bone marrow transplant specifically used 30 Gy.

DR. ROSENBERG: So you would advocate a range, okay.

DR. JIANG: So just a comment going to back to the effectiveness, the comment made over there just now. So my understanding is there's no specific studies published on effectiveness. But the fact that the disease is sort of gone, that's what I heard from the presentation, does the FDA accept that as evidence of effectiveness? To me, that seems pretty effective.

MS. MORRIS: Janine Morris, FDA. Certainly. The reason why we're here today is to hear from you in terms of what is adequate safety and

effectiveness in order to make a classification determination. And we take what has been said today under advisement and make a decision.

DR. ZHOU: Andrew Zhou. I think in order to look at the effectiveness, you need to have some sort of control group. It doesn't matter what control group you can define. So I wonder if -- Dr. Leitman says that you cannot do the randomized trial. But can you do observational trial with a control group? In other words, you can have two groups: one use radiated blood, one do not use, and you follow over time to say what's the rate of the disease occur. So the differences will tell you something about the effectiveness of that treatment.

DR. ROSENBERG: I'll let you jump in on that.

DR. LEITMAN: There are lots of animal studies. There's mouse models of transfusion-associated graft versus host disease called the F1 hybrid model, where a homozygous component is transfused into a heterozygous recipient that shares a haplotype. And you can reproducibly produce runting disease, which is graft versus host disease in mice with unirradiated splenocytes from the appropriate donor, and you can prevent that by irradiation of those cells.

DR. ZHOU: But no such study done human?

DR. ROSENBERG: I assume there would be ethical problems with this study that you're suggesting.

DR. DODD: But I thought you just referred to a study -- I mean

it was over time, right, so you had a cohort was -- didn't -- but before and after, and unless you expected major -- I mean, really sudden shifts in the population, going from a rate of 25%, which is what I think you quoted, to virtually nothing seems pretty striking. I guess it would have been nice to have that material presented.

DR. LEITMAN: Yeah, I can't remember the first author.

DR. ROSENBERG: Dr. Brezovich?

DR. BREZOVICH: Okay. Ivan Brezovich. Question to the FDA. Does the FDA have the authority to specify, for example, dose homogeneity within the radiation chamber? What would prevent otherwise the manufacturer to come out with a perfectly working device which has the homogeneity, this plus/minus 60%, which would exceed the 1,500 rad minimum or exceed the -- I mean be below the 1,500 or exceed the 3,500, so the unit would work just as specified, but it would not be effective?

DR. ROSENBERG: Ms. Morris?

MS. MORRIS: Janine Morris, FDA. So I'm not sure if I completely understand your concern. But if we would determine that this is a Class II device, and when we get into the Panel questions, we will be asking you what you think the special controls should be, and we can clearly specify those. We also take into consideration the devices that have already been cleared, look at those specifications. And we can be as specific and as general as we feel is necessary to allow a reasonable assurance of safety and

effectiveness.

Now, once we make that decision and that is published in the Federal Register, a new device that might come in, and perhaps they're of different characteristics, we would evaluate that in terms of substantial equivalence and compare it to the ones that we have now said are Class II. And we would decide is there sufficient information; have they changed the indication for use; is it now for something different than what we're describing today; are the technological characteristics different; do those changes in technological characteristics raise new types of questions? If they do raise new types of questions, we might find it not substantially equivalent, and it would become a Class III device, and it would have to be evaluated on its own. If there are safety and effectiveness questions but they don't rise to the level of a Class III, we would ask for data to support its substantial equivalence.

So the mechanisms are in place even after we make a decision to make sure that we maintain a reasonable assurance of safety and effectiveness. Does that answer your question?

DR. BREZOVICH: Ivan Brezovich. Thank you. It fully answers my question.

DR. ROSENBERG: Dr. Leitman, Dr. Zhou, and then we'll probably have time for a break.

DR. LEITMAN: I want to get back to the dose rate question. So

what we recommend and what's in the literature as a recommendation is when one purchases a cesium irradiator, for example, one buys it fully loaded. So these are pencil sources of cesium, and you can order it with one, two, or three. So you can get a central strength of source of as high as 51 Curie, for example, in one of the standard machines, the IBL -- one of the standard machines. And that comes as three 1700 sources. You can buy a single, double, or triple.

We always advise -- it's very expensive that you pay money for the source, of course, for the encapsulation of the source. The higher the central dose, the loading dose, the higher the dose rate. The higher the dose rate, the shorter of time of the irradiation and the longer the lifespan of that instrument. Since cesium-137 has a half-life of 30 years, you want that instrument to last for several generations of blood bankers in your facility. So there's technical reasons why you want a fully-loaded irradiator with the maximal strength of source.

But biologically, for health reasons, you also want a fully loaded source. At the dose rate that we irradiate blood components, which is at least 1,000 cGy per minute and more like 1,200 to 1,500 in a fully loaded new irradiator, the survival of cells that have received sub-lethal damage is essentially zero. When you get down to the dose rates that you were discussing, there is a potential for survival of cells in the product lymphocytes that have sub-lethal damage. And that would raise

carcinogenic potential, which is of critical importance to us in the field because we're giving these products often to people who don't need them. There are many centers in the country that irradiate all products in their center because at least 50% of their population has the diseases that were discussed today and they don't want to make an error.

So it is standard to giving irradiated products to someone who doesn't need it, and you want to make sure that there is no carcinogenic potential. So the higher dose rate devices are important in that regard.

DR. PAYNE: And did I hear you correctly, you were talking about 1 Gy per minute, 1,000 cGy per minute, or I mean 100 --

DR. LEITMAN: That's 10 Gy per minute.

DR. PAYNE: Ten Gy per minute, 100 cGy per minute?

DR. LEITMAN: 1,000 --

DR. PAYNE: Ten --

DR. LEITMAN: It's 1,000 cGy per minute. I still think in terms of rad, but it's 1,000 cGy, which is 10 Gy per minute. Yeah, 10 Gy --

DR. PAYNE: Yeah, 10 Gy per minute. Okay.

DR. ROSENBERG: Yes?

DR. ZHOU: So if I understand correctly, so it's not require all the transfusion need irradiated blood, is that right? So if that's the case, then you could have a control if, in practice -- transfusion need the irradiated blood that you got a problem with?

DR. ROSENBERG: Dr. Landgren?

DR. LANDGREN: So I just wanted to briefly chime in on Dr. Leitman's comments before. I think the lack of effective data -- we discussed kind of the inherent limitations, where you have a rare outcome, so you need to have a huge study in order to test it. And it's not ethically possible to even think about doing a study like that. So I mean, I just wanted to broaden the perspective of that. This is not a unique situation to the clinical field when it comes to blood irradiators. This is something that we actually are quite familiar with in the context of many drugs. We don't know how many drugs work, but you cannot really hold back the drug and have to go back and reprove it. Once something has been ruled out, you're kind of stuck. So I think we have to just face the facts.

So that's one thing. And also setting up the type of models you discussed before with the animal models and all that, they have also their inherent limitations. So you will always be kind of back to where we are right now. We have already passed the point of no return.

DR. ROSENBERG: Okay. We'll take --

DR. BABB: May I ask one question?

DR. ROSENBERG: Quick?

DR. BABB: One?

DR. ROSENBERG: Sure.

DR. BABB: Given the inherent ethical and even statistical

limitations on conducting a study to demonstrate elimination or even mitigation of the graft versus host disease, I'm wondering if it could be considered adequate to demonstrate efficient T-cell lymphocyte deactivation under the implication that doing so would be sufficient to eliminate graft reaction.

DR. ROSENBERG: We'll have something to think about over our 10-minute break. Return at 5 of 3. Thank you all.

(Off the record at 2:45 p.m.)

(On the record at 2:55 p.m.)

DR. ROSENBERG: So what we're going to do is we're going to go to the Open Public Speaker section. I think we have one. And then we'll go back to our discussion.

Let me get to my script. Lieutenant Commander Anderson will now read the Open Public Hearing disclosure process statement.

LCDR ANDERSON: Both the Food and -- oh.

DR. ROSENBERG: The DFO will read the disclosure process statement at the beginning of the Open Public Hearing as it is written below. No additional disclosure questions will be asked of the participant. It will be the choice of the speaker to disclose or not to disclose any relationship with the Sponsor and/or competitor. However, no one will be denied the opportunity to speak based on this choice. If a person has entered the room after the DFO has read the Disclosure Process Statement, the DFO may

reread, not ad lib, the same statement.

LCDR ANDERSON: Both the Food and Drug Administration and public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. ROSENBERG: Okay. There has been one request to speak during this open hearing session. Mr. Allene Carr-Greer -- M. Carr-Greer. Excuse me. Welcome.

MS. CARR-GREER: Thank you. So Allene Carr-Greer, and I work for AABB, formerly known to many of you as the American Association of Blood Banks. So I am an employee of AABB, and that's probably the limit

of any conflicts that I may have.

AABB is an international not-for-profit association representing individuals and institutions involved in the field of transfusion medicine and cellular therapies. We are described in the opening paragraph, and I would just comment that of the nearly 2,000 institutions, this is comprised of blood centers, blood banks, hospital transfusion services, and I would say that most of them are well acquainted with the use of blood irradiators and have been for decades now.

AABB appreciates the opportunity to provide comments as the Panel considers the appropriate device classification for blood irradiators. Irradiators, regulated as devices found to be substantially equivalent to predicate devices, have been used safely and effectively to prevent graft versus host disease for more than 30 years.

The FDA has provided a summary of the literature review they performed, and the results demonstrate that blood irradiators have had few published problems identified over a long period of time and demonstrate a reasonable assurance of safety.

The FDA published a guidance document in 1993 -- and that's now been made clear to us that that is a Class II special control, I think, seems like it is -- recommendations regarding license amendments and procedures for gamma irradiation of blood products or the recommendations for standard operating procedures, the radiation dosages

and validation of the doses and use of indicated devices, which signal appropriate exposure of the blood product to radiation.

Previous to 1992, AABB standards for blood banks and transfusion services recommended irradiation of directed blood donations from first degree family members to reduce the risk of GVHD, transfusion-associated GVHD. By 1993 this recommendation had been extended to all blood-related donors in a directed donation event. AABB standards also required that a method is used to indicate that irradiation has occurred with each batch of blood that is irradiated.

So as you consider the questions before you today, AABB believes that additional measures are not needed for use of blood irradiators. Classification should be determined to be Class I or Class II, depending on evaluation of the measures currently in use. All measures listed as general controls for a Class I designation are in use for the irradiators. FDA has suggested some special controls that could be considered for a Class II designation, some of which are already in place.

AABB does not believe it's appropriate to require postmarket surveillance and patient registries. Indicators or other methods to indicate that appropriate irradiation of a blood product has occurred are already required by FDA and AABB. And there was some discussion, I know, about is a guideline recommendation a requirement. And I'm here to tell you that if the FDA writes a guidance document and makes a recommendation, blood

centers, blood banks, transfusion services that operate a blood irradiator consider that a requirement.

Class III designation, requiring clinical trials and premarket approval is not, in our opinion, appropriate for blood irradiators.

Thank you.

DR. ROSENBERG: Thank you.

Does anyone else wish to address the Panel at this time?

(No response.)

DR. ROSENBERG: Does the Panel have any clarifying questions for the Open Public Meeting presenter?

Yeah, Dr. Harvath?

DR. HARVATH: Liana Harvath. I just wanted to go back to my original point and make sure that I'm understanding exactly our purpose when we look at your questions. So do I do that now or later?

DR. ROSENBERG: No, we'll do that in a little bit. This is in reference to the Open Public Meeting.

DR. HARVATH: Oh, okay, no. I thought the AABB commentary was absolutely in line with practice.

DR. ROSENBERG: Any other questions or clarifications for the presenter?

(No response.)

DR. ROSENBERG: I now pronounce this portion of the Open

Public Hearing to be officially closed, and we will proceed with the remainder of today's agenda.

Yeah, Dr. Harvath?

DR. HARVATH: Okay. I'd like to go back to this purpose which is really our focus on the device and the classification of the irradiation device and then keeping that a separate topic from the transfusion-associated GVHD, because as we've heard in the discussion, there has been decades of basic science looking at the immunology of GVHD that Dr. Leitman has talked about as well as citation of the case reports when people who should have received irradiated blood product unfortunately did not get an irradiated product and had fatalities. And that's been well documented in the literature.

So when we're looking at these questions, at least I'm thinking of looking at specifically the classification of the irradiator devices, knowing that what we need to do is focus our attention on will those devices work at delivering the radiation dose to the blood component and keep that separate from thinking about a clinical trial for preventing GVHD, because such a trial ethically won't be able to be conducted.

So could FDA clarify if I'm still thinking correctly about the question?

DR. ROSENBERG: Okay. And just for information, we're in the Panel deliberation now.

And Ms. Morris?

MS. MORRIS: Yes. You have appropriately characterized the topic of today's discussion in determining a classification for these devices.

DR. ROSENBERG: Thank you.

Yeah, Dr. Leitman?

DR. LEITMAN: Dr. Leitman. I'd like to comment that in the field, the industry, the blood collection industry, is satisfied with the performance of freestanding blood irradiators. They've been in use for decades, as we've heard. They do what they're supposed to. They're very easy to use; you put a component in and you hit a button. And once a year, a manufacturer comes and -- a representative comes and does a preventive maintenance and a dosimetric evaluation. So the user doesn't do that, has a professional do that. And the industry accepts that 1,500 to 3,000, that range of dose, it's not uniform, there's a range, we accept that. And the reason we accept that is that a larger canister has a greater degree of inhomogeneity, but you get more components in, so it's an operational ease of performance of the irradiation; it saves time.

So I don't think the industry has a problem with these irradiators. It seems to be -- the whole deliberation seems to be a remnant or a leftover of never having classified this device before, not that there is new safety or use issues.

DR. ROSENBERG: Ms. Morris?

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

MS. MORRIS: Janine Morris, FDA. Yes. Actually, this is just completing our process of a remaining unclassified device, and we're required to have an open meeting, and we are just trying to finalize this process.

DR. ROSENBERG: Okay. So the question of safety and effectiveness, were there other questions that the Panel would want to raise concerning safety of these devices that have not already been addressed?

(No response.)

DR. ROSENBERG: And any other questions concerning effectiveness of these devices, which we assume means irradiating to 25 Gy in a reasonable period of time?

DR. ZHOU: Andrew Zhou. I still have a small concern about effectiveness. Maybe that's a practice in medicine right now, but still I'm wondering whether the FDA -- not for this session -- this is fine -- what they recommend -- in the future do some study, look at the historical control or look at the previous datas and then try to have some sort of control and then to compare with this.

DR. ROSENBERG: Okay. I don't know how we could do that, but that's kind of -- I think this is device-related. We're assuming that radiating to 25 Gy is effective. So I don't think that's up for -- I think -- how do we have safe device that effectively radiates to that level of radiation, not the whole concept of preventing GV --

DR. ZHOU: I think this is kind of not just device; this is also the treatment.

DR. ROSENBERG: Dr. Payne?

DR. PAYNE: Let me comment and again use my radiation oncology background. And that is, as I said earlier, in radiation therapy, we have linear accelerators. They're Class II devices. And what do we use them for? We use them to treat cancer. That's what they're used for. We're not treating hangnails or something else. We're treating cancer. We're treating patients with cancer. And nowhere that I've ever seen it says that of the patients who have cancer, this device has to be effective in curing Y% of the cancers or Z% of the cancers. It's just we know it kills cells. We know if cells are killed, targeted cells are killed, then tumors shrink and people get better, but not everybody.

And, anyway, I think the analogy between the blood irradiator and the linear accelerator is a reasonably similar analogy. And so I guess I'm just saying that I think it's the same. I think it's Class II. I think maybe my comment, and I'm not the expert here, but I think it would be appropriate to talk about homogeneity of dose. I think I'd like that term rather than a dose range, because you never know what's going to happen, but you know, whatever you put into the target volume. So you might use the word target volumes, homogeneity, and then I think a dose rate, that is appropriate, and it shouldn't be below a certain amount. It could be probably anything above

a certain amount. I think those would be appropriate.

And then I think also from the safety standpoint, we really didn't talk about it, but you know, I have been involved in some -- I've read things, and stuff, in food irradiators, and you have to have interlocks, control of the room, all of the proper controls. So I think if, you know, now that you're going to classify this thing, I think you're going to need to have appropriate language. Take it right out of the radioactive material manuals. But you're going to have all of the appropriate interlocks and so forth.

And then also, a demonstration, as you indicated, that at some -- there will be a periodic demonstration of the dose uniformity, not only that it was designed to do that, but that on some sort of a periodic basis, it's tested. You put TLDs or some other thing -- somebody does it from a recognized lab probably -- that it be validated or certified that it does meet the homogeneity values, so forth.

That's it.

DR. ROSENBERG: All right. Do any Panel members have any other questions for FDA? Ms. George?

(No response.)

DR. ROSENBERG: At this time, let us focus our discussion on the FDA questions, which are on the back of our agendas. Copies of the questions are in your folders. I want to remind the Panel that this is a deliberation period among Panel members only. Our task at hand is to

answer the FDA questions based on the data in the Panel packs, the presentations we have heard this morning, and the expertise around the table. With this said, I would ask that each Panel member identify him or herself each time he or she speaks to facilitate transcription.

Please show the first question.

DR. O'HARA: Michael O'Hara. Question 1:

The key risks to health of blood irradiators include improper radiation dose to blood or blood products, radiation exposure to the user, electrical shock. Please identify any additional risks to health that should be addressed with respect to blood irradiators used to irradiate blood or blood products to prevent TA-GVHD.

DR. BOURLAND: Dan Bourland. I had one comment on this. Depending on mechanisms, there could be mechanical or crush injury relative to shielded doors being closed and things like that. Small, but you know, these are the things we do is put our fingers in the wrong place.

DR. ROSENBERG: Speak for yourself.

(Laughter.)

DR. ROSENBERG: Other comments surrounding Question No. 1?

(No response.)

DR. ROSENBERG: Ms. Morris, with regard to Question No. 1, the Panel believes that these are the issues to be considered together with

potential mechanical injuries.

MS. MORRIS: Thank you.

DR. ROSENBERG: Is that adequate?

MS. MORRIS: Yes, it's adequate.

DR. ROSENBERG: Oh, I'm sorry. Yeah. Ms. George?

MS. GEORGE: I guess the way I read those was is that I don't actually think of those as a risk because I look at those as already being addressed through many -- if this is -- if we decide that that this is a Class II and with the special controls, that the combination of the design controls, processes, the verification/validation, the associated performance standards of the 60601 safety standards which then correlate to NFPA 99, where the hospitals and any establishment that has -- I think it's more than five people in it -- have to comply with OSHA, and then if it's a radiation item, they have to have an RSO and all of those kind of requirements, those would all be a natural output. And I would expect -- hopefully you guys are going to agree, but I would expect for the past 35 years, that those things have already been in place.

DR. ROSENBERG: I think the clarification is that the current -- this addresses the current situation as Ms. George has identified.

MS. MORRIS: Yeah, Janine Morris with the FDA. The purpose of this question, for these devices, what are the risks. It's not talking about what the classification is yet. We just want to make sure have we identified

all the existing risks for this type of device.

DR. LEITMAN: I'm sorry --

DR. ROSENBERG: Yeah, Ms. Leitman and then --

DR. LEITMAN: Leitman, NIH. The devices that contain cesium are extraordinarily heavy. They're between 4,000 and 5,000 pounds. So in any document that describes -- classifies them, the need for an engineering assessment of floor-loading capacity of where it should sit is necessary. So for example, in our irradiator, which is on the ground floor over the underground parking garage, we put an aluminum strip that comes out by about six inches on each side of the irradiator, and I'm told that disperses the weight just enough so someone's car won't get smashed if the radiator goes through the floor. But an assessment of floor loading on installation is necessary.

DR. BREZOVICH: Yeah, Ivan Brezovich. Well, the three physicists here apparently agree that dose uniformity is an issue. Does FDA believe that this issue has been or will be properly addressed?

MS. MORRIS: Janine Morris, FDA. That's the purpose of the meeting is to get your input as to whether or not it needs to be addressed and how it should be properly addressed. And also -- Janine Morris, FDA -- that could be part of the discussion as we go to the other questions. Right now we're just talking about what are the risks. Later on, we talk about how do you mitigate those risks.

DR. BOURLAND: I'm sorry. I did have one other comment --

DR. ROSENBERG: Please.

DR. BOURLAND: -- but it may be outside the purview. This is Dan Bourland. And that relates to the radiological security aspects. Now, I know they're handled elsewhere, but they are still a reality. And as many of us have found, the additional controls for this purpose, sometimes they are unique based on the actual design of the system. So I don't know whether this is some opportunity to look at that and have a interagency agreement or something, but --

DR. ROSENBERG: There was some discussion about the post-9/11 rules if I remember right.

DR. BOURLAND: But there could be, for instance, design aspects that help address that --

DR. ROSENBERG: Oh.

DR. BOURLAND: Integrated instead of add-ons.

DR. ROSENBERG: Okay. So the safety of the sealed source itself.

Okay. One other clarification. The questions actually are not on the handout but are going to be projected. Are we done with Question 2 -- Question 1?

Oh, Dr. Leitner [sic]?

DR. LEITMAN: One last comment on dose homogeneity. The

manufacturers provide a graphic similar to what Dr. Davey showed giving one the distribution of dose -- if you target 100%, it will give you from 50% to 200% -- throughout the radiation chamber. And you can do with that what you like. So for a while, what we were doing is putting a lucite spacer at the bottom of our canister so that all our products were right in the middle of the canister where they got close to 100%.

So a user can take that information and decide they'd like to put their product in the area of the field where you're most likely to get 100%. Also, if you fill the irradiator entirely -- the canister entirely with products, then you're in a liquid environment, the ionizing radiation is passing through water, and that give you a different homogeneity or dose distribution than if you pass it through air with only one component in.

And, again, manufacturers describe this in their product materials. So as long as the manufacturer is open about what affects dose homogeneity and what the characteristics of that are, there is not much you can do with a fixed source and a rotating target. It's very different than linear acceleration, where you get almost 100% targeted dose. But it's the best that you can do, I'm told, in a freestanding irradiator.

DR. ROSENBERG: FDA, was that helpful?

MS. MORRIS: Yes, it was.

DR. ROSENBERG: Okay. Now I think we're ready for Panel Discussion Question 2.

DR. O'HARA: Mike O'Hara. Class I medical devices are those where general controls are sufficient to provide a reasonable assurance of safety and effectiveness. Discuss whether you believe general controls alone adequately mitigate the risks associated with blood irradiators used to prevent TA-GVHD.

DR. ROSENBERG: Thank you.

Who would like to start this one out? Dr. Gilcher?

DR. GILCHER: I think that the general controls are adequate but not adequate enough to eliminate the need for special controls.

DR. ROSENBERG: Dr. Bourland?

DR. BOURLAND: Dan Bourland. I agree with those comments. The controls that have been taken advantage of for the past, I guess -- well, since '93, but obviously prior to that, I believe, they were being done anyway, because it was realized what dose rates were needed and how the dose needed to be delivered. So the general guidelines have worked very well. But maybe they actually aren't general. They probably are specific guidelines.

DR. ROSENBERG: Dr. Brezovich?

DR. BREZOVICH: Yeah. I believe those guidelines which have been so far followed voluntarily, I believe they should be from now on followed -- should be mandated.

DR. ROSENBERG: I'll just go through the other clinicians.

DR. HARVATH: Oh, clinician?

DR. ROSENBERG: That's fine.

DR. HARVATH: I believe the CBER guidance that is being followed by blood establishments actually qualifies as special controls. I think of Class I devices for the general controls more to be like the minimum floor-level controls for any establishment that is manufacturing a device and that you look above that to the next level. So I think that what is being done right now exceeds general controls and that general controls are definitely needed, at a minimum. But what is being actually done is higher than general controls and that what we have are more specific controls that would kick it up to the next level, Class II.

DR. ROSENBERG: Thank you.

DR. LEITMAN: I agree that freestanding blood irradiators require additional special -- this is Leitman, I'm sorry -- additional special controls over and above general controls. And I'd like to remind the Panel and the FDA that at least in our institution and I think almost every institution, an operator cannot simply operate the device without undergoing special training by the health physicist that services our branch in radiation biology, in use of the blood irradiator, in emergency procedures, and in understanding the radiobiology of radioisotopes, that they do decay with time, and that the time of exposure needs to be adjusted every 6 to 12 months depending on whether you have a cobalt or a cesium-137 source,

because they decay at different rates. And that's usually part of the standard operating policy for the device, is that someone in the department resets the timer at a periodic interval, and that's critical for adequate performance of the device.

And all those kind of things kick it up to special controls. It's not a simple piece of machinery. It takes a lot of training to understand optimal use.

DR. ROSENBERG: Thank you. Dr. Rentas?

DR. RENTAS: Frank Rentas. The way the FDA has described the different classes in here, I do agree that general controls may not be enough, although as you look at Class I there, you got cGMP. Well, cGMP includes a lot of things. And, you know, some of the guidelines that the FDA put out, that's basically what they are, cGMP.

I think what this Committee probably should discuss is which special controls -- it seems to me like everybody agrees that this is going to go to a Class II. However, the FDA is listing five or six special controls. And I think we probably need to talk about -- I'm very happy with the way things are right now, with the number of general and special controls that we have. And I don't think anything else needs to be added.

And I think that's something that needs to be discussed because they talk about patient registries and things like that, which I'm not -- you know, I don't think -- my personal opinion is we don't need to go

that far. But I think we need to discuss that as a panel here.

DR. ROSENBERG: Ms. Morris?

MS. MORRIS: Janine Morris, FDA. Yes. When we get to the next question, if we believe that a Class I is not suitable for these devices, then we'll be asking you about whether or not a Class II is adequate, and we'll be talking about special controls and specifically ask you if you would be considering Class II, what should the special controls be. And we were just giving examples of what they could be, but it's during the Question 3 that we actually want your feedback.

DR. ROSENBERG: Might as well just keep going.

Dr. Zhou?

DR. ZHOU: Yeah. Based on the information we have gathered today, I feel like we do need special control for Class II.

DR. DODD: I have nothing to add.

DR. LANDGREN: Nothing to add. I concur we need special rules.

DR. ROSENBERG: Ms. George? Nothing to add? Okay. Thank you.

Okay. So I think the answer, the consensus of the group for Question 2 is that Class I controls would not be adequate for the device class in question.

MS. MORRIS: Thank you.

DR. ROSENBERG: Question No. 3, please?

DR. O'HARA: Class II medical devices are those for which special controls in addition to general controls are necessary to provide a reasonable assurance of safety and effectiveness.

Is there sufficient information to establish special controls for blood irradiators?

Would the addition of special controls to general controls mitigate this risk?

What should the special controls include?

DR. ROSENBERG: Okay. We'll just start with Dr. Bourland and we'll probably just go around.

DR. BOURLAND: Dan Bourland. And I just took the list of special controls that had been suggested; those include performance standards, postmarket surveillance, patient registry, guidelines, and design controls. And I think three of those -- and then there are others which are unnamed -- but there are three of those that I think are relevant: performance standards, the guidelines, which in a sense already exist, and design controls, and that those would be the special controls, categories to include. And that means not postmarket surveillance or patient registries.

DR. ROSENBERG: Please?

DR. BREZOVICH: Yeah. I agree. No postmarket surveillance, but as far as specifications is concerned, I think the manufacturer should at

least always provide the dose homogeneity and some indications of dose rate.

DR. ROSENBERG: Dose data? Would that be sufficient?

DR. BREZOVICH: Dose data if it includes dose distribution within the chamber for all possible fillings of the chamber with exclusions: Don't ever go beyond that much and don't go below and stuff like -- use bolus materials if you are using only one sample, only one bag, if it's a bag irradiator.

DR. ROSENBERG: Thank you.

DR. HARVATH: I agree with what's been said and would like to -- this is Liana Harvath. I would like to say that the special controls in place appear to be the "Gamma Irradiation of Blood Products" document from the Center for Biologics Evaluation and Research that was issued on July 22nd, 1993. The title specifies gamma irradiation, but it may be that other sources of irradiation that are used for these products in devices that would be used for irradiating blood products should follow this same basic guidance that's here.

DR. ROSENBERG: Okay.

DR. LEITMAN: Leitman. So I agree with everything that's been said. I would like to offer FDA some specifics to require of manufacturers, in terms of design controls and performance standards. Dosimetric distribution measured both in air and with the canister or chamber filled

with water should be provided by the manufacturer. Central dose rate has been mentioned; I want to mention it again. The decay of the source and the residual strength of the source should be provided in a document that gives monthly strength of source. And we have that now, so every month we can see how much we have left, and we can calculate what the dose rate is. And a recommended dosimetric evaluation interval; it's generally yearly for cesium-137, but they should provide that to the user.

And the other thing our current provider gives us is onsite training at their yearly preventative maintenance. It's very helpful. So I provide -- the senior staff provides some, but it's not quite the same as the manufacturer, as a representative who really understands the instrument and what to do in emergency procedures if there's a lock.

DR. ROSENBERG: Dr. Rentas?

DR. RENTAS: I agree with everything that has been said. The only thing -- and I believe it was already mentioned -- is that as you update these guidelines, x-ray irradiators need to be included as part of the guidelines as well. These were written back in 1993, and we just didn't have those out there. I think a lot of hospitals right now are moving away from radioactive materials and using x-ray irradiators, so I believe they need to be included as well.

DR. ROSENBERG: Would there be something special for linear accelerator irradiators the same way?

(No response.)

DR. ROSENBERG: Thank you.

DR. ZHOU: Andrew Zhou. I agree with what is said, but I also want to mention about the postmarketing surveillance even though I think some against that. But I think this is very severe disease, has a potential misuse. Even for one misuse, that has big consequences. So they could have some sort of the kind of postmarketing surveillance so we can keep track of why people misuse -- either misuse dosage or misuse patients.

DR. ROSENBERG: Okay.

DR. DODD: Lori Dodd, nothing to add.

DR. BOURLAND: Nothing to add.

DR. GILCHER: One thing that I would like to add -- I agree of course with everything that's been said -- is operator controls. And what I mean by that is operation -- or operator certification and not allowing just anyone to walk up and play with the buttons and push them, that there has to be some security system that allows a person to use the device and nobody else can use that device.

DR. LANDGREN: Ola Landgren, nothing to add.

DR. JIANG: I have nothing to add. I just want to echo one thing I think I've heard, that the guidance document that's in place now that's for gamma irradiations, perhaps we're asking specifically for x-ray.

DR. ROSENBERG: Ms. George?

MS. GEORGE: I guess you could tell I had things to say. A couple things. I concur with the Class II and the special controls. I did want to comment on a couple of things that I heard said around the room. I think making training available is something that should be a part of the process. But forcing, mandating training is a very different challenge because it puts a challenge on the manufacturer as well as on yourselves because then you would not be able to do your own training if you ask the FDA to make training mandatory. So keep that in your thoughts as well.

As far as the guidance, the FDA is actively doing lots of guidance work -- right, Marjorie? Right, Mary? And they actually have a very detailed plan in going back and looking at all their guidance documents and trying to get them as up-to-date as possible. So, you know, you guys should also watch for those guidances, and they would love to have your comments and insight of how to enhance those guidances. I know that because they love when they hear from us.

And then the suggestion I would have with regards to some of the dose comments that were made, there's a huge amount of effort that is going on with the FDA and stakeholders of all the other imaging modalities and radiation devices and gamma devices, et cetera, where we are actively partnering together to ensure that we have consistency in what is communicated across the industry on those parameters and things like that. And I think that, you know, those were great inputs that you gave to them. I

think that if there is an opportunity from a manufacturer's standpoint to have things aligned, harmonization is always a nice thing. It would also make it easier for the FDA to be able to review and make sure that our devices are safe and effective.

And then as far as the guidance document and the performance standards and things like that, I totally agree with that and, obviously, design controls because that's a norm.

Thank you -- oh, one last thing. On the postmarket, there was a comment made about adding postmarket. I think there's two things of postmarket. Some of the things that are supposed to be done at all times is whenever there is a complaint on the device, that there should always be the complaint go back to the manufacturer so that it can be investigated, trended, evaluated to determine if the failure were to occur again, if a death or serious injury could occur. And if it's radiation-specific and it's not associated with a death or injury or a malfunction of the device, we do have imposed on us radiation-specific reporting requirements that we have to fill out and communicate with the FDA.

So as users, tell your manufacturers when something doesn't work or when there is a user error because those are things that they need to get back so that they can effectively investigate the causes and then, in the future, enhance the human factors so that you don't have the knobology playing and somebody jumping in that shouldn't be.

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

DR. ROSENBERG: Dr. Payne?

DR. PAYNE: Just a couple of comments. I hate to encourage the FDA to micromanage, but at the same time, something to think about, and that is, going forward, any new devices are probably going to be computer-controlled. And from that standpoint, I can suggest thinking about that you would have an authorization process, a password authorization process, namely only somebody who has been trained and likewise has the password can use the device. And the reason I say this is that some devices have been used that were not set up like this, in some CT scanner situations, and so forth. So that's one thing.

Secondly, and that would be since it is going to be most likely a computer-controlled device, make sure that the radiation records, in other words, it'll be time or whatnot, that becomes a part of a permanent-type record so you have the assurance that the right person used it and that they used it in the right manner and you have a record of that. That's all.

DR. ROSENBERG: And Dr. Bourland, Brezovich, and Harvath -- and Leitman --

DR. BOURLAND: Okay. Dan Bourland here. And I just want to make one comment about dose homogeneity. It is very difficult to have great homogeneity when you have a single source in a cylindrical or point source type approach. And so the point there is to make sure that the homogeneity is reasonable and that the user understand what it is. It would

be a great burden on manufacturers to have to redesign source geometries. That would, I think, could be quite a burden at least for the sealed source approach. So we need to keep that in consideration.

My main concern was to see a 15 Gy minimum dose when 15 Gy minimum dose was the one problem in I think the Europe trial. So maybe 15 -- I think it was 15 Gy was delivered to some number -- blood to some number of patients. So but maybe that's a user guideline, not a device guideline.

DR. BREZOVICH: Ivan Brezovich. Over the last three decades or so in being in radiation therapy and dealing with radiation, I've seen x-ray tubes fail in many different ways. Since we are dealing now with x-ray irradiators, my concern would be that a tube can fail in a way that is not immediately apparent. It gives the appearance to the operator that it's working properly; yet it is producing less radiation that probably would be more likely -- or much more radiation than we think it is. And all those strips that we put on the blood samples, they are usually just yes or no devices, but they would not, for example, show an excessive dose or it may even not show enough if it's just slightly below the 1,500 cGy.

Now, what we do with accelerators to prevent that from happening is that each accelerator has an iron chamber in it which monitors the dose within 1% roughly. Now, we may not need that accuracy. But then after each treatment, we have a positive indication that the patient actually

did get the dose. And I know it would be from the industry point of view not easy to implement that. But I've seen with animal irradiators which use x-ray tubes iron chambers being part of the device, and after each treatment you see if the radiation has been actually delivered.

DR. ROSENBERG: I mean, automatic exposure controls are pretty standard in diagnostic radiology. So I don't know if that would be that burdensome, but that would be more of a technical question.

DR. LEITMAN: Leitman. So postmarket surveillance was mentioned, and then I think Ms. George just brought up a couple of good points. If you look at the manufacturer's track records of complaints, you'll find that complaints/malfunctions of the freestanding, sealed source cesium-137 irradiators are extremely rare. They're very sturdy. You know, the battery will wear out or something like that, and it would be very obvious because the turntable is not turning. But nothing else goes wrong.

I personally don't use an x-ray irradiator, but I listen to complaints of my colleagues and they're legion -- I think that perhaps Dr. Rentas referred to that -- with the x-ray tubes not lasting for the number of hours they were supposed to last, with the door jamming, with multiple other things. So I think keeping a registry if you could of unexpected mechanical events related to the irradiator. I'm not sure if the FDA would keep that or if you'd ask manufacturers to submit it to you.

But to look at the -- there is a strong tendency right now of the

NRC to try and get rid of freestanding cesium-137 and cobalt irradiators. And that's been a point of contention and discussion with the user community. And part of the reason the user community is so opposed to that is the alternative, the x-ray irradiators, have a bad track history in terms of mechanical issues.

MS. MORRIS: Janine Morris, FDA. I just wanted to point out that what you're describing is really covered under general controls.

DR. LEITMAN: Oh, okay.

DR. ROSENBERG: Thank you for that clarification.

Yeah. Harvath?

DR. HARVATH: Yes. Liana Harvath. There was a mention of patient registries. And I wanted to just mention that the document CBER released on July 22nd, 1993 dealing with "Gamma Irradiation of Blood Products," there is a special section titled Records and Fatalities. And I believe that if this special controls document is followed as written, which includes standard operating procedures, notifying FDA within a very specific time period of a fatality associated with transfusion-associated GVHD, that that would pretty much suffice for a concern about patients who are affected by a product that was used in one of these irradiator devices and that it would not be necessary to generate a separate patient registry if the special controls which have been in place are followed.

DR. ROSENBERG: Dr. Landgren, do you have a question?

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

(No response.)

DR. ROSENBERG: Are there other comments, suggestions?

(No response.)

DR. ROSENBERG: So let me try and summarize. I think the group views that with the current process in place, that there is sufficient guidance for a safe and effective device. The group has suggested that there may be additional information in terms of dosimetry and, for certain devices, ensuring that they actually are doing their function at the time, and additional concerns for safety and security in terms of using the irradiators and personnel training concerning the irradiators, although some of that may already be in place.

Group, is that close?

(No response.)

DR. ROSENBERG: Ms. Morris, is that useful?

MS. MORRIS: Yes. That's useful. And if I could just hear confirmation that you're recommending that this can be classified as a Class II, with both general and special controls?

DR. ROSENBERG: Yes. The consensus is it could be a Class II with general and special controls. Thank you.

Further questions/comments from the Panel?

Okay. Dr. Bourland?

DR. BOURLAND: This is I think rare, but electrons alone have

been used in conveyer belt configurations relative to sterilization of, for instance, medical supplies. And it's only a function of energy of whether they could be useful for blood products. So that may be something to consider, that besides x-ray and sealed source, there could be electron.

DR. ROSENBERG: So future irradiation devices may be coming down the path and would have to have an equivalent biological result compared to the current standard of 25 Gy of photons, okay.

MS. MORRIS: Janine Morris with FDA. Yes. So when we would have new technologies once we make this classification, then we would evaluate those and make sure that they were substantially equivalent, and we would take that in terms of its performance and to effectively do what the current devices do.

DR. ROSENBERG: Okay. I think we are done, then, with the questions.

At this time, the Panel will hear summations, comments, or clarifications from the FDA.

DR. O'HARA: Michael O'Hara. I don't have any.

DR. ROSENBERG: Wow. Thank you very much.

I would like to ask Ms. Madeline Lawson, our consumer representative, and Ms. Elizabeth George, our industry representative, and Dr. Marlana Vega, our patient representative, if they have any additional comments.

You're given a chance. Take it.

(Laughter.)

MS. LAWSON: I would just like to say this has been very enlightening, and I appreciate the recommendations from the expert panel.

MS. GEORGE: And I concur with that. Thank you very much.

DR. ROSENBERG: Thank you all. Thanks to everybody.

I would like to then thank the Panel, the FDA for their contributions to today's meeting.

Ms. Morris, do you have any final remarks?

MS. MORRIS: Just to thank everyone from yesterday as well as today for doing an outstanding job. Thank you.

DR. ROSENBERG: The April 12, 2012 meeting of the Radiological Devices Panel is now adjourned.

Thank you all very much.

(Whereupon, at 3:55 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

RADIOLOGICAL DEVICES PANEL

April 12, 2012

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

CATHY BELKA

Official Reporter

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947