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MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

+ + + + +

57th MEETING - MORNING SESSION

+ + + + +

MONDAY,

MAY 8, 2000

+ + + + +

The Panel met at 8:00 a.m. in Salons F and G of the Gaithersburg Marriott Washingtonian Center, 9751 Washingtonian Blvd., Gaithersburg, Maryland 20878, Dr. Thomas V. Whalen, Panel Chair, presiding.

PRESENT:

- THOMAS V. WHALEN, M.D., Panel Chair
- JOSEPH V. BOYKIN, JR., M.D., Voting Member
- MAXINE F. BRINKMAN, R.N., Consumer Representative
- ROBERT J. CERFOLIO, M.D., Temporary Voting Member
- PHYLLIS CHANG, M.D., Voting Member
- DAVID L. DEMETS, Ph.D., Voting Member
- MARK K. FERGUSON, M.D., Temporary Voting Member
- SUSAN GALANDIUK, M.D., Voting Member
- THOMAS LEE KURT, M.D., M.P.H., Temporary Voting Member
- SALLY L. MAHER, ESQ., Industry Representative
- ROBERT L. MCCAULEY, M.D., Voting Member
- DAVID KRAUSE, Ph.D., Executive Secretary

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PRESENT: (CONT.)

APPLICANT REPRESENTATIVES:

DAVID BRUSICK, Ph.D.  
LARRY KAISER, M.D.  
JOSEPH LOCICERO III, M.D.  
MARY LOU MOONEY, M.S., RAC  
BRADLEY POFF, D.V.M.  
MURRAY R. SELWYN, Ph.D.  
JOHN WAIN, M.D.  
ULLA WALLIN, M.S.

FDA REPRESENTATIVES:

CHARLES N. DURFOR, Ph.D.  
ROXI HORBOWYJ, M.D.  
KATHERINE MERRITT, M.S., RAC  
STEPHEN P. RHODES, M.S.  
CELLA WITTEN, Ph.D., M.D.

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## C-O-N-T-E-N-T-S

	<u>PAGE</u>
Call to Order, Conflict of Interest, Temporary Voting Member Deputization and Opening Remarks Dr. Krause . . . . .	5
Panel Introductions Dr. Whalen . . . . .	8
Update Since the Last Panel Meeting . . . . .	12
Open public hearing . . . . .	13
<b>Applicant Presentation, Focal, Inc., FocalSeal-L Synthetic Absorbable Sealant</b>	
Introduction, Mary Lou Mooney . . . . .	14
Product Overview and Preclinical Data Summary Bradley Poff . . . . .	17
Clinical Need and Study Design Overview Joseph LoCicero . . . . .	28
Clinical Results John Wain . . . . .	38
Panel questions about FocalSeal-L sealant . . . . .	53
<b>FDA presentation</b>	
Lead Reviewer Introduction Charles Dufor . . . . .	65
Preclinical Toxicology Review Katharine Merritt . . . . .	66
FDA Clinical Perspective Roxi Horbowj . . . . .	72
Panel Questions to FDA . . . . .	83

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C-O-N-T-E-N-T-S (cont.)

PAGE

Panel Lead Reviewers:

Clinical Study

Dr. Ferguson . . . . . 85

Preclinical Toxicology

Dr. Kurt . . . . . 92

Comments and Questions . . . . . 99

Panel Questions . . . . . 131

Vote and Recommendation . . . . . 177

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## P-R-O-C-E-E-D-I-N-G-S

(8:16 a.m.)

1  
2  
3 DR. KRAUSE: Good morning, everyone. Can  
4 everybody please find a seat and sit down so we can  
5 start the meeting?

6 Okay. Good morning everyone and welcome  
7 to this the 57th meeting of the General and Plastic  
8 Surgery Devices Panel. My name is David Krause and I  
9 am the executive secretary of this panel. I'm also a  
10 biologist and a reviewer in the Plastic and  
11 Reconstructive Surgery Devices Branch in the Division  
12 of General and Reconstructive and Neurological  
13 Devices.

14 I would like to remind everyone that you  
15 are requested to sign in on the attendance sheets  
16 which are available at the tables by the doors. You  
17 may also pick up an agenda, panel meeting roster, and  
18 information about today's meeting on the table. The  
19 information includes how to find out about future  
20 meeting dates through the advisory panel phone line  
21 and how to obtain meeting\* minutes or transcripts.

22 Before turning the meeting over to Dr.

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1 Whalen, I am required to read two statements into the  
2 record. The first statement is the deputization of  
3 temporary voting members and the second statement is  
4 the conflict of interest statement.

5 Appointment to temporary voting status.  
6 Pursuant to the authority granted under the Medical  
7 Devices Advisory Committee Charter dated October 27,  
8 1990, and as amended August 18, 1999, I appoint Robert  
9 J. Cerfolio, Mark Ferguson, Thomas Lee Kurt, and  
10 Steven Reger as voting members of the General and  
11 Plastic Surgery Devices Panel for this meeting on May  
12 8, 2000.

13 For the record, these individuals are  
14 special government employees and consultants to this  
15 panel or other panels under the Medical Devices  
16 Advisory Committee. They have undergone customary  
17 conflict of interest review and have reviewed the  
18 materials to be considered at this meeting. The memo  
19 is signed Dr. David W. Feigal, Director, Center for  
20 Devices and Radiological Health, dated April 28, 2000.

21 The conflict of interest statement is as  
22 follows: The following announcement addresses

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1 conflict of interest issues associated with this  
2 meeting and is made part of the record to preclude  
3 even the appearance of any impropriety. To determine  
4 if any conflict exists, that the agency review the  
5 submitted agenda and all financial interests recorded  
6 by the committee participants.

7 The conflict of interest statutes prohibit  
8 special government employees from participating in  
9 matters that could affect their or their employer's  
10 financial interests. However, the agency has  
11 determined that participation of certain members, the  
12 need for whose services outweighs the potential  
13 conflict of interest involved, is in the best  
14 interests of the government. Therefore, a waiver has  
15 been granted for Dr. Joseph Boykin for his interest in  
16 a firm that potential could be affected by the panel's  
17 recommendations. A copy of this waiver may be  
18 obtained from the agency's Freedom of Information  
19 office, Room 12A-15 of the Parklawn building.

20 We would like to note for the record that  
21 the agency also took into consideration another matter  
22 regarding Dr. Robert McCauley. This individual

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1 reported a financial interest in a firm at issue but  
2 in matters not related to the issues to be discussed  
3 by the panel. The agency has determined, therefore,  
4 that he may participate fully in today's  
5 deliberations.

6 In the event that the discussions involve  
7 any other products or firms not already on the agenda  
8 for which an FDA participant has a financial interest,  
9 the participant should excuse him or herself from such  
10 involvement and their exclusion would be noted for the  
11 record. With respect to all other participants, we  
12 ask in the interest of fairness that all persons  
13 making statements or presentations disclose any  
14 current or previous financial involvement with any  
15 firm whose products they may wish to comment upon.

16 At this time, I would like to turn the  
17 meeting over to our chairman, Dr. Whalen.

18 CHAIRMAN WHALEN: Thank you, Dr. Krause.  
19 Good morning, my name is Dr. Thomas Whalen. I'm  
20 professor of surgery at Robert Wood Johnson Medical  
21 School. Today our panel will be making  
22 recommendations to the Food and Drug Administration on

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1 two premarket approval applications. And, just by  
2 note of explanation, seeing a few empty seats in the  
3 front of the room, several of the deputized and  
4 temporary members of the panel are undergoing  
5 requisite training. They aren't sleeping in.

6 But, in the interests of time, we wish to  
7 proceed, despite the importance of what we're doing at  
8 this particular stage, with what Dr. Krause has read,  
9 they can probably get through their lives without  
10 being enriched by that necessary government speak.

11 The next item of business is to introduce  
12 the panel members who are now here and who are giving  
13 up their time to help the FDA in these matters, as  
14 well as FDA staff seated at the table. I would ask  
15 each person to introduce him or herself, stating their  
16 specialty, your position title, your institution, and  
17 your status on the panel as regards voting member,  
18 industry, or consumer rep, or deputized voting member.  
19 Let's start, please, with Dr. McCauley.

20 DR. MCCAULEY: I'm Robert McCauley,  
21 professor of surgery in <sup>\*</sup>pediatrics, University of  
22 Texas Medical Branch in Galveston and chief of Plastic

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1 and Reconstructive Surgery at the Shriners Burns  
2 Hospital. My specialty is plastic surgery. I'm a  
3 voting member of the panel.

4 MS. MAHER: Sally Maher, director of  
5 regulatory affairs, clinical research, for Smith and  
6 Nephew. I'm here as the industry representative.

7 MS. BRINKMAN: Maxine Brinkman. I'm an  
8 R.N. and the director of women's and children's  
9 services at Mercy Medical Center at North Iowa. I'm  
10 the consumer representative.

11 DR. CHANG: I'm Phyllis Chang, associate  
12 professor in the Division of Plastic Surgery and of  
13 Hand Surgery at the University of Iowa, a medical  
14 college. I'm a voting member of the panel.

15 DR. FERGUSON: I'm Mark Ferguson. I'm a  
16 professor of surgery at the University of Chicago and  
17 at the thoracic surgery service there. I'm a guest  
18 member of the panel.

19 DR. KURT: I'm Tom Kurt from the  
20 University of Texas Southwestern Medical Center in  
21 Dallas where I've served as a founder of the North  
22 Texas Poison Center and I'm a clinical professor of

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1 internal medicine. I'm a medical toxicologist and I'm  
2 a temporary voting member.

3 DR. BOYKIN: I'm Joe Boykin, a plastic  
4 surgeon. I'm the medical director of the Columbia  
5 Retreat Wound Healing Center in Richmond and also an  
6 associate professor of the Medical College of Virginia  
7 in plastic surgery.

8 DR. GALANDIUK: My name is Susan  
9 Galandiuk. I'm a colorectal surgeon and an associate  
10 professor of surgery at the University of Louisville  
11 and a voting member of the panel.

12 DR. DEMETS: I'm Dave DeMets from the  
13 University of Wisconsin, a professor in charge of the  
14 Department of Biostatistics and Medical Informatics  
15 and I'm a voting member of this panel.

16 DR. WITTEN: I'm Dr. Celia Witten,  
17 division director of DGRND in FDA. I'm the FDA  
18 representative.

19 DR. CERFOLIO: I'm Robert Cerfolio. I'm  
20 the assistant professor at the University of Alabama,  
21 Birmingham. I'm a non-cardiac general thoracic  
22 surgeon and I'm a temporary voting member.

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1 CHAIRMAN WHALEN: Thank you everyone. I  
2 would like to note for the record that the voting  
3 members present constitute a quorum, as required by 21  
4 CFR, part 14.

5 Next, I would like to introduce Mr.  
6 Stephen Rhodes, the branch chief of the Plastic and  
7 Reconstructive Surgery Devices Branch who will update  
8 the panel members on events relevant to this panel  
9 since our last meeting.

10 MR. RHODES: Thank you, Dr. Whalen. I  
11 want to briefly update you on three events since we  
12 last met March 1, 2, and 3. In that panel meeting,  
13 the panel made recommendations on three saline-filled  
14 breast implants. Two, the panel recommended approval  
15 with conditions. One, the panel recommended not  
16 approvable. We're still working on all three of  
17 those.

18 One other item is we have recently  
19 reclassified a suture. The so-called Gore suture, an  
20 expanded Teflon suture, from Class III to Class II.

21 And, lastly, we also recently reclassified  
22 the esophageal and tracheal prostheses from Class III

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1 to Class II.

2 That concludes my update. Thank you.

3 CHAIRMAN WHALEN: Thank you, Mr. Rhodes.

4 We will now be proceeding to the first open public  
5 hearing session of this meeting. I would like to  
6 remind all persons who are addressing the panel to  
7 please speak clearly into the microphone as the  
8 transcriptionist is depending on this means of  
9 providing an accurate record of this meeting.  
10 Parenthetically I would also add we're using a  
11 somewhat different AV system from what we had  
12 hopefully envisioned would be here and would normally  
13 be here, so we may have to take some pains to pause at  
14 certain times to make sure that we have an accurate  
15 record of this meeting.

16 We would request that all persons making  
17 statements during this open public hearing of the  
18 meeting disclose whether or not they have any  
19 financial interests in any medical device company.  
20 Before making a presentation to the panel, in addition  
21 to stating your name and affiliation, please state the  
22 nature of your financial interest, if any, and whether

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1 any of your travel expenses or accommodations have  
2 been paid for by someone other than yourself.

3 Prior to this meeting, we have received no  
4 formal requests from anyone in the public to speak,  
5 and so I would if there is anyone here that wishes to  
6 address the panel, to please signify by standing and  
7 raising their hand.

8 Very well, since there are no other  
9 requests to speak to us in this session, we will  
10 proceed to the open committee discussion of the first  
11 premarket approval application. I would like to  
12 remind public observers of the meeting that, while  
13 this portion of the meeting is open to public  
14 observation, public attendees may not participate  
15 unless specifically requested by the panel.

16 We will begin first with the sponsor's  
17 presentation.

18 MS. MOONEY: Thank you, Dr. Whalen. Good  
19 morning. My name is Mary Lou Mooney. I'm the vice  
20 president of Clinical, Regulatory, and Quality for  
21 Focal, Incorporated. We appreciate the opportunity to  
22 present the FocalSeal-L Sealant for review by this

1 panel and thank you for your preparation and  
2 participation.

3 Our presentation agenda is as follows.  
4 The product overview and preclinical summary will be  
5 presented by Dr. Brad Poff. Dr. Poff is the director  
6 of preclinical services at Focal and was the  
7 veterinary surgeon responsible for conducting and  
8 overseeing many of the preclinical studies that were  
9 performed.

10 Next, the clinical need and study design  
11 overview will be presented by Dr. Joseph LoCicero.  
12 Dr. LoCicero served as the independent data monitor  
13 for our pivotal U.S. study.

14 Finally, Dr. John Wain, the principal  
15 study investigator, will review the clinical results.

16 In addition to these presenters, I would  
17 like to introduce other attendees here on behalf of  
18 Focal who will be available to address any questions  
19 that you may have. From Focal, Ulla Wallin, director  
20 of clinical affairs and Dr. Peter Jarrett, senior  
21 director of materials, R&D.

22 Additionally, we have Dr. Larry Kaiser,

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1 principal investigator from the University of  
2 Pennsylvania, which was the largest enrolling center  
3 in the U.S. trial; Dr. Murray Selwyn, who oversaw the  
4 management of the study database and served as the  
5 study statistician; Dr. Fred Reno, a consulting  
6 toxicologist, who assisted with the selection and  
7 review of the preclinical studies; and Dr. David  
8 Brusick, consulting toxicologist with expertise in  
9 genetic toxicology. Dr. Brusick is currently adjunct  
10 associate professor of microbiology and genetics at  
11 Howard University Medical School and Georgetown  
12 University, respectively.

13 By way of background, FocalSeal-L Sealant,  
14 formerly known as AdvaSeal Sealant, is a synthetic,  
15 absorbable surgical sealant. The FocalSeal-L Sealant  
16 has been marketed in the European Union for over two  
17 years and was recently approved for marketing in  
18 Canada for use in pulmonary surgery.

19 We would now like to begin our  
20 presentation. I would ask that you hold any questions  
21 until the conclusion of our presentation. At that  
22 time, we will be happy to answer any questions related

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1 to our presentation or to the package of information  
2 supplied to you by the FDA.

3 I would now like to introduce Dr. Brad  
4 Poff who will present the product overview and  
5 preclinical data summary.

6 DR. POFF: Good morning. My name is Dr.  
7 Brad Poff. I'm a veterinarian employed by Focal and  
8 responsibility for the preclinical research.

9 FocalSeal-L Sealant is intended for use as  
10 an adjunct to standard closure of visceral pleural air  
11 leaks following pulmonary surgery. FocalSeal is based  
12 on hydrogel technology. The hydrogel is a polymer  
13 that retains a significant fraction of water in a  
14 structure. When fully hydrated, FocalSeal is over 90  
15 percent water.

16 Owing to the fact that hydrogels are  
17 mostly water, they have several unique properties that  
18 make them highly bio compatible. They present a  
19 hydrophilic surface that minimizes protein and cell  
20 attachments and their soft lubricous nature minimizes  
21 mechanical and frictional irritation to the  
22 surrounding tissues. FocalSeal is a totally synthetic

1 hydrogel. It contains no animal or human components.

2 The sealant is applied to the target  
3 tissue in two liquid parts, a primary solution and a  
4 sealant solution, and polymerized using blue-green  
5 visible light to form an adherent conformal hydrogel.  
6 The sealant adheres to tissue via mechanical interlock  
7 with the primary sealant components with the tissue  
8 interstices. Because adherence is mechanical and does  
9 not require a chemical reaction with tissue proteins,  
10 it produces minimal reaction and irritation of the  
11 tissues.

12 FocalSeal is designed to adhere to the  
13 target tissue site and provide seal integrity for up  
14 to 14 days. This ensures that seal strength is  
15 maintained through the critical wound healing period.  
16 The seal then degrades gradually through dehydrolysis  
17 and is essential resorbed within approximately 21  
18 months.

19 This is a schematic showing the major  
20 constituents of the sealant polymer. Polyethelene  
21 glycol makes up the central domain. Biodegradable  
22 segments of polylactic acid in the case of the primer

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1 solution and trimethylene carbonate in the case of the  
2 sealant are attached to the PEG molecule. Finally, a  
3 polymerizable acrylic ester endcap is attached to the  
4 biodegradable segment.

5 This schematic shows the life cycle of the  
6 sealant. The frame on the left shows the sealant in  
7 solution as applied. The acrylic ester endcaps are  
8 hydrophobic and aligned into the cells. This  
9 facilitates quick polymerization by exposure to blue-  
10 green visible light. Polymerization is complete after  
11 exposure to one 40-second light cycle. This converts  
12 the liquid into a soft, smooth, flexible, and well-  
13 adherent gel. Hydrolytic degradation begins  
14 immediately and follows an exponential curve until the  
15 gel loses all structural integrity at approximately 21  
16 months.

17 The biodegradable segments are susceptible  
18 to hydrolysis and the sealant breaks into its original  
19 constituent components and small degradation products.  
20 These are cleared through the kidneys or locally  
21 metabolized. Because individual molecules are  
22 released, as opposed to particles, as occurs with

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1 absorbable sutures, FocalSeal elicits the  
2 predominately individual macrophage response as  
3 opposed to a foreign body giant cell response.

4 Each of the major components of the  
5 sealants has been widely used in other clinical  
6 applications. Polyethylene glycol is commonly used as  
7 a vehicle for intramuscular injection formulations and  
8 trimethylene carbonate and lactide are used in  
9 absorbable sutures, clips, and bone screws. And,  
10 finally, acrylates are used in orthopedic cements.

11 The formulation excipients used in  
12 FocalSeal all have previous human use in drugs or  
13 devices, with the exception of T-butyl hydroperoxide.  
14 While the safety profile of T-butyl hydroperoxide is  
15 similar to other organic peroxides in human use, T-  
16 butyl hydroperoxide is classified as a non-carcinogen  
17 and, lastly, the patient dose, based on the average  
18 volumes used in this clinical trial, is negligible and  
19 consumed during polymerization.

20 This sequence of application is shown to  
21 outline how the material was put down. Following  
22 standard tissue closure, the primer solution is thrust

1 into the treatment site. The primer is of low  
2 viscosity, which allows it to easily flow into all the  
3 tissue interstices. Next, a small amount of sealant  
4 solution is applied and briefly brushed into primer.  
5 And, finally, additional sealant solution is expressed  
6 over the site and a 40-second light cycle is  
7 initiated.

8 The result is conformal, adherent  
9 hydrogel. The sealant adheres to the tissue by a  
10 mechanical interlock with the surface topography and  
11 the polymerization process produces a negligible  
12 amount of heat.

13 The following is a video demonstration of  
14 an application sequence in an ex vivo pig lung. You  
15 will notice a staple line across here and you can see  
16 the profile of the hydrogel on the staple line.

17 (Videotape shown)

18 Next I'd like to show an intraoperative  
19 video from a case at the University of Pennsylvania.  
20 The treatment site is at the staple line that you see  
21 oriented across the screen here.

22 (Intraoperative videotape shown)

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1 I'd like to now provide a brief synopsis  
2 of pertinent preclinical studies. The sealant has  
3 shown excellent biocompatibility in preclinical  
4 studies. Testing was conducted in accordance with ISO  
5 10993 and demonstrated that the sealant was non-sito-  
6 toxic, non-sensitizing, a moderate irritant on  
7 intracutaneous extract injection, as is typical for  
8 absorbable materials. Non-toxic systemically, non-  
9 hemolytic, and non-pyrogenic.

10 In addition, a three-month intraperitoneal  
11 implant study showed that the sealant was non-toxic up  
12 to 30 times the anticipated clinical dose. Further,  
13 a six-month implant study showed that the sealant was  
14 non-toxic up to 50 times the anticipated clinical  
15 dose.

16 Testing in accordance with the ICH  
17 guidelines for genetic toxicology demonstrated that  
18 the sealant was non-mutagenic in three separate  
19 assays, including two mammalian cell studies. A  
20 weakly positive result in a mouse lymphoma 24-hour  
21 exposure is uninterpretable due to the fact that this  
22 exposure period was recently added to the ICH

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1 recommended protocol. It is still unvalidated and may  
2 be subject to test method related artifacts. Of note  
3 is the fact that various laboratories have reported  
4 inconsistencies in results using this 24-hour exposure  
5 with other test compounds.

6 In light of the non-mutagenic findings in  
7 three well-established and validated assays, it was  
8 concluded that the sealant does not represent a  
9 mutagenic risk.

10 Available data show no evidence of a  
11 carcinogenic risk associated with implantation of  
12 FocalSeal-L. Because the sealant is composed  
13 primarily of water, very small quantities of  
14 components are delivered to the patient. Moreover,  
15 all of the major components have a history of safe use  
16 in other approved devices and drugs. Additionally, in  
17 a rat-implant study conducted for a duration  
18 comparable to that of a carcinogenicity study, no  
19 implant associated tumors were noted. Relevant  
20 findings were limited to spontaneous tumors of a type  
21 and frequency common to aging rats and comparable to  
22 both historical controls and published literature.

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1 Long-term implant studies in multiple  
2 species and in multiple tissue sites have demonstrated  
3 that the sealant shows a consistent benign tissue  
4 response. The response consists primarily of  
5 mononuclear or individual macrophages with an  
6 occasional foreign body giant cell. This tissue  
7 response was limited to the sealant tissue interface  
8 with no extension or adverse effect on adjacent  
9 tissues. The mild chronic inflammatory response  
10 adjacent to the sealant was typical of that observed  
11 in other reabsorbable medical devices.

12 This is a photo micrograph of a FocalSeal-  
13 L treated in a canine lung five months  
14 postoperatively. You can see the sealant on the trail  
15 here with the surrounding capsule on the treatment  
16 site, the lung. Note that the lung is normally  
17 expanded. There is no extension of the response into  
18 the lung tissue. As typical for a period out this  
19 long, you start to see some ingrowth of tissue into  
20 areas that are degrading.

21 And a close-up<sup>\*\*</sup> of the histology shows you  
22 that we have an outer fibrovascular capsule. This is

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1 what's responsible for healing and sealing the wound,  
2 the air leak, with an inner layer of macrophages,  
3 individual macrophages, adjacent to the sealant  
4 material. A layer of individual macrophages like this  
5 is consistent with the device where a degradation  
6 product that's easily phagitized.

7 Contrast the reaction I've just shown you  
8 of FocalSeal to that observed surrounding bovine  
9 pericardial strips. This material has an FDA-cleared  
10 indication for stopping air leaks following pulmonary  
11 surgery. Note the pronounced mixed inflammatory cell  
12 response adjacent to the implant and also note that  
13 this devices takes greater than two years to be fully  
14 incorporated at the treatment site.

15 This table shows a comparison of FocalSeal  
16 with other commercially marketed medical devices that  
17 degrade and form PLLA. An example of such a device  
18 would be an orthopedic fixation hinge, screw, or  
19 plate. Both contact soft tissue and, in the case of  
20 an orthopedic device, the absorption time is quite  
21 long to provide the initial strength that's required  
22 for fixation, whereas, with the FocalSeal, it's

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1 approximately 21 months for absorption.

2 Both produce a mild chronic inflammatory  
3 tissue reaction. However, this reaction doesn't  
4 start, in case of PLLA, until about one year and  
5 continues through degradation. FocalSeal's response  
6 starts immediately and it's, as I've shown you, with  
7 a thin fibrous encapsulation and individual  
8 macrophages adjacent to the material.

9 These photo micrographs show that  
10 comparison between FocalSeal at 150 days and a PLLA  
11 device from the literature at four years post-op.  
12 Both have a fibrous encapsulation. This is the lung  
13 tissue site that you see on the frame. And both have  
14 individual microphages, foamy microphages adjacent to  
15 the implant material, showing a similar chronic  
16 inflammatory response between the two devices.

17 Contrast with the comparison between  
18 FocalSeal and vicryl suture at both four months and  
19 eight months. In both time points, we see individual  
20 microphages starting to invade into the sealant  
21 material. The sealant material is up on top on both  
22 frames. And at eight months, we see streaming

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1       macrophages working their way into interstices and  
2       breaking down areas within the hydrogel.

3                 In contrast, vicryl suture, you can see  
4       the filaments, the suture filaments in various places,  
5       produce a foreign body giant cell response with  
6       multiple foreign body giant cells surrounding the  
7       filaments of the suture which are still present at  
8       eight months with surrounding foreign body giant  
9       cells.

10                The tissue adherence and sealing efficacy  
11       of FocalSeal-L has been evaluated in multiple en vivo  
12       models designed to simulate clinical conditions.  
13       We've tested the material on normal intact staple  
14       lines, as well as staple lines where we removed every  
15       other staple to create leaks. We've made pleural  
16       incisions adjacent to staple lines to simulate tearing  
17       that occurs along the staple line. And, lastly, we've  
18       done apical amputation models where we cut back into  
19       the lung to expose an open three millimeter bronchus,  
20       beyond what you'd expect to encounter clinically. And  
21       also I should note that this application was on  
22       parenchyma as well as the visceral pleura.

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1           In all of these studies, FocalSeal has  
2 shown good adherence and 100 percent sealing efficacy.

3           Finally, the physical properties of the  
4 sealant material were carefully designed and tested to  
5 ensure that it would have the necessary flexibility  
6 and strength for its continued application on lung  
7 tissue.

8           In summary, numerous preclinical safety  
9 and efficacy studies have shown that the FocalSeal  
10 sealant has a favorable biocompatibility as  
11 demonstrated in accordance with recognized standards.  
12 The data show no evidence of a mutagenic or  
13 carcinogenic risk and FocalSeal elicits a tissue  
14 response typical of other marketed resorbable devices  
15 and has material properties well-matched for the  
16 intended of the device. Lastly, FocalSeal has shown  
17 reproducible success in effectively sealing air leaks.

18           This concludes the preclinical study  
19 overview and I'd like to turn the presentation over to  
20 Dr. LoCicero to review the clinical need and study  
21 design.

22           DR. LOCICERO: I'm Dr. Joseph LoCicero.

1 I'm a thoracic surgeon in active practice of thoracic  
2 surgery at the Beth Israel Deaconness Medical Center  
3 in Boston, Massachusetts and I'm associate professor  
4 of surgery at Harvard Medical School. Approximately  
5 65 percent of my surgery is lung surgery. The other  
6 35 percent involves diseases of the chest wall,  
7 pleurae, mediastinum, and esophagus. I was paid by  
8 the sponsor for my services as the independent data  
9 monitor and I was reimbursed for my travel to this  
10 meeting today.

11 I was involved early in the process,  
12 participating in the assessment of clinical need and  
13 the study design and I will discuss those with you  
14 this morning.

15 As the surgeons in the audience know,  
16 pulmonary resection involves removal of a tumor and/or  
17 diseased lung tissue. The surgeon closes the  
18 pulmonary wound to eliminate air leaks, if possible.

19 There are limitations to the current  
20 technology. Standard wound closure techniques and  
21 devices such as sutures and staples are designed to  
22 give strength to the wound closure of the lung, but do

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1 not guarantee an airtight seal. Standard wound  
2 closures have limited utility in the lungs where they  
3 are friable.

4 They are also of very limited use in areas  
5 of dissection. By areas of dissection, we mean the  
6 space between the lobes of the lung known as the  
7 fissures. Surgeons often have to open these fissures  
8 in order to perform the operation. These flat  
9 surfaces are very difficult to close without  
10 distorting normal anatomy.

11 Obviously a fairly clear need exists for  
12 better surgical tools to control air leaks. Air leaks  
13 themselves are the frequent morbidity among surgery.  
14 In a recent study it was noted that air leaks were the  
15 most common reason for reexploration. Air leaks are  
16 the second most common reason for delayed discharge  
17 from the hospital.

18 In order to manage an air leak, a chest  
19 tube is required to drain air that collects around the  
20 lung. This adds significant post-operative morbidity.  
21 In my daily practice, <sup>\*\*</sup> I see patients complain  
22 significantly of pain associated with a chest tube.

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1 When the chest tube is removed, that level of pain  
2 decreases significantly. This pain is due to the fact  
3 that the chest tube irritates the parietal pleura,  
4 which has pain fibers. Surgeons are looking for any  
5 way to eliminate chest tubes. Obviously, the best  
6 management for air leaks would be to prevent them.

7 Based on this, our study design was an  
8 open-label, prospective randomized two-to-one trial.  
9 Four centers were involved. These centers were the  
10 Massachusetts General Hospital, the hospital of the  
11 University of Pennsylvania, Rochester Memorial  
12 Hospital, and Johns Hopkins.

13 The study compared a standard tissue  
14 closure with all conventional techniques to standard  
15 tissue closure plus the use of a sealant. Patients  
16 were stratified before randomization into high- and  
17 low-risk groups. This was based on an assessment  
18 which will be covered in the clinical presentation,  
19 but it included a pre-operative assessment of  
20 significance of the patient's lung disease and an  
21 intra-operative component<sup>\*\*</sup> which graded the air leaks.  
22 This was done to maintain comparability between the

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1 treatment groups.

2 The randomization was performed in a block  
3 design with stratification by center and by risk  
4 group. A total of 180 patients were placed in the  
5 study; 125 patients in the treatment group and 55 in  
6 the control group.

7 The first two patients at each center were  
8 considered pilot patients so that the principal  
9 investigator would become familiar with applying the  
10 sealant in a human. These patients were assigned to  
11 the treatment group. Pilot patients were excluded  
12 from efficacy analyses, but were included in the  
13 safety analyses. Patients assigned to the treatment  
14 group get sealant applied to all surgical sites that  
15 were at-risk for developing air leak regardless of  
16 whether air leaks were present at the time of  
17 evaluation.

18 Patients were followed for six months.  
19 This allowed assessment during the peak time of  
20 implant dose expose to the patient. In preclinical  
21 studies, only one-third of <sup>\*\*</sup>the material mass was still  
22 present at six months. The preclinical data showed

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1 that there was a consistency of tissue response even  
2 beyond the six-month period, up to and including 20  
3 months. Because this population had a significant  
4 number of patients with cancer and other co-morbidity  
5 such as other lung diseases and heart disease, we felt  
6 that there would be too many confounding variables  
7 that would allow any meaningful evaluation of implant  
8 beyond the period of six months.

9 In schematic form, patients were evaluated  
10 pre-operatively to check eligibility. This was done  
11 with a history and physical, a chest x-ray, and  
12 standard laboratory testing. After baseline  
13 assessment was completed, patients signed consent for  
14 the study prior to the administration of anesthesia.

15 The operation was conducted in the  
16 standard fashion. All patients were assessed for  
17 intraoperative eligibility based on criteria which you  
18 will hear about in the clinical section.

19 The first two patients were pilot patients  
20 at each center and had sealant applied and were  
21 followed in the usual fashion. The remainder of  
22 patients were randomized intra-operatively following

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1 best attempts by the surgeons to close all air leaks.  
2 Patients in the treatment group then had sealant  
3 applied to all areas at risk. The patients in the  
4 control group went on to closure of the chest without  
5 additional procedures. The surgical team followed all  
6 patients for the period of six months.

7 In designing the study, we had several  
8 meetings concerning the primary endpoint to choose.  
9 After consensus among the surgeons and the sponsor,  
10 the endpoints were discussed and agreed upon with the  
11 FDA reviewers with some consultation from the FDA  
12 panel. Because we were looking for the most objective  
13 endpoint, we chose the percent of patients that were  
14 air-leak free from the time of skin closure in the  
15 operating room through hospital discharge.

16 Our secondary endpoints were two. The  
17 first was for patients who left the operating room  
18 with a leak. We evaluated how long it took for those  
19 air leaks to seal. The second was the percent of  
20 patients who were air-leak free at the time of skin  
21 closure, regardless of future events.

22 Because there were so many confounding

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1 variables, such as patient co-morbidities, surgeon  
2 preference, institutional traditions, managed care  
3 pressures, et cetera, we felt that a study probably  
4 could not be done that evaluated chest tube removal  
5 time or length of stay as primary endpoints. However,  
6 these were assessed in a study for trends and included  
7 in clinical analysis.

8 Endpoints were assessed by evaluation of  
9 air leaks. The chest tubes placed at the time of  
10 surgery cannot be removed until an air leak has  
11 ceased. Consequently, control of air leaks was  
12 important to the discharge of patients. The only way  
13 to assess the ability of any device for air leak  
14 management is to assess the leaks. Improved the  
15 devices that control or eliminate these air leaks will  
16 ultimately benefit the patient.

17 Air leaks were assessed intra-operatively  
18 using the following schema. One resection was  
19 completed in the usual manner. The surgeon used  
20 sutures and/or staples to reduce or eliminate air  
21 leaks. Once the surgeon was satisfied that he had  
22 performed all conventional maneuvers possible to

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1 reduce air leaks, the remaining air leaks were  
2 assessed and graded based on a number of surgical  
3 sites and the amount of air leak from the lung.

4 The amount of air leak was graded from no  
5 air leak to continuous air leak on a scale from zero  
6 to three. At this point patients were randomized and  
7 the sealant was applied to all surgical sites.  
8 Following this, a second test for air leak was  
9 performed and a final grade was given to the patient.

10 In a post-operative period, an assessment  
11 of air leak was performed by evaluating bubbles in the  
12 chest tube drainage system. This was considered  
13 standard of care and is taught to nurses, medical  
14 students, and residents from the first day of exposure  
15 to patients undergoing thoracic surgery. It is  
16 performed on a regular basis on every thoracic  
17 surgical unit throughout the United States.

18 Assessments were made based on protocol at  
19 each individual hospital. For the purposes of this  
20 study, we standardized our assessments at four hours  
21 following closure and then at 12 hours, 24 hours, 36  
22 hours, 48 hours, and daily thereafter until the chest

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1 tubes were removed.

2 Air leak assessments have been well-  
3 accepted as standard measurement for air leak from the  
4 lung. This is a binary endpoint with presence or  
5 absence of bubbles as proof of air leak. Personnel  
6 not involved in the study were the major assessors.  
7 This was generally the nurse taking care of the  
8 patient at the time the assessment was required.  
9 Occasionally, there were discrepancies among  
10 evaluators and, in those cases, the more experienced  
11 assessor evaluation was used.

12 Our safety assessments were performed  
13 prior to discharge on or about the fourth post-  
14 operative day. And, again, at one month, three  
15 months, and six months. A chest x-ray was obtained at  
16 each time point. Laboratory evaluation included  
17 standard blood work, including blood count, BUN,  
18 creatinine, and liver function tests. All adverse  
19 clinical events were documented.

20 Monitoring at each site was performed on  
21 a periodic basis by visits from the sponsor. These  
22 were done to assure uniformity of quality throughout

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1 the study and at the various sites. I personally  
2 performed audits at each site. This involved scrutiny  
3 of all material on each patient I reviewed including  
4 a medical record, a study booklet, the research  
5 documentation, and the actual x-rays. I reviewed all  
6 major adverse clinical events personally and I  
7 performed a random evaluation of 20 percent of the  
8 study patients at each center.

9 Now I would like to turn this over to Dr.  
10 Wain who will talk about the clinical results.

11 DR. WAIN: Good morning. My name's John  
12 Wain. I'm a thoracic surgeon at Massachusetts General  
13 Hospital in Boston and an assistant professor of  
14 surgery at Harvard Medical School. The sponsor has  
15 paid to me a consulting fee for this meeting and also  
16 reimbursed me for my travel and accommodations for  
17 this meeting. In addition, I have recently purchased  
18 a small amount of stock in this company.

19 I served as the principal investigator on  
20 this multi-institutional study which was completed  
21 from 1997 to 1999. As a thoracic surgeon, the  
22 majority of my clinical practice deals with people

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1 with lung disease of various types, most commonly lung  
2 cancer, which requires surgery. As a result, I'm  
3 frequently faced with the problem of control of air  
4 leaks either due to my own surgical interventions or  
5 due to the patient's primary lung disease.

6 As Doctor LoCicero described to you, our  
7 study was an open-label prospective two-to-one  
8 randomized study of the efficacy and safety of this  
9 sealant. 427 patients were screened to enter into the  
10 study. 215 patients met eligibility requirements.  
11 The most common reasons for ineligibility were  
12 inability to obtain consent, a patient exceeding the  
13 age limit for the study, or minor laboratory  
14 abnormalities.

15 The 215 patients signed consent pre-  
16 operatively and then were taken to surgery. 35  
17 patients were excluded during surgery, most commonly  
18 because of a change in the planned surgical procedure  
19 to either pneumonectomy or sleeve resection, which  
20 excluded the patient from the study protocol. Eight  
21 patients, as you've heard, received sealant without  
22 randomization, two at each site. These pilot patients

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1 were included in subsequent safety but not efficacy  
2 evaluation.

3 The remaining 172 patients were stratified  
4 into high- and low-risk categories and then were  
5 randomized in a two-to-one fashion and data on both  
6 safety and efficacy were collected.

7 As you've heard before, clinical sites  
8 included Massachusetts General Hospital, the  
9 University of Rochester, the University of  
10 Pennsylvania, and Johns Hopkins. The enrollment in  
11 each site is shown here, including the two pilot  
12 patients at each institution.

13 Protocol compliance was excellent. Five  
14 percent of sealant patients and six percent of control  
15 patients expired during the follow-up period. Of the  
16 surviving patients, slightly more of the sealant  
17 patients had complete follow-up for the six month  
18 period. Overall, the follow-up for the entire group  
19 was 89 percent.

20 Patient demographics demonstrated a  
21 similar distribution of gender, race, and age between  
22 the treated and control groups. There were no

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1 statistically significant differences between either  
2 the treated or control groups with regards to these  
3 parameters.

4 The primary diagnosis for the majority of  
5 patients in the study was lung cancer. Patients with  
6 tumors metastatic to the lung were the second largest  
7 group of patients. These are, in fact, the target  
8 population for this product. Again, there were no  
9 statistically significant differences between the  
10 treated and control groups with regards to their  
11 primary surgical diagnosis.

12 The majority of subjects were patients who  
13 were either current or former cigarette smokers. A  
14 significant percentage of patients in both the treated  
15 and control groups also had associated lung diseases,  
16 including chronic obstructive pulmonary disease,  
17 emphysema, chronic bronchitis, and asthma, which may  
18 predispose to post-operative air leaks. There were no  
19 statistically significant differences between the  
20 treated and control groups with regard to these  
21 parameters as well.

22 As Dr. LoCicero described, we devised the

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1 stratification scheme for patients felt to be at high-  
2 or low-risk for post-operative air leaks. This scheme  
3 was based on investigator experience and data from the  
4 literature. Eight preoperative risk factors were  
5 identified, including those seen here: smoking,  
6 obstructive lung disease, emphysema, preoperative  
7 chemotherapy or preoperative radiation therapy,  
8 chronic bronchitis, or prior ipsilateral thoracotomy  
9 or a history of tuberculosis. There was no  
10 statistically significant difference between the  
11 treated and control groups with regards to these  
12 preoperative risk factors.

13 Intra-operatively, three additional risk  
14 factors were tabulated for stratification purposes.  
15 These factors included greater than four surgical  
16 sites at which air leak may occur; normal or fragile  
17 lung tissue, the latter being defined as either  
18 extensive bullosa disease or fibrotic non-compliant  
19 lung tissue; and standard or extensive surgery, the  
20 latter being defined as patients who required either  
21 complete intrapleural resection of adhesions or  
22 extensive intra-fissural dissection in patients with

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1 incomplete pulmonary fissures. No statistically  
2 significant differences, again, were noted between the  
3 treated and control groups with respect to these  
4 parameters.

5 Prior to randomization, patients were  
6 intra-operatively assigned, then, to either a low- or  
7 high-risk category by summation of the pre-operative  
8 or intra-operative risk factors for each patient.  
9 Patients with zero to four risk factors were  
10 considered low-risk and patients with five or more  
11 were considered high-risk. A similar proportion of  
12 treated and control patients were in the high-risk  
13 category. There was no statistically significant  
14 difference detected between these two groups.

15 The most frequently performed surgical  
16 procedure in the study was a single lobectomy. The  
17 second most commonly performed procedure was a single  
18 wedge dissection. There was no statistically  
19 significant difference between the treated and control  
20 groups with regards to the type of the surgical  
21 procedure performed.

22 Prior to randomization, approximately

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1 three-quarters of patients in both the treated and  
2 control groups had air leaks, despite the best  
3 surgical efforts to minimize these with standard  
4 surgical techniques. A majority of patients in both  
5 the treated and control groups who had air leaks also  
6 had more than one air leak. Again, there was no  
7 statistically significant difference detected between  
8 the treated and control groups with regards to the  
9 number of air leaks per patient.

10 When categorized by site of their leak,  
11 all types of sites had air leaks in both the treated  
12 and control patients. In particular, air leaks were  
13 common at areas of adhesiolysis and dissection,  
14 reasons that are not easily amenable to standard  
15 mechanical methods of leak control. In fact, there  
16 was a significantly larger number of leaks in the  
17 treated group as compared to the control group with  
18 regards to areas of dissection.

19 Most patients required only a small amount  
20 of primer and sealant material with a median amount of  
21 three mils of primer and 7.5 milliliters of sealant  
22 being used. The time for application of the sealant

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1 was relatively short with the median application time  
2 being nine minutes.

3 The efficacy of the sealant was assessed  
4 using several endpoints, as described by Dr. LoCicero.  
5 The primary efficacy endpoint was the percentage of  
6 patients who were air leak free from the time of skin  
7 closure to hospital discharge. And in this analysis,  
8 you can see that patients receiving the sealant were  
9 significantly more likely to remain air leak free as  
10 compared to the control patients by a factor of more  
11 than threefold, a statistically and clinically  
12 significant benefit.

13 A secondary efficacy endpoint to the study  
14 was the mean time to air leak cessation. In this  
15 case, application of the sealant resulted in a  
16 significantly shorter mean time to air leak cessation  
17 as compared to the control group. The actual  
18 difference was between 30.9 hours in the sealant group  
19 and 52.3 hours in the control group, a difference of  
20 almost one full hospital day.

21 An additional secondary efficacy endpoint  
22 was intra-operative sealing of air leaks. This

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1 endpoint is the most accurate assessment of the  
2 ability of the sealant to close identified air leaks  
3 in the lung. 92 percent of patients receiving the  
4 sealant had all air leaks closed with the sealant  
5 application intra-operatively as compared to only 29  
6 percent of patients in the control group who had only  
7 standard methods of closure of air leaks in the  
8 operating room.

9 I should note that as most patients had  
10 more than one air leak site, all patients who were  
11 treated with the sealant had closure of some air  
12 leaks. Only those patients, however, who had all air  
13 leak sites controlled at the time of wound closure  
14 were considered to have achieved this particular  
15 efficacy endpoint.

16 One finding of the study was that a  
17 certain percentage of patients in either the treated  
18 or control groups who were air-leak free at the time  
19 of wound closure subsequently developed air leaks  
20 post-operatively. Notably, the incidence of this  
21 phenomenon was similar in both the treated and control  
22 groups and in both cases developed within 24 hours

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1 post-operatively.

2 Possible explanations for this would  
3 include the nature of the underlying lung tissue,  
4 which may have been predisposed to spontaneous air  
5 leakage or the manner of post-operative management of  
6 these patients, such as the use of vigorous incentives  
7 for elementary or chest physical therapy or, in some  
8 cases, the application of post-operative suction to  
9 chest drainage tubes.

10 Safety results were assessed in all  
11 randomized patients and in the eight pilot patients  
12 who received sealant without randomization. This is  
13 a list of all the clinical events which occurred with  
14 a frequency of greater than 2 percent. A wide variety  
15 of clinical events were noted. The type and frequency  
16 of these events, however, were similar to those  
17 expected in a large population of patients undergoing  
18 lung dissection for cancer and other diseases. There  
19 was no statistically significant difference between  
20 the treated and control groups with regards to any of  
21 these events.

22 On closer analysis, we observed that the

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1 incidence of arrhythmia, anemia, wound infection,  
2 confusion, and empyema were not unexpected and were  
3 similar to those reported rates for multi-  
4 institutional studies of complications following lung  
5 resection. Investigators on review of the incidence  
6 of these occurrences felt that the differences were  
7 not clinically significant.

8 In point of fact, however, we looked quite  
9 closely at the patients who developed empyema in the  
10 treated group. There were four patients and these  
11 included the clinical circumstances that you see here.  
12 One patient with pneumococcal pneumonia that developed  
13 three months post-operatively. He developed  
14 bacteremia and empyema.

15 One patient who had acute post-operative  
16 hemorrhage, treated without reexpiration, three weeks  
17 later had a chest tube reinserted which yielded old  
18 blood and a positive culture for bacteria.

19 One patient who developed a pneumothorax  
20 post-discharge treated by aspiration, following the  
21 aspiration, the patient returned after two weeks with  
22 an empyema which required a drainage tube.

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1                   And, lastly, a patient with a  
2                   hydropneumothorax that was identified 15 days post-  
3                   operatively after discharge. This patient required a  
4                   chest tube and the fluid, which was green from the  
5                   chest tube, had a positive culture. No further  
6                   interventions were necessary and, again, the consensus  
7                   amongst the investigators was that these events were  
8                   not unexpected given the patient population involved.

9                   The types of clinical events in terms of  
10                  severity were similar between the treated and control  
11                  groups. Notably, more than 90 percent of all adverse  
12                  events occurred by 75 days post-operatively. There  
13                  was no statistically significant difference between  
14                  the treated and control groups.

15                 In pre-clinical studies, one question  
16                 related to renal function with application of the  
17                 sealant material. When we evaluated this in our  
18                 patients, we found that, with regards to the BUN  
19                 parameter as a measure of renal function, no  
20                 statistically significant difference between either  
21                 the treated or control patients during the time of  
22                 six-month follow-up.

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1                   Similarly, in evaluation of creatinine  
2 levels in the treated and control groups during the  
3 six months of follow-up, there was no statistically  
4 significant difference between the two groups.

5                   And, lastly, there was no statistically  
6 significant difference between the treated and control  
7 groups with regards to white blood cell count during  
8 the follow-up period. There was the anticipated rise  
9 in the early post-operative period in both groups that  
10 then declined to normal level during the time of  
11 follow-up.

12                   We performed several additional analyses  
13 of the information collected from the study.  
14 Measurement of chest tube drainage demonstrated no  
15 statistically significant difference between the  
16 treated and control groups. In fact, at each time  
17 point, the amount of drainage was slightly less in  
18 patients receiving the sealant, the red bars here, as  
19 compared to the control patients.

20                   Personally, if a patient is not leaking  
21 air, I would remove the chest tubes when the drainage  
22 is about 250 ccs per day or less, an amount frequently

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1 reached early in our study patients.

2 As pointed out, our primary efficacy  
3 endpoint, the percentage of patients who were air-leak  
4 free from wound closure until the time of possible  
5 discharge achieved statistical significance. We also  
6 observed favorable trends pursuant to application with  
7 regards to the time for wound closure to chest tube  
8 removal and the time for wound closure to hospital  
9 discharge. The latter parameter was a mean of 7.4  
10 days with sealant patients and 10.1 days for the  
11 control patients.

12 The multi-factorial nature of causes for  
13 prolonged hospital stay and the fact that the study  
14 was not designed with sufficient statistical power to  
15 evaluate these endpoints does not allow extension of  
16 further conclusions from these interesting  
17 observations.

18 In summary, then, in this multi-  
19 institutional study, we found that the application of  
20 the sealant for the control of air leaks following  
21 pulmonary resection achieved a clinical and  
22 statistically significant difference for all study

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1 endpoints. The percentage of patients air-leak free  
2 in the treatment group was more than threefold the  
3 control group and the duration of post-operative air  
4 leaks was reduced by almost one full hospital day. In  
5 addition, favorable trends in chest tube removal and  
6 hospital discharge times were noted.

7 Equally importantly, of course, there were  
8 no significant differences in the incidence or  
9 severity of adverse events in patients receiving the  
10 sealant as compared to control patients.

11 In conclusion, the use of FocalSeal-L  
12 sealant has been shown to provide clinically  
13 significant results for its intended use. The  
14 benefits of the sealant seem to clearly outweigh the  
15 probable risk for its use. Thank you.

16 MS. MOONEY: That concludes our formal  
17 presentation. Again, we'd be happy at this point to  
18 answer any questions on the specific presentation or  
19 other information contained in your information  
20 packages. I should mention that we did provide in  
21 front of your name plates<sup>\*\*</sup> some preformed gel samples  
22 of the sealant material so that you could take a look

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1 at that and see actual product samples.

2 CHAIRMAN WHALEN: Thank you. Going around  
3 the panel, are there any comments about the sponsor's  
4 presentation or questions? Dr. DeMets.

5 DR. DEMETS: Yes. You made a comment as  
6 to the majority of the patients were evaluated by  
7 independent or third party. Could you be specific as  
8 to what that percent was?

9 MS. MOONEY: At FDA's request, we did go  
10 back and take a look at any events that were evaluated  
11 actually were changed from original assessments and I  
12 believe that total was about 20 out of 180 patients.  
13 And we looked at analysis of the study endpoints and  
14 there was no impact on the study endpoints.

15 CHAIRMAN WHALEN: Dr. Galandiuk, anything?  
16 Dr. Boykin.

17 DR. BOYKIN: A question probably for Dr.  
18 Wain. Just an insight on the experience going back in  
19 on the patient who'd been sealed with the product but  
20 required reoperation. Can you tell a little bit about  
21 that?

22 DR. WAIN: There were only two instances

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1 when that occurred and each time the sealant was found  
2 to be at its appropriate site, that is, where it had  
3 been initially placed, not free in the pleural space  
4 or distracted from the lung tissue itself.

5 DR. BOYKIN: Yes, specifically how did you  
6 find the tissue in terms of inflammatory response?  
7 How did it handle to resealing and how did you reseal  
8 it?

9 DR. WAIN: None of the patients required  
10 actual resealing. The tissue itself was normal. The  
11 area where the sealant was was still clear and the  
12 sealant itself was still intact. And the surrounding  
13 tissue was not overly fibrous or less or more inflamed  
14 than one would normally expect for a reoperation.

15 CHAIRMAN WHALEN: Dr. Kurt.

16 DR. KURT: Yes, I have two questions.  
17 First about allergic reactions or sensitization. No  
18 particular comment was made concerning adverse  
19 reactions such as skin rashes, allergic reactions, et  
20 cetera. The second, I noticed there was a difference  
21 in proportion of controls in the studies of the groups  
22 in the four centers and what was the necessary

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1 difference in the controls versus the patients?

2 MS. MOONEY: The first question. There  
3 were no noted allergic reactions or sensitizations in  
4 the patients. And, in terms of the difference in the  
5 control, I'm presuming you may be speaking of the  
6 center for Johns Hopkins where I think we had a little  
7 disproportionate distribution. That was attributable  
8 to the small sample size there and the particular  
9 block randomization that was used in terms of the  
10 sequencing, the random sequencing of treatment and  
11 control.

12 We also did have one patient at the time  
13 of surgery where the nurse opening the randomization  
14 envelope incorrectly identified the patient as being  
15 randomized into the treatment arm.

16 CHAIRMAN WHALEN: Dr. Ferguson.

17 DR. FERGUSON: I have two questions. I  
18 think probably both best directed to Dr. Wain. Just  
19 a follow-up on Dr. Boykin's question about the reentry  
20 patients. Could you say something about whether or  
21 not the adhesions between the sealant and the parietal  
22 pleura?

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1 DR. WAIN: In the areas where the sealant  
2 was applied, there was not adherence of that part of  
3 the lung to the parietal pleura. In areas where there  
4 was not sealant, there was adhesions, as you would  
5 normally expect.

6 DR. FERGUSON: And the second question has  
7 to do more with procedural issues and the  
8 determination early to make decisions about chest tube  
9 removal and discharge. I presume that the jury of  
10 decisions about or absence of air leaks was made by  
11 the surgical team as opposed to the floor nurses or  
12 the attending physician?

13 DR. WAIN: That's correct. There was a  
14 sheet at each patients' bedside where defined time  
15 points post-operatively, the presence or absence of  
16 air leaks could be assessed and recorded and that was  
17 typically done by the nurses. But then the decision  
18 regarding chest tube removal was typically made by the  
19 surgical team, as you said.

20 DR. FERGUSON: And the surgical team,  
21 presumably, was not blinded<sup>ed</sup> as to the treatment group  
22 of the patient.

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1 DR. WAIN: They weren't specifically  
2 blinded. In practice, they usually were in that the  
3 house officers that include patients on the floor were  
4 infrequently the ones participating in the operation.

5 CHAIRMAN WHALEN: Dr. Cerfolio.

6 DR. CERFOLIO: Yes, I have a couple of  
7 questions. Actually, five of them. Chest x-rays,  
8 were they done daily on these patients?

9 DR. WAIN: Yes. Chest x-rays were done  
10 daily while the chest tubes were in place.

11 DR. CERFOLIO: Okay. Were they portable  
12 chest x-rays or PA laterals in the department?

13 DR. WAIN: They were typically done  
14 portably, although it wasn't defined in the study  
15 protocol. The typical practice was a portable chest  
16 film for patients when they were on suction and a  
17 chest film, a PA and lateral film, when the tubes were  
18 on waterseal or off suction.

19 DR. CERFOLIO: Okay. I noticed in this  
20 chart of clinical events on slide number 61 you have  
21 residual space. Is that how you're defining the  
22 presence of a pneumothorax? Is a pneumothorax

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1 equivalent to a residual space?

2 DR. WAIN: It would not be. A residual  
3 space would be the space remaining after a pulmonary  
4 resection where there is not complete reconfirmation  
5 of the lung yet to fill the thoracic space, whereas a  
6 pneumothorax would be a patient who had a change in  
7 what one would expect for the normal post-operative  
8 residual air space present.

9 DR. CERFOLIO: Okay. Because I don't see  
10 on that chart the number of patients with  
11 pneumothoraces. And I assumed you were equating one  
12 with the other. You're really not. So you're saying  
13 those are residual spaces the lung is not going to  
14 fill. Can you tell me how many patients in the  
15 FocalSeal group versus the control has pneumothoraces,  
16 then?

17 DR. WAIN: I believe it is on that slide,  
18 it's just a very small slide. It's the fifth line  
19 down between cancer progression and thoracic wound  
20 infection. Oh, excuse me.

21 DR. CERFOLIO: So that's your pneumo --  
22 okay.

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1 DR. WAIN: There.

2 DR. CERFOLIO: So you've got eight per  
3 seven. So really there was very little -- eight  
4 percent versus seven percent -- very little  
5 statistical difference in that.

6 DR. WAIN: Correct.

7 DR. CERFOLIO: Okay. So just tell me how  
8 you're defining the definition between a residual  
9 space and a pneumothorax again? How does one define  
10 that?

11 DR. WAIN: Yes. Well, the residual space  
12 is something after a lung resection upon removal of  
13 the chest tubes, it's very uncommon that the lung  
14 immediately has the same confirmation as the bony  
15 thorax so that there is a space, particularly for  
16 upper lobectomies, that's frequently seen. That would  
17 be a residual air space.

18 Now you would expect that to have some  
19 characteristics. Namely, it should correspond  
20 anatomically to the point of the division of the lung  
21 and the other contour should relate then to the chest  
22 wall. If you had a contour that was different, say a

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1 contour that was convex rather than one that was  
2 concave, then that would suggest that there was air in  
3 there under pressure. And then that would be a  
4 pneumothorax.

5 The second phase of pneumothorax would be  
6 someone who had a minimal residual air space or had a  
7 residual air space that appeared to be getting smaller  
8 and then returned after discharge with then a new or  
9 enlarging air space that wasn't --

10 DR. CERFOLIO: That's great. And I'm just  
11 trying to get to the bottom line because I want to ask  
12 you one question on that and that is I saw two percent  
13 of your patients, three patients in the focal group  
14 and none in the control, had residual spaces. And you  
15 talked about four people who had the empyemas all in  
16 the treated group and none in the control group. And  
17 the two patients that had the residual space that were  
18 treated, were either one of those or both of those or  
19 none of those, did they develop empyemas? What was  
20 the natural history of the residual space in the  
21 treated group?

22 In other words --

1 DR. WAIN: Yes, those weren't the empyema  
2 patients. None of those patients with the residual  
3 air space had empyemas.

4 DR. CERFOLIO: Great. Okay. So in the  
5 patients who had residual space despite being treated,  
6 their space was fine. It did not -- like most  
7 residual spaces, nothing happened to it.

8 DR. WAIN: That's correct.

9 DR. CERFOLIO: Okay. Great.

10 CHAIRMAN WHALEN: Dr. Chang.

11 DR. CHANG: Two questions. Can you  
12 qualitatively describe the amount of heat generated  
13 from the polymerization reaction? My limited clinical  
14 experience would be with the heat generated from  
15 methyl methacrylate, but that's a 10 out of 10. On a  
16 scale of one to 10, with 10 being the heat generated  
17 from methyl methacrylate reaction and mixing those  
18 polymers, what's the amount of heat, very, you know,  
19 qualitatively, from the light?

20 MS. MOONEY: Dr. Chang, if you look back  
21 on the screen here, we have a back-up slide that  
22 addresses that question just behind you. In terms of

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1 the heat liberation with the FocalSeal sealant, as  
2 you'll see, the peak temperature that's reached is 42  
3 degrees C and as was previously mentioned in the  
4 presentation, the polymerization duration is 40  
5 seconds. That's compared to PMMA or bone cement,  
6 which typically reaches a peak temperature of  
7 approximately 90 degrees C and that duration or set-up  
8 time typically takes five to 15 minutes.

9 DR. CHANG: And the other question is the  
10 comment in the presentation that both treated and  
11 untreated groups did develop some air leak within 24  
12 hours, whether or not it was successful at the time of  
13 skin closure. Retrospectively or as a recommendation  
14 for practice, is there any way, if you were to redo  
15 your protocol, to control for the clinical practice of  
16 using suction or not using suction, since air is  
17 usually put up in drainage tubes your blood would be  
18 lower. Just your thoughts on that.

19 DR. WAIN: Yes, I think, retrospectively.  
20 Initially, the study was designed not to try to change  
21 how we would care for the patients, but, given our own  
22 experience with the efficacy of the sealant intra-

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1           operatively, retrospectively or in the future, we  
2           would design a study where we would not use suction at  
3           all.

4                     DR. CHANG: Thank you.

5                     CHAIRMAN WHALEN: Ms. Brinkman. Ms.  
6           Maher.

7                     MS. MAHER: No questions.

8                     CHAIRMAN WHALEN: Dr. McCauley.

9                     DR. MCCAULEY: I just had one question.  
10          Relative to the patients that died in the treatment  
11          group, was there any opportunity to go back at autopsy  
12          and survey the sites of the FocalSeal for both  
13          histologic, looking at it grossly and also for  
14          histologic examination?

15                    DR. WAIN: Unfortunately not. We did not  
16          obtain autopsy data on any of the patients who died.

17                    DR. MCCAULEY: Were any of them autopsied?

18                    DR. WAIN: They were not autopsied.

19                    CHAIRMAN WHALEN: Dr. Galandiuk.

20                    DR. GALANDIUK: Actually, I have one  
21          question. Since some of these surgeries were done for  
22          malignancy, did the FocalSeal create any kind of

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1 artifact that might affect the CT scans that are used  
2 to follow-up the patient later?

3 DR. KAISER: I'm Larry Kaiser. I'm from  
4 the University of Pennsylvania and was the lead  
5 investigator at that center. My expenses to this  
6 meeting have been reimbursed by Focal, but I have no  
7 financial interest in either this company or any  
8 medical device company.

9 I think, Dr. Galandiuk, you make an  
10 interesting point and early in the study we thought we  
11 might actually be able to see some of the material on  
12 chest radiographs. And, depending on how the chest  
13 radiographs are obtained, occasionally you can see it.  
14 But in follow-up of these patients over a long period  
15 of time, no, we've not been able to see any of this  
16 material and have not seen anything that would confuse  
17 us in terms of determining metastatic disease or a  
18 second primary, for instance.

19 CHAIRMAN WHALEN: I'd like to thank the  
20 sponsor then and I would ask that, as the sponsor  
21 vacates the table, that <sup>\*\*</sup>FDA come forward to begin  
22 their presentation. We'll go right into that.

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1 DR. DUFOR: Good morning. My names is  
2 Charles Dufor and I'd like to introduce the FDA team  
3 that will be presenting to you this morning.

4 First, once again to remind you that the  
5 product that is under discussion is supplied as a  
6 synthetic-free polymer in two vials of a low-viscosity  
7 primer and a single syringe of FocalSeal sealant. The  
8 device is applied to pleural air leaks as an adjunct  
9 to standard closure methods after pulmonary surgery.

10 Today the FDA presenters to the advisory  
11 committee, I myself, Charles Dufor, I am the lead  
12 reviewer; Dr. Katharine Merritt was the lead  
13 preclinical reviewer; and Dr. Roxi Horbowyj did the  
14 clinical review.

15 Other members of the review team that are  
16 in presence today and are available to address any  
17 questions that you may have are Dr. Sam Arepalli who  
18 performed the chemistry review of this application;  
19 Dr. Rosalie Elespuru, who, like Dr. Merritt, is a  
20 research scientist and product reviewer in FDA's  
21 Office of Science and Technology within the Center for  
22 Devices and Radiological Health. And also Ms.

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1 Silverman, Phyllis Silverman, who performed the FDA's  
2 statistical review of this application.

3 With this, I would like to introduce Dr.  
4 Merritt.

5 DR. KRAUSE: I would just like to tell the  
6 panel members that I put a draft of each speakers'  
7 presentation at your space and you can follow along as  
8 the FDA people present their presentations.

9 DR. MERRITT: Thank you. I am Katharine  
10 Merritt and I would like to present the FDA  
11 perspective on the preclinical studies.

12 The bulk of the preclinical studies were  
13 biocompatibility testing. Biocompatibility testing is  
14 done by standard procedures as described in ISO and  
15 ASTM. And these are the recommended procedures.  
16 However, these procedures are based on testing the  
17 solid material. ASTM finally has dealt with porous  
18 materials and recently with the implant site of  
19 absorbables. Procedures for materials that polymerize  
20 in situ are not described and they pose a challenge.

21 For the biocompatibility of FocalSeal,  
22 this does polymerize in situ. It has a complex

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1 chemistry with the reactive moieties and a short half-  
2 life. And they are a challenge to tests in vitro.

3 In terms, as resorbables, the tissue  
4 response is not the usual benign fibrous capsule seen  
5 with solid materials. For the biocompatibility of  
6 FocalSeal, standard biocompatibility tests were  
7 performed with consideration for these challenges.

8 Many of the tests, in vitro tests, were  
9 done with extracts. And in this case, they were done  
10 with the extracts of the polymerized material.  
11 Generally extracts are done with polar and non-polar  
12 solvents to extract the different moieties. In this  
13 particular case, the cytotoxicity test was done with  
14 complete medium, which is a non-polar extract.  
15 Irritation and sensitization were done with saline, a  
16 polar extract. Acute systemic toxicity was done with  
17 saline, a polar extract. And the genotoxicity tests  
18 were done with a mixture of saline, a polar, and DMSO,  
19 a non-polar extract.

20 The implantation tests were done using  
21 polymerizing material. \*\* These were done very  
22 creatively and very extensively with nice procedures.

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1 These were done in the rat, which is the standard  
2 model for implantation and the dog study, which was  
3 done to model the lung resection and the use of the  
4 sealant.

5 The two procedures in the rat. One was an  
6 IP implantation and one was an intramuscular  
7 implantation.

8 In terms of the genotoxicity studies,  
9 three in vitro tests were done. The Mammalian cell  
10 mutation was done with the mouse lymphoma tests.  
11 There was a saline extract, a DMSO extract. It was 72  
12 hours at 50 degrees centigrade using standard  
13 extracting protocols. And then they involved they  
14 were mixed and diluted and they used a four-hour and  
15 a 24-hour exposure to cells. As you've already heard,  
16 the 24-hour exposure to cells gave a weakly positive  
17 result.

18 The chromosomal aberration test was done  
19 with a mixture of saline and DMSO extracts. These  
20 extracts were pooled and diluted and there were  
21 negative results.

22 The Ames test was done with Salmonella

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1 typhimurium. There was an extraction and DMSO for 24  
2 hours at 37 degrees centigrade and this test was  
3 negative.

4 In terms of genotoxicity testing, there is  
5 a great deal of science going on as to what type of  
6 tests should be done. At this standpoint, there are  
7 standard protocols, but for all of them, there are  
8 questions on the value of some of these tests. And  
9 materials that polymerize in situ add even more  
10 questions to the testing procedures.

11 ISO 10993-3 is working on the standard  
12 protocols and the testing matrix that should be used.  
13 At this current time, they are recommending a three-  
14 test initial test protocol: the Ames test, the  
15 Mammalian cell mutation test, and a chromosomal  
16 aberration test. And when you follow the flow chart,  
17 when one of these tests is positive, tests for  
18 carcinogenicity should then be considered.

19 In terms of the implantation study in the  
20 rat, an 80 to 90 day IP implantation study was  
21 undertaken. And this demonstrated that the material  
22 had not resorbed during this time period. And it was

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1 estimated that about 36 percent of the material still  
2 remained at six months. There was, as you have seen,  
3 a macrophage response and early on in the IP studies,  
4 there was an indication that perhaps some giant cells.  
5 In review of the histology, these responses were  
6 consistent with the chronic inflammation that's  
7 associated with resorption of material.

8 The longer time intramuscular implantation  
9 revealed that the material was being resorbed slowly.  
10 The long-term rat implantation was a 20 month  
11 intramuscular implant study and it indicated that, at  
12 the end of 20 months, the material was almost gone.  
13 The inflammatory response was resolving, however,  
14 tumors were identified in the rats. There was one  
15 fibrosarcoma found at one implant site and the  
16 question was whether or not it was related to the  
17 implanted material. Probably not. There was no  
18 material found actually in the tumor.

19 It was decided at this time that it might  
20 be possible to compare these results to those of  
21 historical controls. In terms of genotoxicity and  
22 carcinogenicity, the rat intramuscular implantation

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1 study was about the lifespan of the rat and it was  
2 felt that it might possibly serve as the  
3 carcinogenicity study even though there were no  
4 concurrent controls.

5 The use of these data and compared to  
6 historical controls, the carcinogenicity model itself  
7 in the rat has limitations and the statistical number  
8 here gave us a limited power. However, in evaluating  
9 the results, the incidence and time of appearance of  
10 tumors was similar in the test animals and in the  
11 historical controls.

12 In terms of the implantation in the dogs,  
13 this model, the device usage actually went along.  
14 What I had the data from was the 20 month study,  
15 although I believe this has gone longer. At the end  
16 of the 20 month study, the material was almost  
17 completely resorbed, the pathology was consistent with  
18 the resorbing material, there were no local or  
19 systemic effects, and there were no tumors.

20 In conclusion, the implantation studies  
21 demonstrate that this material is slowly resorbed and  
22 there is an active inflammatory response for over 20

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1 months. There is weak evidence for genotoxic effect.  
2 The carcinogenic effect was similar to that of the  
3 historical controls in terms of incidence and timing,  
4 however, this study had limited power. And we pose to  
5 the panel the question of what are the implications of  
6 having a chronic inflammatory response that is  
7 occurring for over 20 months and in sight of the fact  
8 that we have inconclusive data on genotoxicity and  
9 carcinogenicity?

10 I will turn this over to Roxi.

11 DR. HORBOWYJ: Good morning. I'm Roxi  
12 Horbowyj and I'm the clinical reviewer for this  
13 application and I will present the FDA's clinical  
14 perspective on FocalSeal-L as presented in PMA  
15 submission 990028. A little bit of background of the  
16 device as well as clinical study objectives design,  
17 outcomes, and the summary.

18 The device, as you have heard, is a di-  
19 functional macro-monomer product, polyethylene glycol  
20 and trimethylene carbonate in acryloyl chloride  
21 polymerization. The polymerization is done in three  
22 steps and is facilitated by light, Y Eosin, and t-

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1 butyl peroxide.

2 The device is a clear, flexible, adherent  
3 hydrogel which is approximately 73 percent water by  
4 weight, according to the PMA submission protocol and  
5 is expected to be a barrier to air leak over 14 to 30  
6 days while tissue heals and then degraded into a  
7 water-soluble product.

8 There was a European study performed  
9 before the U.S. investigation was undertaken. And in  
10 this European study, patients who were studied were  
11 consenting non-pregnant adults, predominately male and  
12 with bronchogenic carcinoma. The patients were  
13 followed for 60 days. There were 30 patients  
14 randomized through the FocalSeal group and 26 patients  
15 randomized as a control.

16 Findings from this study included that the  
17 incidence of no air leak from skin closures or  
18 discharge was 83 percent for the FocalSeal-L patients  
19 and 23 percent for control patients. 83 percent here  
20 and 23 percent are calculated on the basis of the  
21 total number of patients in the cohort, so success  
22 would have been calculated at -- the number would have

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1        been 83 percent of 30, 23 percent of 26. Other  
2        findings from the study were that randomization was  
3        ineffective for homogeneity between groups and it was  
4        felt that a risk assessment for post-operative  
5        morbidity was needed.

6                    There was also noted an increased  
7        incidence of broncho-pleural fistulae in FocalSeal  
8        sealant treated patients. And the hypothesis was and  
9        is that FocalSeal sealant applied to the bronchial  
10       stump acted as a mechanical barrier to adjacent  
11       overlap and adhesion, thereby eliminating a natural  
12       source of revascularization, causing slowed healing,  
13       therefore broncho-pleural fistulae.

14                    As you've heard, the objective of the  
15       clinical study in the U.S. was to determine the safety  
16       and effectiveness of FocalSeal-L sealant for use as an  
17       adjunct to standard closure of visceral pleural air  
18       leaks incurred during pulmonary surgery.

19                    The design was prospective, conducted at  
20       four centers. Patients, as well as chest tube air  
21       leak observers, were masked and the study data was  
22       audited by unmasked investigators. Randomization was

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1 two-to-one and performed after air leak evaluation  
2 grading, a one-time attempt for air leak reduction  
3 with standard techniques, intra-operative exclusion  
4 criteria assessment, as well as risk assessment and  
5 assignment for post-operative morbidity into high and  
6 low groups. And this risk assessment tool was  
7 designed for study. It's not a validated tool.

8 Patients who were randomized for purposes  
9 of the sealant had the sealant applied to all  
10 parenchymal surgical sites. That is suture and staple  
11 lines, as well as areas of dissection and  
12 adhesiolysis. Patients who were randomized to control  
13 received the standard surgical pleural closure at air  
14 leak sites.

15 All of the patients were followed up for  
16 effectiveness for hospital discharge. The follow-up  
17 for safety was for six months.

18 The first two patients who entered the  
19 study, per center, were to be dropped from the  
20 effectiveness analysis. A learning curve, however,  
21 was not otherwise addressed.

22 The target population in the U.S. pivotal

1 study consisted, then, of consenting non-pregnant  
2 adults with greater six months expected survival time  
3 undergoing elective lobectomy, wedge, or segmental  
4 resection via open thoracotomy and with non-extensive  
5 adhesiolysis and well-established hemostasis during  
6 the procedure.

7 No other sealants were to be used and no  
8 pneumonectomy, sleeve resection, or bronchoplasty  
9 patients were to included due to the increased  
10 incidence of broncho-pleural fistulae that occurred in  
11 such European patients.

12 Endpoints for effectiveness, the primary  
13 endpoint was the incidence of no air leak from skin  
14 closure to hospital discharge. Very specifically in  
15 the U.S. clinical protocol, which is in the PMA  
16 submission, this was referred to as a proportion of  
17 patients who remained air leak through hospital  
18 discharge.

19 Secondary effectiveness endpoints included  
20 incidence of no air leak at skin closure, specifically  
21 in the protocols stated as the proportion of patients  
22 who are air leak free at the end of surgery. And the

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1 second secondary effect was time to no air leak,  
2 specifically in the protocol, in the PMA with  
3 reference to duration of chest tube placement  
4 dependent on the air leak.

5 The safety endpoints were adverse events  
6 were evaluated up to six months.

7 Other parameters that were collected  
8 during this study included chest tube drainage per  
9 patient per day; time to chest tube removal; time to  
10 hospital discharge. Device residence time in patients  
11 was not studied and preclinical and clinical outcome  
12 relations have not been validated.

13 From the standpoint of outcomes, patient  
14 population, there were 125 patients randomized to  
15 FocalSeal and only 55 randomized to control, with a  
16 two-to-one randomization scheme. Over 80 percent of  
17 patients in both groups were categorized as low-risk  
18 and over 80 percent of patients completed the studies  
19 in both groups. The distribution of primary surgical  
20 diagnoses, as you've seen in the sponsor's slide as  
21 well, were comparable between groups.

22 As far as device outcome use is concerned,

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1 the range of volumes used was somewhat broad, but the  
2 mean and medians were comparable. There is, however,  
3 no standard of maximum primary sealant values proposed  
4 to date. The operative time averages, as presented in  
5 the PMA, were 160 minutes for FocalSeal randomized  
6 patients and 163 minutes for control, comparable with  
7 a mean time of 13 minutes for application of the  
8 device.

9 There were four out of 125 patients, or  
10 three percent of patients, who were considered  
11 failures through the technical inability to apply the  
12 device.

13 From the standpoint of effectiveness in  
14 the cohort, not including the eight pilot patients,  
15 looking at the patient, the sponsor's primary  
16 endpoint, which is here, and secondary endpoints, you  
17 can see that there is a clinically and statistically  
18 significant difference for both endpoints. However,  
19 as the sponsor has also presented, there was a  
20 comparability of recurrence of air leaks in both  
21 groups, which is not statistically significant and  
22 it's not clinically significant. These occurred

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1 within 24 hours in each group, mostly. Which then  
2 says that the non-recurrence of air leaks for a number  
3 of patients who became air leak free and stayed air  
4 leak free throughout hospital discharge was  
5 comparable.

6 When these patients are added to the  
7 effectiveness cohort, just to look at the whole  
8 patient cohort, there is not much of a difference seen  
9 by adding the eight pilot patients with either the  
10 primary implant or the secondary implant, recurrence  
11 or non-recurrence.

12 If, however, you look at just the pilot  
13 patients, you see that the primary and secondary  
14 endpoints together are somewhat similar, although the  
15 number of patients, the incidence of patients, who  
16 remained air leak free through hospital discharge is  
17 lower for the pilot patients than it is for the other  
18 patients who were in the efficacy cohort alone. And  
19 their recurrence rate is higher than the recurrence  
20 rate of the efficacy cohort and than the recurrence  
21 rate of the control.

22 The reasons for this are not clear. It's

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1 not clear if this just sort of an effect of small  
2 numbers, chance, of learning that went on between the  
3 first two patients and other patients, and also the  
4 impact of this on the overall. It's not known.

5 From the standpoint of days to events. As  
6 the sponsor has presented, there were differences in  
7 days to no air leak. If you look at the difference  
8 between medians and I think the medians to be  
9 considered here, as there was a difference the medians  
10 for the groups. There is a difference of about .7  
11 days between the mean median for the FocalSeal control  
12 groups for days to no air leak. However, there is no  
13 difference in the medians for days to drainage less  
14 than 125 ccs per day, which is a common indication  
15 that is used for removal of chest inserters. No  
16 difference for the median of days to chest tube  
17 removal or hospital discharge.

18 So the reasons for this are not clear.  
19 There is no learning curve or clear analysis that has  
20 been presented to address potential confounding  
21 factors that may have affected air leak occurrence or  
22 the time to events.

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1 From the standpoint of safety. There are  
2 adverse effects that can be expected in patients who  
3 undergo thoracic surgery, as we know. However,  
4 infection is the clear surgical complication or  
5 adverse event that is most studied and has been  
6 presented in many surgical texts as well as in CDC  
7 guidelines. Typically wounds are classified as  
8 "clean," "clean-contaminated," "contaminated," or  
9 "dirty." And wounds such as elective lobectomy,  
10 wedge, and segmental resection via open thoracotomy  
11 are usually considered to be clean-contaminated cases.

12 In classic texts, the incidence of wound  
13 infections for clean-contaminated cases are usually  
14 three to four percent. Also in a recent CDC guideline  
15 review, Surgical Infections, the incidence of surgical  
16 site infection in thoracic surgery is expected to be  
17 in the range of 0.5 to 3.9 percent. The control group  
18 incidence of infections fell within these ranges,  
19 however the wound infections and empyema rates for the  
20 FocalSeal treated groups did not. The reasons for  
21 this are not clear. Whether this is in effect the  
22 numbers, chance, or device is not in evidence.

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1           The incidence of cancer progression were  
2           10.4 percent in the FocalSeal treated group and 7.3  
3           percent in control. We're looking at the incidence  
4           per stage between arms, the incidence of cancer  
5           progression from that view was comparable. The  
6           incidence of death also had a comparable distribution,  
7           cause of death between arms.

8           In summary, FocalSeal cohort compared to  
9           control had an increased proportion of incidence,  
10          percent incidence, of patients with no air leak at  
11          skin closure and no air leak from time of skin closure  
12          to discharge. And there was a reduced time to no air  
13          leak from the standpoint of the median time, reduction  
14          being about .7 days.

15          However, there was no difference in the  
16          percent incidence of patients with air leak occurrence  
17          and there was no difference, therefore, with the  
18          incidence of patients with no air leak occurrence.  
19          There were a number of patients who became closed and  
20          stayed closed.

21          There were no difference in the median  
22          time to chest tube removal and time to hospital

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1 discharge. The learning curve and co-variate,  
2 confounding effects are not know.

3 From the standpoint of safety, the  
4 FocalSeal group compared to control had a greater  
5 incidence of wound infection and empyema. There were  
6 no differences in incidence of cancer progression per  
7 stage during six month follow-up in these small  
8 cohorts. The effect of FocalSeal-L, an in situ  
9 polymerized resorbable device on the incidence and  
10 progression of cancer in humans is not known beyond  
11 six months at this time.

12 Thank you.

13 CHAIRMAN WHALEN: Thank you. That, then,  
14 concludes FDA's presentation. Going around the panel,  
15 then, and asking if there are any questions of FDA,  
16 starting with Ms. Maher.

17 MS. MAHER: No questions.

18 CHAIRMAN WHALEN: Ms. Brinkman.

19 MS. BRINKMAN: No.

20 CHAIRMAN WHALEN: Dr. Chang.

21 DR. CHANG: No questions.

22 CHAIRMAN WHALEN: Dr. Cerfolio.

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1 DR. CERFOLIO: No questions.

2 CHAIRMAN WHALEN: Dr. Ferguson.

3 DR. FERGUSON: No questions.

4 CHAIRMAN WHALEN: Dr. Kurt.

5 DR. KURT: No.

6 CHAIRMAN WHALEN: Dr. Boykin.

7 DR. BOYKIN: No questions.

8 CHAIRMAN WHALEN: Dr. Galandiuk.

9 DR. GALANDIUK: No questions.

10 CHAIRMAN WHALEN: Dr. DeMets.

11 DR. DEMETS: No.

12 CHAIRMAN WHALEN: Very well, prior to the  
13 reading of the actual questions, we'll proceed as our  
14 step to the discussion by the panel. But I think, in  
15 view of our actually being a little bit ahead of time,  
16 we'll take a 10 minute break at this juncture and  
17 reconvene before that step.

18 (Recess.)

19 CHAIRMAN WHALEN: Thank you. We'll  
20 reconvene and we're going to panel discussion. And,  
21 as is the normal case, we'll begin with lead  
22 reviewers. The two reviewers that we have for lead

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1 this morning are Dr. Ferguson on the clinical study  
2 and Dr. Kurt on considerations of toxicology. We  
3 begin with Dr. Ferguson.

4 DR. FERGUSON: Well, thank you. I don't  
5 think I have to provide any background as to the  
6 potential utility or clinical importance of a  
7 substance or device that would seal pleural leaks  
8 after thoracic surgery. What I'd like to do is talk  
9 briefly about strengths and weaknesses of the  
10 information as presented and then discuss some of the  
11 concerns I have regarding the information.

12 In terms of the strengths. First, the  
13 centers that were chosen to participate in the  
14 clinical study are all recognized for their clinical  
15 excellence. I believe the study was performed well,  
16 as designed, in that there was good distribution of  
17 patients among the centers. The findings among the  
18 centers were all similar and there was relatively  
19 complete data collection at each center.

20 The product itself being non-biological,  
21 that fact is very favorably viewed by clinicians.  
22 And, at least in my opinion and, obviously, more

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1 experts' opinion is forthcoming, the toxicity of the  
2 substance is generally low.

3 The initial sealing efficacy was good,  
4 which is one of the secondary endpoints of the pivotal  
5 clinical trial. Of those in the treatment group with  
6 air leaks prior to receiving treatment, the success  
7 rate was 82 percent, which was 78 out of 95 patients.  
8 There was a significant decrease in the time to air  
9 leak cessation provided by the product, 31 hours  
10 versus 52 hours, which may have some clinical  
11 significance.

12 The results of the primary implant that  
13 was chosen for the study suggests that there was some  
14 clinical benefit offered by the product. Of the  
15 valuable patients, that is, omitting the pilot  
16 patients, 39 percent of the treatment group and 11  
17 percent of the control group had no air leak from time  
18 zero, that is, at the time of closure of the chest  
19 wound until the time of discharge. This difference  
20 also may have clinical significance.

21 Now we'll look at the weaknesses of the  
22 study. The first is a question as to whether the

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1 primary endpoint was chosen correctly. There was a  
2 relatively small number of patients who were leak free  
3 at the end of the operation prior to randomization:  
4 24 percent in the treatment group and 29 percent in  
5 the control group. And this makes it difficult to  
6 study the natural history of the air leak in these  
7 patients and I suggest that a more meaningful primary  
8 endpoint might have been the proportion of patients  
9 who were air-leak free at time zero that remained air-  
10 leak free until discharge. And I'll touch back on  
11 this a little bit further when discussing my concerns.

12 The second set of weakness is that there  
13 is a potential bias in assessing some of the stated  
14 endpoints and summarized endpoints that were not part  
15 of the formal pivotal clinical trial and that they  
16 were somewhat soft. Specifically, there's no stated  
17 definition of air leak, although the sponsors feel  
18 that this is probably obvious, air leak being one of  
19 the secondary endpoints. In fact, skilled observers  
20 can sometimes differ on whether a leak is present  
21 based on the time of day of observation and on the  
22 effort made by the patients in coughing or producing

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1 or generating intrathoracic pressure to generate  
2 intrabronchial pressure and disclose a subtle air  
3 leak.

4 There is also a potential bias in the time  
5 to chest tube removal. This is sometimes based on the  
6 amount of fluid drainage and the duration of the  
7 absence of air leak, as well as other non-specific  
8 factors. Unfortunately, there's no algorithm stated  
9 in the pivotal trial for chest tube removal and, thus,  
10 this decision is open to bias.

11 Similarly, for time to discharge, this is  
12 highly dependent on the time that it took chest tube  
13 removal, but it is also dependent on a host of non-  
14 specific factors. And as the sponsor has so stated,  
15 it is quite difficult to devise an algorithm for  
16 discharge, nevertheless, this decision is thus open to  
17 bias.

18 Also, I believe that, in a practical  
19 sense, the investigator, the residents, the medical  
20 students, the clinical research nurses all who are  
21 involved in patient care and evaluation would have  
22 likely been aware of the group assignment and, thus,

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1 there was a potential for bias in decisionmaking based  
2 on this.

3 The protocol didn't incorporate a method  
4 of assessing the severity of air leak. There are a  
5 couple of different techniques for doing this in the  
6 post-operative period, not dissimilar to what was used  
7 intra-operatively to grade severity of air leak. And  
8 this might have provided some information as to the  
9 utility of the substance.

10 Protocol didn't incorporate an algorithm  
11 for the use of suction on the pleural drainage devices  
12 and this also can impact on the duration of air leak.  
13 Within the PMA, the sponsor provided Kaplan-Meier  
14 curves for cessation of air leak from the time of  
15 chest tube removal, but did not provide long-range  
16 test evaluation of these curves, which to my eye at  
17 least looked quite similar.

18 And now I would like to summarize my  
19 concerns and I think the toxicology discussion will  
20 focus on my first concern as well. A chronic study  
21 suggests that 35 percent of this material is still  
22 present in the large animal studies at six months.

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1 The propensity for adhesion formation at these  
2 locations is not clear and no comment could be made on  
3 that based on the clinical studies because of the low  
4 number of reentry patients.

5 The chronic inflammation that persists at  
6 these sites long term, the effects are uncertain in  
7 regards to clinically important treatment for lung  
8 cancer patients and follow-up of lung cancer patients,  
9 particularly with regards to radiation therapy, which  
10 is often given after resection and to screening for  
11 recurrence of disease using PET scanning which uptakes  
12 in areas of high metabolic activity.

13 There is a trend towards higher incidence  
14 of wound infection, as has been discussed. And some  
15 of the infections in the treatment group were delayed  
16 beyond the period when they would normally have been  
17 anticipated to occur. And whether this relates to the  
18 chronicity of the implanted material is unclear.

19 Despite the advantage evident in the time  
20 air leak cessation, there is no discernible  
21 advantage in the time of chest tube removal, the  
22 median time being four days in each group, or the time

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1 to discharge, the median being six days in each group.

2           Parenthetically, it's unclear to me why  
3 there was a two-day difference in both groups between  
4 the median time to chest tube removal and the median  
5 time to discharge in the clinical setting. We try to  
6 get this number to approach zero.

7           Now if a different primary endpoint is  
8 chosen, then I suggest that a more appropriate  
9 endpoint is the proportion of patients who are air  
10 leak free at time zero that remain air leak free until  
11 the time of discharge. Then we see no difference  
12 between treatment and control groups. And this would  
13 include the valuable patients as well as the pilot  
14 patients.

15           In the treatment group, there is 108  
16 patients who are air leak free at time zero and there  
17 was a persistent lack of air leak in 46 valuable  
18 patients and two pilot patients for a total remaining  
19 air leak free of 44 percent. And in the control  
20 group, it was 38 percent, which does not approach  
21 statistical significance." And thus using this  
22 endpoint you can determine there's no clinical

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1 advantage to the product.

2 DR. KURT: I appreciate being invited to  
3 speak before a plastic surgery committee and I would  
4 like to say, as a medical toxicologist in my medical  
5 school training, I spent a long elective portion in  
6 plastic surgery with Dr. Frank Masters at the  
7 University of Kansas and where the Padgett Dermatone  
8 I was properly ensconced and revered.

9 Next, I would like to point out to you, as  
10 a medical toxicologist, I have served as an FDA  
11 medical officer in the past and I have served on the  
12 Clinical Chemistry, Clinical Toxicology Committee, but  
13 I've also had some experience in dealing with  
14 plastics, medically with dental laboratories, with  
15 occupational exposures in a variety of circumstances,  
16 and written about this in the literature.

17 And my job, I think, is to describe to you  
18 the worst possible case scenario. Because when you  
19 think of a toxicologist, you don't think of a  
20 pharmacologist, you think of something going wrong  
21 with a toxicologist. So what I would like to do is  
22 describe to you difficult cases or the worst-case

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1 scenario. But, nonetheless, I would like to reassure  
2 you that none of the substances that are listed in  
3 this product are in the National Toxicology Program  
4 list of carcinogens, which is the interagency agency  
5 that reviews potential carcinogens from the standpoint  
6 of the FDA, USDA, EPA, et cetera.

7 So you'll see that there are three lists  
8 that I've put together. First the list that you can  
9 see of the raw materials that are used in the sealant,  
10 the formulation materials and the manufacturing  
11 materials. And I've starred some of these, such as  
12 the hydraquinone, as being a possible sensitizer. The  
13 peroxide as being a potential irritant.

14 But I would like to point out to you that  
15 the medical literature that would substantiate this in  
16 occupational exposures has been at concentrations that  
17 are considerably in excess of those that are in the  
18 product.

19 Let me see the next transparency, please.

20 As toxicologic considerations always deal  
21 with a dose, and here we have a single packages. I  
22 think we need to consider whether or not there will be

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1 some possible uses of this product where there would  
2 be more than a single packages. And there are also  
3 considerations about components that might be given  
4 off that are not necessarily the product itself that  
5 are off-gassed as molecule components of some of the  
6 products.

7 In the sensitization consideration, I  
8 would like to point out that there are, in general,  
9 four categories in plastics that are considered  
10 sensitizers: the aldehydes such as formaldehyde and  
11 butylaldehyde; the amines; anhydrides that you see in  
12 epoxies; the isocyanates that you see in urethanes.  
13 And in this instance there are a couple of amines such  
14 as triethanolamine and the trimethylene that's used in  
15 the manufacturing process that are potential  
16 sensitizers, but they're in such low concentrations  
17 that they wouldn't necessarily be considered  
18 sensitizing in this situation.

19 I also noticed that the tert-Butyl  
20 hydroperoxide was being used. It is a kind of a  
21 catalyst that is used in some plastic operations, a  
22 catalyst such as methylethylperoxide are quite

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1 strong irritants. And I think that the concentration  
2 that is reported here, while it could be potentially  
3 a questionable irritant, has not been confirmed in any  
4 scientific literature as being an actual irritant.

5 My considerations in exposure here do not  
6 just deal with the patient but also the surgeon and  
7 the surgical staff involved and special patients that  
8 are involved such as cancer patients for which this is  
9 in part directed and the device manufacturing  
10 employees.

11 Can we have the third transparency,  
12 please?

13 So on the acute health questions, I would  
14 say that the toxicologic considerations that you can  
15 see on the top portion of that. I'm sorry that it's  
16 somewhat faded. There are no considered acute  
17 toxicologic considerations based upon the  
18 concentrations that are in this product in my  
19 experience in reviewing this in the scientific  
20 literature. In sensitization, there are potential  
21 sensitizations involving triethanolamine,  
22 hydraquinone, et cetera to the patient, but the

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1 concentrations involved in the product are at such  
2 percentages that they wouldn't necessarily be expected  
3 to be sensitizers.

4 Then there are chronic health questions.  
5 Chronic health questions involves potential repeated  
6 use of this product. Things that are sensitizers with  
7 chronic or repeated use, a patient could be sensitized  
8 with repeated use. We don't necessarily have any  
9 information about this with this product. There's the  
10 potential of retention of the sealant within a body  
11 cavity for a long period of time, such as more than a  
12 year and we don't have potential information about  
13 this.

14 And we have the question of potential  
15 tumor promotion in one of the FDA questions in  
16 existing potential cancer patients and whether or not  
17 there is a tumor promoter involved. But, again, that  
18 would be negated by the National Toxicology Program  
19 studies of the individual ingredients, but I would  
20 like to have the vital statistician, Dr. DeMets,  
21 comment on the numbers involved and the question of  
22 cancer promotion.

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1 The next transparency, please.

2 Questions that I have that came up from  
3 the review of this is that there could be possibly  
4 unapproved use of an approved product where innovation  
5 will result in additional uses, where multiple  
6 packages would result in additional excessive doses,  
7 or mixing with other components such as with burn  
8 ointments to be used on the surface such as the ear  
9 which would be otherwise hard to address where there  
10 would be a coating of such product.

11 This could also be hazardous to the  
12 surgical staff. The question would come up whether or  
13 not, if the surgeon touches the ends of one of the  
14 wands with your latex rubber gloves, whether or not  
15 your gloves would stick together and possibly  
16 interfere with the integrity of the glove. Perhaps  
17 there might be a factor dealing with infection under  
18 these circumstances. Well, so what would occur if  
19 this product, used in a sealed fashion, but hasn't  
20 necessarily hardened, with the integrity of a person's  
21 glove if the glove comes in contact with the wand?

22 If a kind of radiopaque substance is

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1 added, not necessarily barium sulfate, which would not  
2 be indicated in the body cavity, but something such as  
3 ringabrethin, perhaps you can see radiographically how  
4 long this product is still in place, a year or more  
5 after use. However, that would also raise the  
6 question such as a radiographic product interfering  
7 with radiographic studies or imaging studies such as  
8 a PET scan and whether or not there could be some  
9 residual tumor in an area.

10 The next question that I had has already  
11 been answered concerning the heating of the product.  
12 If you heat something that contains a vinyl or acrylic  
13 component to where it gets close to the point of  
14 combustion sometimes organic cyanides can be given off  
15 and the heating in this situation wasn't sufficient  
16 for that to necessarily occur.

17 The next transparency, please.

18 This transparency raises two questions and  
19 recommendations. The question exists despite the fact  
20 that none of these are listed in the National  
21 Toxicology Program list of <sup>ff</sup> carcinogens of whether or  
22 not tumor promotion should exist in this situation,

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1 and I think that needs to be clear biostatistically  
2 and with a possible future study involving animals.

3 The next deals with postmarket reporting,  
4 because this is an entirely relatively new product in  
5 this use, and only adverse reactions of a serious or  
6 life threatening nature are required to be reported  
7 back to the FDA. I would suggest requiring that all  
8 reactions or complications, particularly those  
9 involved with infection or empyema be reported back,  
10 particularly within the first two years, to see  
11 whether or not there are problems involving these  
12 complications that would not necessarily be life  
13 threatening.

14 Thank you for hearing me, and this  
15 summarizes what I have to say.

16 CHAIRMAN WHALEN: Thank you, Dr. Kurt, and  
17 Dr. Ferguson. Well, that completes the two formal  
18 panel reviews. It's appropriate at this juncture for  
19 any panel member who wishes to make comment or indeed  
20 ask questions of either FDA or the sponsor to do so.

21 I apologize to Dr. McCauley for leaving  
22 him out the last time we went around the horn. That's

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1 one of the hazards of being in that end seat, but  
2 we'll begin with you, Dr. McCauley.

3 DR. McCAULEY: I suppose I shouldn't have  
4 brought up that small amount of information.

5 I had a question related to some of the  
6 rat studies and a question related to chronic  
7 inflammation. Is there any data to suggest increased  
8 differences in cytokines in these rat studies to  
9 suggest that the chronic inflammation has a systemic  
10 effect such as cytokines like interleukin 1-alpha or  
11 IL-6 have been known to be elevated in chronic  
12 inflammatory states? Is there any data to suggest  
13 that you have any of these cytokines elevated in these  
14 animal studies?

15 CHAIRMAN WHALEN: You're addressing the  
16 question to the sponsor?

17 DR. McCAULEY: The sponsor.

18 MS. MOONEY: Dr. McCauley, we don't have  
19 specific data to those entities, but I would mention  
20 that in all of the subchronic and chronic rat implant  
21 studies that were performed, there were general  
22 systemic evaluations conducted concurrently with the

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