U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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MEETING

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THURSDAY,
JUNE 12, 2008

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The Advisory Committee met in Salons A, B, and C at the Hilton Washington DC/North, 620 Perry Parkway, Gaithersburg, Maryland, at 8:00 a.m., David J. Birnbach, M.D., Panel Chairperson, presiding.

Reporter: Eric Mollen

PANEL MEMBERS PRESENT:

DAVID J. BIRNBACH, M.D., Panel Chairperson
CLAUDE D. BRUNSON, M.D., Voting Member
HUGH A. CASSIERE, M.D., FCCP, Voting Member
KAREN B. DOMINO, M.D., M.P.H. Voting Member
VALLUVAN JEEVANANDAM, M.D.,
Temporary Voting Member
JAMES W. LILLARD, JR., Ph.D., M.B.A.
Temporary Voting Member
JOSEPH LOCICERO, III, M.D.
Temporary Voting Member
ROBERT G. LOEB, M.D., Voting Member
SHARON-LISE NORMAND, Ph.D.,
Temporary Voting Member
CAROLYN PETERSEN, M.S.,
Consumer Representative
ANDREW L. RIES, M.D., M.P.H., Temporary
Voting Member
DAVID SPINDELL, M.D., Industry
Representative
JAMES STOLLER, M.D., M.S. (O.D.A.),
Temporary Voting Member
L.D. TIMMIE TOPOLESKI, Ph.D., Temporary
Voting Member
BENSON R. WILCOX, M.D., Temporary Voting
Member
THOMAS E. WISWELL, M.D., Voting Member

FDA PARTICIPANTS:

NEEL PATEL, M.Eng., Panel Executive
Secretary
CHARLES DURFOR, Ph.D., Plastic and
Reconstructive Surgery Devices Branch,
Office of Device Evaluation
ROXOLANA HORBOWYJ, MSChE, M.D., FACS,
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CHANG S. LAO, Ph.D., Division of Bio-Statistics, Office of Surveillance and Biostatistics
DANICA MARINAC-DABIC, M.D., Ph.D., Chief, Epidemiology Branch, Division of Post-Market Surveillance, Office of Surveillance and Biometrics
MARK MELKERSON, Director, Division of General, Restorative and Neurological Devices

SPONSOR PARTICIPANTS:

JERRY MEZGER, President and CEO, NeoMend
ROBERT CERFOLIO, M.D., University of Alabama Birmingham
DANIEL MILLER, M.D., Chief, General Thoracic Surgery, Emory University
DAVID OST, M.D., Associate Professor of Medicine, Pulmonary Disease, New York University
PATRICK J. PARKS, M.D., Ph.D., Advanced Scientist, 3M Medical Division
GARRETT WALSH, M.D., Professor of Surgery, Department of Thoracic and Cardio-Vascular Surgery, M.D., Anderson

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

8:00 a.m.

CHAIR BIRNBACH: Good morning. I would like to call this meeting of the Anesthesiology and Respiratory Therapy Devices Panel to order. I am Dr. David Birnbach, the Chairperson of this panel.

I am a Professor of anesthesiology, obstetrics and gynecology and public health and Director of the Center for Patient Safety at the University of Miami, Miller School of Medicine.

If you haven't already done so, please sign the attendance sheets that are on the tables by the doors. If you wish to address this panel during one of the open sessions, please provide your name to Ms. Anne Marie Williams at the registration table.

If you are presenting in any of the open public sessions today and have not previously provided an electronic copy of your presentation to the FDA, please arrange to do

so with Ms. Williams.

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

Mr. Patel, the Executive Secretary for the Anesthesiology and Respiratory Devices Panel, will make some introductory remarks. Mr. Patel.

MR. PATEL: Before I begin, I'd like to note that Dr. Gerald Schulman is not present today, due to attend an unexpected emergency. He was originally listed on the participant -- as a participant in the meeting roster posted on the Center for Devices and Radiological Health Advisory Committee's website. I will now read the conflict of interest statement, followed by the appointment of temporary voting members statement.

The Food and Drug Administration has convened today's meeting of the Anesthesiology and Respiratory Therapy Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the Industry Representative, all members and consultants of the panel are Special Government Employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

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

FDA has determined that members and consultants of this panel are in compliance

with Federal ethics and conflict of interest laws. Under 18 US Code Section 208, Congress has authorized FDA to grant waivers to Special Government Employees who have potential financial conflicts, when it's determined that the Agency's need for particular individual services out-weighs his or her potential financial conflict of interest.

Under Section 712 of the Food and Drug Cosmetic Act, Congress has authorized FDA to grant waivers for Special Government Employees and regular Government employees with potential financial conflicts when necessary, to afford the Committee essential expertise.

Related to discussions of today's meeting, members and consultants of this panel who are Special Government Employees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and for purposes of

18 US Code Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADA's, teaching, speaking, writing, patents and royalties and primary employment.

Today's agenda involves the discussion of a Premarket Approval application for the ProGEL Surgical Sealant sponsored by NeoMend Incorporated.

The device is indicated to reinforce soft tissue were weakness exists, as an adjunct to the standard procedure, such as sutures or staples for closing intra-operative air leaks. This is a particular matters meeting during which specific matters related to the PMA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 US Code Section 208 and 712

of the Food, Drug and Cosmetic Act.

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

Dr. David Spindell is serving as the industry representative acting on behalf of all related industry and is employed by Abbott Laboratories.

We would like to remind members and consultants that if discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the panel of any financial relationships they may have with the firms at issue.

Pursuant to authority granted under

Medical Device Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27, 1990 and as amended August 18, 2006, I appoint the following individuals as voting members of the Anesthesiology and Respiratory Therapy Devices Panel for the duration of the fiscal year ending on June 12, 2008:

Dr. Joseph LoCicero, Dr. Benson Wilcox, Dr. Valluvan Jeevanandam, Dr. Andrew Ries, Dr. Tim Topoleski and Dr. Sharon-Lise Normand.

For the record, these individuals are Special Government Employees and are consultants to this panel, or other panels, under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at the meeting. This was signed by Dr. Daniel Schultz, Director for the Center of Devices of Radiological Health and dated May 8, 2008.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices of Radiological Health and dated October 27, 1990 and amended August 18, 2006, I appoint Dr. James Lillard and Dr. James Stoller as temporary voting members on the Anesthesiology and Respiratory Therapy Devices Panel for the duration of the meeting on June 12, 2008.

For the record, Dr. Lillard is a member of the Transmissible Spongiform Encephalopathies Advisory Committee and the Center for Biologics Evaluation and Research. Dr. Stoller is a consultant to the Pulmonary-Allergy Drugs Advisory Committee and the Center for Drug Evaluation and Research.

These individuals are Special Government Employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. This was signed by Dr. Randall Lutter, Deputy Commissioner for Policy and

dated May 27, 2008.

Before I turn the meeting back over to Dr. Birnbach, I'd like to make a few general announcements.

Transcripts of today's meeting will be developed from Neal Gross & Company and the phone number is 202-234-4433. Information on purchasing videos of today's meeting can be found on the table outside of the meeting room. Presenters to the panel who have not already done so, should provide FDA with an electronic copy of their remarks.

Members of the public and the press are not permitted in the panel area at any time during the meeting and including breaks. The press contact for today's meeting is Peper Long.

I request that reporters wait to speak to FDA officials until after the panel meeting, and finally, please silence your cell phones. Thank you very much. Dr. Birnbach.

CHAIR BIRNBACH: Good morning,

everyone. At this meeting, the panel will be making recommendations to the Food and Drug Administration on the Premarket Approval application or PMA P010047 for the ProGEL Surgical Sealant from NeoMend Incorporated.

Before we begin, I'd like to ask our panel members and the FDA staff seated at the table to introduce themselves to you. Please state your name, your area of expertise, your position and your affiliation. We'll start at the end of the table with Dr. Spindell.

DR. SPINDELL: David Spindell. I'm the industry representative, the Divisional Vice President of Medical Affairs for Abbott Laboratories.

MS. PETERSEN: I'm Carolyn Petersen. I'm the Consumer Representative. I am a managing editor with Mayo Clinic Internet Services and I have a Master's degree in sports medicine and exercise physiology.

DR. RIES: I'm Andy Ries. I'm a

pulmonary critical care physician. I'm a Associate Dean and professor of medicine and family and preventive medicine at the University of California, San Diego.

DR. JEEVANANDAM: My name Valluvan Jeevanandam. I'm the Chief of Cardiac and Thoracic Surgery at the University of Chicago.

DR. WILCOX: Ben Wilcox, I'm former Chief of Thoracic and Cardiovascular Surgery at the University of North Carolina.

DR. LOCICERO: Joseph LoCicero. I'm a thoracic surgeon, Chief of Thoracic Surgery at Maimonides Medical Center in Brooklyn.

DR. WISWELL: Tom Wiswell, I'm a neonatologist. I'm with University of Florida and I practice in Orlando.

DR. LOEB: Robert Butch Loeb, I'm an anesthesiologist, Associate Professor at University of Arizona.

DR. DOMINO: Karen Domino, I'm a Professor of Anesthesiology at University of Washington in Seattle.

DR. BRUNSON: Claude Brunson, Professor and Chairman of Anesthesiology, University of Mississippi Medical Center.

DR. CASSIERE: Hugh Cassiere, pulmonary critical care physician, Chief of Cardio-thoracic Critical Care and Director of the Cardio-thoracic Intensive Care Unit, North Shore University Hospital.

DR. STOLLER: I'm James Stoller. I'm a pulmonary critical care doctor, Professor of Medicine at the Cleveland Clinic and I'm the Head of Respiratory Therapy at the Cleveland Clinic.

DR. LILLARD: James Lillard, I'm an Associate Professor at the University of Louisville. My expertise is in innate and adaptive immune responses in mucosal tissue, including the lung.

DR. NORMAND: I'm Sharon-Lise Normand. I'm a Professor of Health Care Policy and Professor of Biostatistics in Harvard Medical School and in Harvard School

of Public Health.

DR. TOPOLESKI: Tim Topoleski, I'm a Professor of Mechanical Engineering at UMBC, the University of Maryland, Baltimore County. My area of expertise is bio-materials and bio-mechanics.

MR. MELKERSON: I'm Mark Melkerson. I'm the Division Director for the Division of General, Restorative and Neurological Devices and if you take the Chair's prerogative here, just a quick introduction.

This product is a respiratory product that has basically had review issues from two different divisions. I'm sitting at the table because we're in the process of consolidating the respiratory devices under one group. They'll be under the Division of Anesthesiology, if I'm getting it right, Dental, Anesthesiology and Respiratory Products, under Dr. Chiu Lin's division.

So, this is a transfer of power of the products from one group to the other, but

as you notice, the panel is made up of members from both our plastics and reconstructive surgery panel, as well as the anesthesiology panel, because the device crosses both groups.

CHAIR BIRNBACH: Thank you. Dr. Danica Marinac-Dabic will give us the post-market approval study update.

DR. MARINAC-DABIC: Good morning ladies and gentlemen, Dr. Birnbach, Mr. Melkerson, distinguished members of the panel. My name is Danica Marinac-Dabic and I'm the Chief of Epidemiology Branch at the Office of Surveillance and Biometrics here at CDRH and the Epidemiology Branch is the unit that is in charge of the review, monitoring and oversight of post-approval studies imposed by the PMA order, also known as a conditional approval.

The group has 20 epidemiologist's and they're mostly MD's with a PhD in epidemiology or Master's in Public Health and in the recent years, we have been increasingly involved in the pre-market review, in addition

to our review of the post-market progress of the studies.

I would like today to first give you a brief overview of the progress that has happened in the last couple of years, in terms of the post-market transformation in the area of post-approval studies and first, I would like to talk briefly about why we need post-approval studies, what are our post-approval studies program transformation goals and also, to talk to you about what are our early accomplishments in this area and to share with you, our vision for the future.

These are some of the reasons why the post-approval study is needed. Even after the initial establishment of the reasonable safety and effectiveness, there still might be some unanswered post-market questions that are not essential for the approval of the product, but certainly, are of interest for the FDA as a public health agency and also, beneficial for us to inform the public, the clinicians,

our patients, who are ultimately our main stake holders.

We certainly would like to gather essential post-market information and to see how the products are performing in the real world situations. We would like also to balance some of the pre-market burdens for our industry and try to answer some of those questions that are of interest in the post-market, again, keeping in mind that those are -- should not be essential questions for establishing reasonable safety and effectiveness.

Also, we would like to account for panel recommendations in -- when we think about the post-approval studies, because we value your input, your clinical and analytical input in the need for post-approval studies and certainly, we take that into serious consideration when we design post-approval studies.

This is what is our legal

authority, to impose the post-approval studies for continuing evaluation and reporting on the safety, effectiveness and reliability of the device for its intended use.

Again, objective of the post-approval studies are to evaluate device performance and potential device related problems in a broader population over an extended period of time, after pre-market establishment of reasonable device safety and effectiveness.

Again, post-approval studies should not be used to evaluate unresolved issues from the pre-market phase that are important to the initial establishment of device safety and effectiveness.

Just an illustration, truly, that the post-approval studies are an example of our desire to balance the least burdensome evidence to support Premarket Approval of products, but also to ensure continued product safety and effectiveness and reliability.

As I said, the new CDRH post-approval studies program encompasses design, tracking, oversight and review responsibilities for the studies mandated as a condition of approval. This program helps ensure that well designed post-approval studies are conducted effectively and efficiently and in the least burdensome manner.

During the past couple of years, the CDRH had made significant commitment of resources to enhance the post-approval studies program with the following major goals.

To enhance scientific rigor of post-approval studies, to establish and maintain accountability for the post-approval study commitments and also, to build information management system for the post-approval studies information and also, to build bridges between the post-market knowledge and the pre-market device evaluation, meaning that whatever knowledge we

help gain during the post-approval studies, we would like to certainly share with our pre-market colleagues, so they can implement those and keep those in mind as they review the products when they are coming for the approval, and finally, we would like to increase the transparency with the public.

These are the major areas in which we have made already significant accomplishments. Those are the areas of oversight, tracking and review of post-approval studies. We have issued the guidance document and also, created a web-page containing all post-approval studies that are currently ongoing since 2005.

We initiated post-market advisory panel updates and we started important initiatives to build public health partnerships.

So let's go down the list. As far as the oversight, many of you know that the oversight had been transferred to the Office

of Surveillance and Biometrics in 2005, with only first of a kind devices at that time, but then the full transfer occurred last year.

So now, the post-approval study oversight is in the Office of Surveillance and Biometrics and historically, as you know, had been in our pre-market offices, ODE and Office of In-Vitro Diagnostics.

So since 2005, we have developed and instituted the automated tracking system for post-approval study commitments. This is an important piece of accomplishment because this system is based on the post-approval study time lines incorporated into study protocols and agreed upon by the sponsor and the CDRH at the time of the approval.

This system certainly represents CDRH's determination to ensure that all post-market commitments are fully met.

Now, as far as the changes in the review process, I'd like to highlight for you here, what are the major differences between

the review, as it had been done historically and what are the new changes now that have been implemented.

Over the last two years, the epidemiology staff had been gradually integrated in the PMA review teams. To advance the least burdensome approach, the epidemiology staff has pro-actively committed significant resources to an early dialog with the sponsors, to help them design post-approval studies.

So during the pre-market phase, if there is a need for post-approval studies, the epidemiologists from CDRH work inter-actively with the manufacturers to, very early in the review process, outline expectations and hopefully, by the time of the product approval, we have the finalized post-approval study protocol.

If the device is going to panel, then you will see the epidemiologists will be a part of the FDA review team that will give

you a presentation and outline for you, the rationale for post-approval studies and possible questions.

So what happens when the product is approved? Upon the device approval, the epidemiologists assume the lead responsibility in the review of the interim reports. The PMA review team continues to be engaged and informs.

So even though now, the epidemiologist becomes the lead reviewer for the post-approval, we still keep informed, our pre-market colleagues and the rest of the Center's experts and this concept of epidemiology lead and the post-market team availability is envisioned to couple the epidemiologic expertise in observational study designs, with the product's specific technical expertise that is definitely in our pre-market office, Office of Device and Evaluation. This also ensures the feedback of post-market knowledge to the pre-market.

This is the link to our guidance document that was issued in 2006 and revised in 2007 and in the guidance document, we have outlined the expectations for post-approval studies and how to handle reports and how to create them in reports.

We clearly spelled out the reporting status definitions for altering reports and you can see the definitions on this slide. We also have study status definitions that would capture all possible scenarios, as the study is moving towards completion from the initiation post-approval.

Another accomplishment that I would like to share with you is our newly established web-page that went live last year, and all post-approval studies that had been initiated for 2005 are in that website.

We also share the study progress and the reporting status, and this is how the page looks like. When you go to the page, you can link it also to our PMA database. You can

find the applicant's name, device name, medical specialty, the date when PMA was approved and also, taken from the approval order, what the exact words for the post-market study commitments are in there.

We also are able to track multiple studies for each PMA and at the end, which is not seen clearly on the screen, is the progress of the study, both in terms of the reporting, compliance and the study progress.

We have received very good feedback from the stake holders on the content of this and would be really interested also, to hear what the panel thinks about that, to make improvements in the web-page.

This is something that might be of panel's interest. We have started this initiative of providing panel members with updates on the post-approval studies and we started this last year. We first presented the general post-approval update to the panel in November 2007 and since then, at every

panel meeting, we will provide those updates.

Those are very general updates on the progress of the program and just general status of the studies from the panel's clinical area of expertise.

However, there is another specific post-approval studies initiative that we started also last year, where we would like for the specific PMA and specific post-approval study to bring the manufacturer, invite them, give them the opportunity to help us present this to the panel and ask specific questions and these are so-called specific post-approval studies updates.

We feel that the success of the post-approval studies program cannot be done only if FDA talks to the FDA, meaning pre-market to the post-market. We feel very strongly that we need to build public health partnerships and partnerships with other entities, clinical community, professional associations, manufacturers, patients,

consumers and we started a series of the workshops last year.

One was in May 2007, when we already had discussed a number of issues. We continued dialog with stake holders and two conferences are planned for 2008 and 2009.

Finally, I would like to share with you what our vision is. We would like to make sure that only important post-market questions are addressed and again, the accent here is on important and post-market.

We don't want post-approval studies to be answering all, so-called `nice to know' type of questions. We want to make sure that they are within our regulatory authority, but also, we would like to make sure that they're post-market questions and not pre-market questions.

So keep that in mind as you all discuss the need for the post-approval study during your deliberations.

We would like also to make sure

that the studies are realistic, they are founded in good science and provide useful results that can be then placed into labeling for the product.

We would like to make sure that the studies are timely and accurate and that all our stake holders are kept apprised, including the patients, consumer, clinical community, manufacturers and others, and collaboration certainly to be stressed throughout, both here with pre-market and post-market interactions, but also in the outside world, and if we do this pro-actively, we hope that enforcement options are rarely going to be used.

Again, the work of my group is all about building bridges between analytical world and the clinical community and between the pre-market and post-market, we are very committed to this and we know that however, that this vision and goals represent higher expectations and those heightened expectations often bring heightened concerns about burdens,

workload, both internally and externally, perceived fairness and added value and it is up to us to discuss those with our stake holders openly, responsibly and cooperatively.

We have to continue to build these bridges within the pre-market and post-market, in order to be successful in this post-approval studies program. We understand the concerns, but we have to put them into larger context of asking and answering the right post-market questions.

We also welcome exchange of ideas on diverse methodologies that may be cost effective, innovative and productive and we value all analytical approaches and data sources that will give us high quality answers to the right post-market questions.

I thank you very much for your time and again, this is my contact information, if you would like to send me some of the ideas of how we can improve. Thank you very much.

CHAIR BIRNBACH: Thank you. We will

now proceed with the open public hearing portion of this meeting. Both the FDA and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency at this open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of any individual's presentation.

For this reason, FDA encourages you, the open public, hearing or industry speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses, in connection with your attendance at this meeting.

Likewise, FDA encourages you, at

the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Prior to the meeting, we received no formal requests to speak during today's open public hearing sessions. Would anyone like to address the panel at this time?

(No audible response.)

CHAIR BIRNBACH: Being that no one wants to address the panel, we will now proceed to the sponsor presentation for the ProGEL Surgical Sealant.

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

We will now begin with the sponsor

presentation.

DR. MEZGER: Thank you and good morning. First, I would like to thank each of the members of this panel for their time and attention to the review of our PMA for the ProGEL Surgical Sealant.

My name is Jerry Mezger and I'm President and CEO of NeoMend. I'll first give you a brief introduction of our company and why we are here today. Then Dr. Garrett Walsh, an investigator in our clinical study, will talk about the clinical need for products like the ProGEL Surgical Sealant.

Dr. Walsh will be followed by Dr. Pat Parks, who is an advanced scientist with 3M. 3M originally developed this product and Dr. Parks has been involved with it from the beginning.

Dr. Parks will describe the design of the ProGEL Surgical Sealant and the studies conducted prior to the start of this clinical study.

Dr. Dan Miller, an investigator in our clinical study, will then describe the design of this study and present the results, and Dr. Robert Cerfolio, who is not an investigator in this study, but who has done extensive research in this field, will summarize our presentation and provide his conclusions.

Joining us today and also available to answer any questions the panel may have, are the following individuals:

Dr. James Fann, who is a medical advisor to NeoMend and an Associate Professor at Stanford University, Dr. Judith Ulreich, who helped design and conduct the immunological testing of the sealant, from the University of Arizona, Dr. Patrick Murray, a nephrologist and a Professor of medicine at the University of Chicago and Dr. David Ost, a pulmonologist and Associate Professor of medicine at New York University.

NeoMend was founded in 1999. We're

a small company, dedicated to the development of hydrogel based and bioresorbable surgical sealants.

This sealant was an important strategic acquisition by NeoMend from 3M in 2007 and it utilizes the very same technology being developed independently by NeoMend since 1999.

We acquired the sealant last year, as we recognized the established need for better surgical sealants, especially a sealant for sealing lung air leaks, following lung resection surgery.

ProGEL was the first of a family of products we're developing to meet these needs. I'd now like to turn this over to Dr. Garrett Walsh, who will describe the clinical need for the panel.

DR. WALSH: Good morning. I'm Garrett Walsh. I'm from University of Texas, M.D. Anderson Cancer Center. I'm a thoracic and cardiovascular surgeon at that institute.

I was part of the original 3M study. I was the principal investigator from our institution and I've been asked to be a consultant for NeoMend, in preparation of this important day for them, and for all of us, quite frankly.

I spent most of my life dealing with lung cancer and malignancies. Lung cancer is the number one killer of men and women in this country and we will see an increase in lung cancer surgery over the coming years with earlier detection of these tumors.

Presently, about 100,000 surgical procedures for lung cancer are done. About 85 percent of the patients in our study underwent procedures for malignancies, both lung cancer and metastectomies for other lesions that involve the lung.

Typically, when we do pulmonary surgery, we either remove a segment, a wedge or a lobe or an extended resection that may

include one or more lobes on the right.

Generally, the only tools that we have available right now to us are staples and sutures to help control air leaks. Air leaks is a major problem. About 40 percent of thoracic surgical cases are complicated by air leaks.

Why is air leaks so important? The longer the patient has an air leak the longer they have to stay in the hospital, the longer a chest tube has to stay in place, the greater the risk that they will develop a complication related to the air leak, such as pneumonias, empyemas, trap-lung and this can lead to other multi-system organ problems.

Anything that we can do to reduce air leaks is going to have a significant benefit to our patients.

This is an example of a patient undergoing a pulmonary metastectomy. This is the portion of the lingula, of the left lung, that's elevated, and then typically, it is

wedge-resected with a stapling device and these are typical stapling devices that are used in both open thoracic procedures and minimally invasive procedures done through port access.

You can see that there is a row of staples that are placed on the lung. It gives a linear titanium staple, and I certainly apologize to the chest surgeons on the panel, who live this every day as well.

At the end of a procedure, we use a tried and true bicycle underwater test to see if in fact, our dissections of the fishers or the staple lines are intact, and as you can see, although the lights are a little high, you can see that there are bubbles at the bottom of the fissural dissection of this wedge resection. It is hard to believe that all of us have come from all across the country today, to talk about bubbles, but this is basically what we are going to talk about. A leak from the lung essentially contaminates

the pleural space. This is a serious problem.

Depending on the amount of tissue that is removed, your problem is accentuated. This is a simple segmental resection. This is an example of a patient of mine who six weeks ago had a procedure similar to the one that I have shown, a pulmonary metastectomy for metastatic colorectal carcinoma.

This was a re-do operation. He had multiple lesions that were removed. He developed a prong air leak that necessitated a hospital stay for about 10 to 14 days. He was eventually discharged, but readmitted last week with empyema. This is what happens at the time of surgery, where we have to decorticate that lung.

This patient presently is on a ventilator, on pressure supports requiring dialysis. This patient may die as a result of a prolonged air leak.

So as we said, it really depends on the amount of lung that's removed and what we

have to do and these are diagram representations of a segmented resection, wedge resection or lobectomy.

I'd like to spend a few moments -- and again, I apologize to the chest surgeons and intensivists in the panel, who this is intuitive to, but this is a confusing part, when we talk about residual spaces after pulmonary resection.

The terminology is confused because a radiologist may term something a pneumothorax, but that means a different thing to a thoracic surgeon.

If I use the example in this of a right upper lobectomy, if the patient has the remaining middle and lower lobes, it takes approximately four to six weeks for the lung to fully expand into the post-lobectomy space.

During this four to six weeks, there is contra-lateral shift of the mediastinal, the heart moves over, the diaphragm elevated and eventually, that space

is complete.

If you have a residual space after a pulmonary resection and there is no air leak, there is no problem. That space will fill with fluid. The contra-lateral mediastinal shift will occur and with time, the lung will expand and the space will be obliterated. If you have an air space with an air leak, that is the big problem and that is why we are here today.

Right now, we have very few things that we can do as surgeons to help this. We understand, those of us who do this every day, that the most important part of our dissection is often the meticulous dissection of the lung, either from the chest wall or the fissure, to minimize the air leaks that develop during the procedure.

Right now, our technical options include either further stapling of the lung, suturing of the lung or things such as pleural tents to reduce the residual space in the

post-lobectomy space, muscle flaps, or even such things as phrenic nerve crushes to elevate the diaphragm to eliminate the space.

These maneuvers are not always effective and often have consequences associated with those maneuvers, obviously bleeding and injury to the phrenic nerve.

Sealants, as an adjunct to these technical maneuvers, are extremely important. In fact, there are a few sealants on the market right now, and our thoracic surgeons, in our desperation, use these sealants off label to control air leaks because we really have no other product available in the U.S. to help us.

So what do we need? We desperately need, as thoracic surgeons, a sealant that can help keep our patients air-free after pulmonary resection. We need a sealant that is easy to apply, easy to use and mostly importantly for health care resources, cost effective. I'll turn it over to Patrick.

DR. PARKS: Thank you for this opportunity to go over our design of pre-clinical studies and in addition to the information that you received, I will add that I have no financial interest in NeoMend.

The ProGEL Surgical Sealant first began work at 3M in the mid 1990's. The design of the material was based upon using two well known materials, one of them polyethylene glycol, which has been used in many other medical products, and the other was the use of human serum albumin. It has a long history of being used safely, has a long clinical history of use and in addition to that, the biochemistry was acceptable for our design.

The chemistry is summarized here in this single line at the bottom of the slide. Polyethylene glycol was modified with a reactive group. The N-hydroxysuccinimide was given off. What resulted was a cross-link albumin. It was cross-linked using succinate.

The succinate in turn, was connected to the polyethylene glycol.

When used, the ProGEL was put together in two separate cartridges. The concept is that this material then would mix in vivo and polymerize in vivo. This is what the finished product would look like, immediately prior to application.

The sealant, as we designed it, was specifically designed to be used as an adjunct to standard closure for sealing air leaks. We were guided by performance requirements and input from thoracic surgeons.

At the time of our design, we were interested in finding a material that was more useful than fibrin glues, which were being used at that time, and from our input from thoracic surgeons, developed the guidelines for use given here.

First, we were told that we needed a sealing strength that must withstand three times the pressure observed in a routine

clinical environment. In a numerical way, we needed a number greater than 100 millimeters of mercury as a burst strength.

We also knew that we had to have material that remained compliant during lung expansion and also remained compliant during contraction.

Our gel time target as we received this information was to make the material gel within eight to 40 seconds. We felt that this was long enough to seep into puncture sites. It was short enough to stay on the wound site without running off, and we also aimed to achieve acceptable gel strength within two minutes.

Our goal also was to have the material present during the time of natural healing in the body and have the residence time be less than 30 days. Our pre-clinical studies then focused on device performance by compatibility and the results in animal studies.

As given in our design verification, we see that the burst strength met our requirements of being greater than 100 millimeters of mercury. Our test results indicated it was greater than that. The gel time also was satisfactory, falling within our range of eight to 40 seconds.

In our studies on the mechanism of degradation, the chemistry that I showed you using a succinate, we found that the results were hydrolysis. We saw no evidence in vivo of cellular or enzymatic break down.

The degradation products, as we could track them, were made of native human serum albumin in its natural biologic state. We also gave off the modified polyethylene glycol, a 3,500 molecular weight material. It was rapidly cleared and primarily excreted through the urine.

As far as the residence time was concerned, we studied both in vitro and in vivo residence time. The in vitro testing

that we did was hydrolysis and buffer. We saw that the disks of sealant material were in tact after seven days. By 14 days, they had undergone complete dissolution.

Using histology from in vivo studies in pig lungs, we observed that the sealant was present in our efficacy study at seven days. In separate studies, we found that the sealant was completely absorbed by 14 days.

The biocompatibility testing was done in accordance with ISO 10993. In addition to that, because the material polymerized in vivo and degraded in vivo, we also did pharmacokinetic studies.

The studies are summarized in the next few tables. In the interest of time, the study type is given in the left column. The testing is greatly abbreviated and given in the central column and the results are given on the right.

Of the studies given here we see

that irritation had no irritation in the extracts. We found that in situ, the material was moderately irritating in one study and mildly irritating in ocular studies.

In all other studies, cytotoxicity, pyrogenicity, hemolysis and acute systemic toxicity, we found no evidence of abnormal results.

Genotoxicity, we found again, no evidence of abnormal results and in the case of sub-chronic toxicity, we had a single isolated series of abnormal results. We had in female rats, using a 50 time dose that would be used in humans, found hemorrhage in the intestinal mucosa at day eight.

When ever we extended this to day 28, these findings were gone and under the assumption that the problems that we saw were the result of the gel characteristics, the ability to take up fluid, we repeated the experiments by instilling saline into the same operative site and removed the problem.

In sensitization, as a consequence of using human serum albumin in guinea pigs, we demonstrated both type 1 and type 4 immune type, hypersensitivity reactions due to cross-species differences.

We attempted to create guinea pig albumin in order to avoid this problem, but we could not get the endo-toxin levels down to the point where they were satisfactory.

So as a consequence of that, we instead looked at human repeat patch testing, using human subjects, human serum albumin and found no evidence of sensitization.

As far as the in vivo pharmacokinetics were concerned, we found that by day 14, approximately all the material was gone, 91 percent of it had been recovered, about half of all radio-labeled cross-linker was recovered in the urine within the first day.

Part of our design considerations were to use a high molecular weight

polyethylene glycol. We were familiar from the experimental literature that low molecular weight polyethylene glycol in the range of approximately 300 to 350 molecular weight can be nephrotoxic.

This nephrotoxicity results in proximal tubular damage, swelling of the proximal tubulars and acute tubular necrosis. So we had knowledge then that we could look for morphologic evidence of renal disease if it did occur.

So what we did was to choose a polyethylene glycol molecule 10 times greater than the known toxic dose because it was in an acceptable range.

Again, as I mentioned previously in our sub-chronic toxicity studies, we found a single set of abnormal results. This was a day eight hemorrhage of intestinal mucosa, using the 50 times the human dose in female rats.

In these types of studies, we did

extent morphologic analysis, extensive histology and the sub-chronic toxicity histology showed no evidence of renal abnormalities.

Animal efficacy was studied in a seven day pig study. We induced severe leaks greater than one liter per minute. These were sealed at the time of surgery, successfully. There were no leaks at day seven. The original leaks stayed sealed.

Histologically, at the time of necropsy we saw no evidence of foreign body giant cell formation. We saw no evidence of macrophage infiltration. There was normal tissue healing and no evidence histologically of an immune response.

Because we are interested in whether or not the material could influence tissue healing, we also did a separate study using a very thin layer of the tissue sealant over multiple wounds on the surface of the lung, and in this study at the end of 28 days,

we found that the sealant was present at four days and at seven days and it was gone in two weeks.

In all of these cases and all these experiments, the healing progressed normally. Again, there was no evidence of an immune response.

So if we can summarize to this point, the sealant polymerizes rapidly in situ. It meets our criteria and adheres to the tissue, consistently sealed lung air leaks in pre-clinical trials, degrades within our design characteristics of 30 days, demonstrated excellent bio-compatibility in normal tissue healing without any evidence of an immune response, and with that, I will continue with Dr. Miller. Thank you.

DR. MILLER: My name is Dr. Dan Miller. I'm currently the Chief of thoracic surgery at Emory University in Atlanta and the Kamal A. Mansour Professor of surgery.

I'm presenting today the study

design and results. At the time of this study, I was a staff surgeon at the Mayo Clinic in Rochester, Minnesota.

The ProGEL Surgical Sealant is intended to be used as an adjunct to standard closure techniques for sealing or reducing air leaks incurred during pulmonary resection. Currently, there are no sealants that are approved and available in the U.S. for this adjunct. ProGEL has not been approved or marketed outside of the United States.

The study design was an open label perspective, randomized two to one, controlled multi-centered study. Standard methods of air leak closure was carried out first and was deemed the control group. In standard methods, the sealant group was standard methods plus the sealant. There are a total of 161 subjects, 103 in the sealant group and 58 in the control group.

Five study centers were selected throughout the United States. There are a

total of 10 surgeons. These surgeons, at each institution, practice was solely dedicated to general thoracic surgery.

Eligibility criteria, patients had to undergo an open thoracotomy, had to have a planned lung resection, had to be more than 18 years of age, signed, informed consent, no known sensitivity to human albumin and no significant clinical condition, complicating evaluation of the sealant per the protocol.

Also too, the patient had to have an air leak demonstrated at the time of pulmonary resection. This was performed by a water immersion test and what was measured was the size of the air bubbles from the leak site.

After the procedure was completed, the patient underwent testing for the intra-operative air leak. If they had no air leak or an insignificant air leak, they were not enrolled and if they did, they were enrolled in the study.

The subjects that were enrolled in the study, the air leaks were recorded for location, type of injury, size and the number of intra-operative air leaks.

The standard techniques were carried out, such as suturing to open or close an air leak and then randomization occurred.

The sealant was applied and it was only applied to the observed air leaks. It was not sprayed over the other portions of the lung where there were no air leaks present and then both groups were then retested and recorded for the intra-operative air leaks.

Chest tubes, which is the number one management tool for prolonged air leaks, all chest tubes were placed on suction, either 20 to 25 centimeters for the first 24 hours. Patients -- chest tubes were then placed at water seal at the discretion of the investigator.

Chest tubes were removed when there were no air leaks present. Also, if there was

an insignificant stable residual space, when drainage was less than five cc's per kilogram for 24 hours or 50 percent less of that during 12 hours.

Heimlich valves were also used during this protocol. For the members of the audience, a Heimlich valve is a device that was developed during the Korean War. This is a device that's placed on the end of a chest tube to allow transportation of patient who has a stable air leak.

This allows patients to be discharged from the hospital if they have an air leak and no other clinical significant problems. The Heimlich valve and chest tube were removed in our patients on a weekly exam and after the air leak had resolved.

So Heimlich valves were used in this study and it has been in standard practice in the United States for over 50 years.

In regards to the measurements of

efficacy, the primary endpoint was a proportion of subjects who remained air leak free from the recovery room through the one month follow up. Secondary endpoints were a proportion of intra-operative air leaks that were sealed after the procedure.

Second was proportion of subjects who were air leak free in the recovery room. Third, duration of post-operative air leaks, the amount of chest tube duration and the length of hospital stay.

Measures of safety were adverse events through one month and then laboratory values was a standard test and the immunologic assays.

In regards to enrollment, 275 patients were screened. One-hundred-fourteen were enrolled, but were not randomized because they had no air leak at the completion of the repair maneuvers.

One-hundred-sixty-one patients were randomized who had intra-operative air leaks,

103 in the sealant group and 56 in the control group who received no further treatment.

The base line characteristics for both these groups were similar. There is no statistical difference in regards to gender, demographics or base line numbers. However, there was a slight increase in patients within the sealant group to have more COPD, more renal disease and had undergone neo-adjuvant chemotherapy prior to surgery.

The indications for surgery, in the majority were malignancy greater than 85 percent and there is no difference between the two groups.

In regards to procedures performed, the majority of the patients underwent oncological procedures such as a lobectomy and there was no difference between those two groups.

However, within the sealant group, there were more patients who underwent an extended resection, and what an extended

resection is, is that when a patient would require more than a lobe to be removed, most commonly a bilobectomy or a lobe plus a segment from another lobe.

In thinking of this, it's what occurs, think of your chest cavity as a bird cage and let's say, on the right side, you have three balloons which corresponds to the three lobes. If you have one balloon that is removed, you have the other two balloons that fill the chest cavity.

Whereas, in an extended resection, you may remove two balloons and only have one balloon to fill that large chest cavity.

So if you're looking at a reason that these patients were more prone to prolonged air leaks, the sealant group met that because there was almost a 10 percent increase in extended resections.

If you look at the intra-operative air leaks that were recorded, there was a statistically significant difference in

regards to the multiple air leaks. Almost 70 percent of the patients in the sealant group had multiple air leaks, to only 50 percent in the control group.

The initial size of the air leaks were similar between the two studies, which ranged from less than two to greater than five.

In regards to the source of the air leaks, it was from multiple airs. It wasn't just the fissure or staple line. It was from torn lungs, suture line, adhesions and there is no difference between the two groups in regards to the site of the air leak.

In regards to the sealant, the majority of the patients where the leaks were successfully sealed with either one or two applications of the sealant in greater than 93 percent of the subjects.

In summary of the study results, the primary efficacy endpoint, which was subject that were air leak free from recovery

room to one month follow up, was statistically significant of 35 to 14 percent.

Secondary efficacy endpoints, there were significantly more patients who had their air leaks sealed in the operating room in the sealant group. There were more subjects who were air leak free in the recovery room and also, the hospital stay was decreased significantly in the sealant group. The other two secondary endpoints did not meet statistical significance, but there was no difference between the two groups.

In regards to the safety endpoints, the clinical adverse effects and laboratory immunologic studies, there was no statistical significance. Let's look at these a little bit more closely.

In regards to the primary efficacy of this study, which was developed with the 3M Corporation, the investigators and the FDA, was to look at the subjects air leak free from the recovery room to the time of follow up at

one month.

In the sealant group, 35 percent of the patients were air leak free during this time, whereas, only 14 percent of the control group. The sealant subjects had a two and a half time more likelihood to be air leak free and with further statistical analysis, the odds ratio was 3.3 and the adjusted odds ratio was five.

This was even more remarkable, despite the base line and balances disfavoring the sealant group, where there were more multiple air leaks within the sealant group and also, more extended resections and the primary efficacy, more of the patients in the sealant group remained air leak free.

If you look at the air leaks that were sealed, there is no difference -- there was multiple air leaks, not only one, two or three and the sealant was superior in all types of multiple air leaks.

Secondary endpoints, intra-

operative air leaks were sealed in the OR, almost a five-fold increase in the sealant and this was statistically significant.

Subjects that were air leak free in the recovery room, again, statistically significant, greater than 54 percent compared to only a third of the control group.

The duration of post-operative air leaks, there was no difference in this duration of two days for both groups. Chest tube duration was also similar between the groups at a meeting of only five days, and this was not statistically significant.

Hospital stay was significantly reduced in the sealant group. When looking at median, there was a reduction of one day and with mean, there was a reduction of two days.

In regards to the Heimlich valve use, a total of 11 patients were discharged with a Heimlich valve, 10 in the sealant group and one in the control group.

Study consideration with regards to

the Heimlich use, one disadvantage is that there was no daily evaluation of the air leak when the patients were sent home with a Heimlich valve. They only were examined on a weekly basis. Also too, the question was, what was the impact of the post-operative air leak and chest tube bias against the sealant group on the use of Heimlich valves, and the question was did this impact the total length of hospital stay?

This is a break down of this. As we mentioned before, all subjects, a mean of two days were decreased in the sealant group and there was no difference in the hospital stay when you take out the Heimlich valve patients.

In regards to the efficacy conclusion, the primary endpoint was achieved with almost a greater than 2.5 air leak free rate in the recovery room to one month and three of the five secondary endpoints met statistical significance and the other two,

there was no difference between the two groups.

In regards to safety, clinically, there is no significant difference in adverse events. There is no device related deaths. There was no empyemas, which Dr. Walsh was talking about earlier, when we have prolonged air leaks, this communication of the air way which has bacteria and other organisms, which could infect a pleural space, and there were no empyemas in our study group.

Also, in regards to laboratory value, there was no significant difference. There were changes in regards to immunity.

Safety findings, there was no physiologic or other physical findings of fiscal or clinical concern. There were no acute or chronic effects and there was no significant difference in any laboratory value tested.

This is a list that is complete, as to regards to adverse events that occurred

within incidents greater than two percent. There was no statistical significance between the two groups. I would like to comment that in regards to death, there was only 4.9 percent deaths in the adverse group and 6.9 in the control group and also, there was no difference in regards to pneumothorax between the two groups.

Also, this is another complete list. There is no difference in regards to adverse events.

If you look at the most frequent severe adverse events between the two groups, pain and atrial fibrillation was the most common in the sealant and the most common in the control group was dyspnea and anemia and again, there was no difference between the two groups.

In regards to deaths, as mentioned earlier, there was only five deaths within the sealant group at 4.9 percent and four deaths in the control for 6.9 percent.

As you look here for listed of cause, this was listed on the death summary, ARDS, pneumonia, air way disease, again, ARDS, and on the control group there was a cadre of causes.

But if you look more into the detail of these cases, first for the sealant group, and this was reviewed by two of the investigators, that the majority of these were not pulmonary related. The ARDS group, this was a patient who had lung volume reduction surgery and went back to surgery because of air leaks and at that time, sealants were placed.

There is one patient who had pneumonia, but the patient had a bowel obstruction leading to pneumonia, so it was not related to the sealant.

Also, one patient had emphysema related complications and the other two patients, the ARDS, which were listed as the cause of death, were actually in the full

spectrum of multi-system organ failure and both of these patients actually had problems with liver disease, chronic alcoholic in-stage liver disease, and so, there is no device related pulmonary causes of death and no consistent pattern.

If you look at the control groups, again, listed before on the death summary was pneumonia, atrial fibrillation, ventricular fibrillation, ARDS, and if you look at these in a more close scenario, three of the four control deaths, ARDS was a late finding related to multi-system organ failure and again, there was no difference between the sealant and the control group.

There is additional post hoc analysis that was carried out by the FDA and there is difference between the groups, not statistically significant, but possible analyze for trends and also, analyze for potential clinical significance.

One of the concerns was in regards

to partial lung expansion, as Dr. Walsh explained earlier, partial lung expansion occurs -- can occur when patients have an extended resection and partial lung expansion does not mean that the lung is trapped or that there is a clinical problem.

After removing lung tissue, there is a normal recovery time that allows the lung to completely fill the chest cavity and this usually takes about four to six weeks to occur, and recorded in this study at the one month follow up, lung partially expanded within the normal limits of a post-operative thoracotomy and the correct term should not be partial lung expansion, but residual pleural space as a preferred term.

This does not imply partial lung collapse. It's always present after removing significant lung tissue, as in our patients, and if there's no air leak present, which is the primary endpoint of our study, if there's no air leak, there's no treatment that is

required.

So, you look at the post hoc sub-group analysis reform and this was looking at chest x-rays at one month. If you look at all subjects within our study, partial lung expansion was noted in 33 percent of our patients in the sealant group and 23 percent of our control group. If you look at the difference pneumothorax, there was no difference between the sealant control group.

So, what was done by the FDA, a post hoc sub-group analysis was requested and a radiologist reviewed a sub-set of chest x-rays, only 40 sealant patients and 20 control patients, and what they found was, is that six of the 40 sealant subjects had a pneumothorax versus none of the patients in the control group.

This was not a study endpoint, so the question is, how is this clinically significant? If an air space is getting larger, then there is concern that the air

leak is present and something should be done clinically. However, if the space is getting smaller as it's supposed to be, then no treatment is required.

So, if you look at these patients a little bit closer, of the six sealant patients, you can see here that out of the six, five of the six had their post -- their residual pleural space reducing at the time of the follow up. Only a single patient required a chest tube at one month follow up, and this was the patient who had had an extended resection, upper and middle lobectomy, had had this -- had undergone five previous thoracotomies and radiation treatment.

It was interesting here, if you look at the space size, these were measurements that were done by the FDA on size of the residual space and this was done on a PA and lateral chest x-ray, which cannot measure volume.

So, out of this entire group, only

one of the 40 sealant subjects had a large pneumothorax at one month follow up and was a consequence of the prior resection, and also too, which is of interest of these six patients, their average time to one month follow up were 13 days shorter in the sealant group compared to the control, means that they were -- did not fall within that four to six week time period, when the residual space would resolve.

In regards to the renal function, which there were some questions in regards to this, we did have a higher number of patients who had some renal issues after the study, but there was statistical significance with this, and if you look at this further and also, looking at the pre-clinical study that was presumed by Dr. Parks, pre-clinical testing showed there was no renal toxicity. The renal toxicity evaluation was extensive. There is no negative studies and in our study, 13 percent of our patients had pre-existing renal

disease compared to nine percent, and also to -- as you know, anesthesiologists and thoracic surgeons, we like to keep these patients very dry in the operating room, and so, keeping these patients dry may lead to increases in creatinine and transit oliguria in the pre-operative period.

So, you look at the nine patients that there were some concern in regards to their renal adverse events, if you look at this more closely in the sealant group, two of the patients had prior kidney dysfunction and also had multi-system organ failure.

One patient had a history of chronic renal disease and came up for base line in a 3.8 and required dialysis during the hospitalization. One patient had on-set of acute renal failure 20 days after surgery, after discharge, four patients had oliguria, three of those had no clinically significant change in renal function, and one subject, with a history of chronic renal failure, also

fell into this group.

There is only one patient out of these nine patients that had an abnormal renal function afterwards that we could not explain.

This is a table form of this, again, which breaks this down. Again, four patients had oliguria, their creatinine normalized over time, the two patients with history of chronic renal disease and the other two, on dialysis.

So, you look at the safety conclusions. There is no statistical clinical difference in any adverse effect in regards to renal function, pneumonia, also most importantly, there was no empyema related to the sealant and also, there is no difference in immunologic laboratory tests evaluated.

DR. CERFOLIO: Well, good morning. My name is Robert Cerfolio, and before you say, "Here comes another one," don't worry, I only have three or four slides. We're almost done, so hang in there.

I'm a general thoracic surgeon at the University of Alabama at Birmingham. I don't have any financial interest in the company. I don't have any stock in NeoMend. I'm just a simple thoracic surgeon that is tired of dealing with air leaks and have done multiple studies trying to figure how best to treat them.

All I'm going to do is really summarize and hit the high points that you've heard this morning, very well put by Dr. Walsh and Dr. Miller.

We all know that pulmonary resection is a standard treatment for non-small cell lung cancer and the data is clear that more and more pulmonary resections are being performed, mainly because we're finding more and more of these nodules because more patients are getting CT scans done routinely and because the number of pulmonary resections are obviously growing, the problem with air leaks is going to continue to grow.

Now, air leaks are not just a little troublesome thing that keeps people in the hospital. They're a big deal. They cause big problems and as you heard from Dr. Walsh, they lead to death.

They are very common. If you look at the literature, they range anywhere from 20 to 50 percent, despite using all of these intra-operative methods that we have available to us and it's frustrating because a lot of times, as the surgeons and anesthesiologists know, we're in the operating room and we put water in the chest and we say what a great job we've done, there's no leak. You go to recovery room and there's a big leak or on post-operative day one there is a big leak, and we all know that these air leaks are not just troublesome things that lead to increase hospital stay, but rather, lead to morbidity, mortality, infection, et cetera.

Furthermore, air leaks add time to the surgical procedure and anything that leads

to more time in the operating room, leads to cost. Cost is bad in a health care society that we have today and increased hospital stay, which air leaks unequivocally lead to, also adds to cost and mortality. So, this is a very important clinical problem.

Now, the real problem is, I sat where you guys were sitting several years ago when FocalSeal came along and I knew that air leaks were a big problem and FocalSeal got approved by the FDA and I used it and you may asking yourself, "Well, what the heck happened to FocalSeal?"

Well, what happened was, although the product was very good and the fact that it was sealing air leaks, which is an important clinical problem was good, the device was cumbersome to place on the lung and because it was a little difficult to put on the lung, you had to spray it on and then you had to get a light and put a light on to it. Surgeons just really never adapted using it and there's also

some other problems with it. So, FocalSeal is no longer available.

So, as of today, I have nothing, no FDA approved product to place on my patients leaking lung in the operating room, which is another reason why this product is so important.

I can also tell you from looking at the FocalSeal data, which was very good, I think this data is even superior to FocalSeal.

Now, the big picture, the big picture is, this company has performed a prospective randomized, multi-institutional study. They've shown you a significant P-value for not only the primary endpoints, but three of the five secondary endpoints.

It shows you that the freedom of air leaks in patients from the recovery room to one month post-op was significantly reduced from 35 percent versus 14 percent. That is an incredibly important difference in not just statistics that are being fooled around with,

and also, it shows you a difference in the intra-operative sealing of air leaks and length of stay, and we've talked about how length of stay is important overall for morbidity, mortality and for cost.

More importantly, we showed you that there was no evidence of device related adverse effects, and I want to go over that a little bit more carefully, because one of the questions we know you're going to have is, is this product trapping the lung? Why were there more pneumothoraces? All of the surgeons on the panel, I think, understand very well, that after you do lung resection, there's often pneumothoraces.

First of all, they're hard to read. Second of all, we know they're difficult to interpret on portable chest x-rays, but probably most importantly, we all know that they really have no clinical significance.

So, I don't think that there was any evidence, certainly no statistically

significant difference, in the pneumothoraces. In fact, if you look at the overall incidents of pneumothorax in the sealant group versus the control group, they are the same. So, I don't think there is a problem here. This product does not trap the lung.

I know you're going to have a question about the renal toxicity. I think Dr. Miller did a wonderful job going through those nine patients saying, "Oh boy, there's nine people that had kidney problems in the sealant group and only a couple in the controlled."

Well, if you look at it carefully, as Dr. Miller showed you, he showed you that really there was one patients in the sealant group that had a creatinine that bumped and it was 1.8 from 1.1. That's not much of a bump, and there are actually two in the controls, and we think these bumps were from how we treat the patient.

There was no statistically

significant difference, no evidence that the sealant had related adverse renal function.

Finally, we put up here the problem with empyemas. That was a concern, if you may recall, with the FocalSeal product because there was a couple of empyemas. In this product from ProGEL, there was no empyemas in the sealant groups and in fact, if you look at the data carefully, there were fewer pneumonias and even fewer deaths in the sealant group.

So, what can we say in conclusion immersed on the data from a prospective multi-institutional randomized study? We can say that the product is very safe. It has high efficacy. It is a very effective sealant and we've all told you that as clinicians that do this every single day, day in and day out, this would be extremely important to our patients.

This would help our patients get better results, which is the whole reason we

got into this ball game and went to medical school in the first place.

The results of this study provide reasonable assurance of safety and efficacy, and the clinical benefits for patients cannot be underestimated. We thank you for your time and your consideration.

CHAIR BIRNBACH: I'd like to thank the sponsor for their presentations. Does anyone have -- on the panel, have a question for the sponsor?

Please remember that the panel may also ask the sponsor questions during the panel deliberations later today, but if anyone on the panel has extensive questions for the sponsor, you may ask them now, so that the sponsor can be prepared to respond in the afternoon.

DR. NORMAND: I just have a question of clarification, so that I can better understand the design, and it really related to slide 49 that the sponsor presented.

I just wondered if somebody could sort of explain to me, in terms of who is actually -- after the subject is randomized to get the sealant or not get the sealant, who is actually counting the number of air leaks, after the sealant is applied?

DR. MILLER: The surgeon.

DR. NORMAND: So, the surgeon who applies it -- so, the surgeon is obviously not blinded and the surgeon is counting. The surgeon knows they applied the sealant and then the surgeon is counting the number of air leaks after the sealant has been applied?

DR. MILLER: Exactly.

DR. NORMAND: And another question, just in terms of the blinding. So, the surgeon is not blinded and counts there, and then at the end of the period, the one month follow up, that's related to sort of the chest tube being taken out or not and sort of -- the blinding, who -- at the primary endpoint, who is actually determining?

DR. MILLER: The surgeon determines when the -- at the one month, that's the usual follow up for these patients.

DR. NORMAND: Okay.

DR. MILLER: And the surgeon determined when the chest tube could come out.

DR. NORMAND: Okay.

DR. MILLER: Now, only 10 patients went home with the chest tube.

DR. NORMAND: I was just asking about the -- who is actually blinded and not blinded, and then the one question I will ask this afternoon is, I'd like the duration of follow up for each patient.

You said one month follow up, but I think you indicated one was 13 days less. So, it will be important, at least from my understanding of the data, to actually know. You've got differential links of follow up for these individuals and it will be important to know the actual distribution of length of follow up. Thank you.

DR. MILLER: Thank you, and also too, I forgot to add that I have no financial disclosures related to this product or to this presentation.

CHAIR BIRNBACH: Dr. Cassiere.

DR. CASSIERE: I have a question regarding the length of positive pressure ventilation on these patients. Do you have a break down of control versus sealant, how many hours they were on positive pressure ventilation?

DR. MILLER: We have no data in regards to that. We do have meeting operating time for both series and they're exactly the same. None of these patients -- all patients were extubated in the operating room when they went to the recovery room.

We also have data just on the patient's required intubation, afterwards when they're on their post-operative period. We do not have any data in regards to use of CPAP or BiPAP during the post-operative period.

CHAIR BIRNBACH: Dr. Wilcox.

DR. WILCOX: Thank you. I'm interested in how you maintain consistency in the operative procedures. There were done at multiple institutions by multiple surgeons at these institutions, including residents, I would imagine.

I would like to know if you have any indication of what the impact of the learning curve that might have been observed in the course of the studies. Were the patients fairly, evenly distributed among the five institutions and were the techniques relatively the same, that is, is the same stapler used in institution A versus institution B, one having three rows of staples, another having two rows and so forth?

DR. MILLER: The surgical techniques used in this was the same across all five institutions. There was a difference in the stapler. Three institutions were Ethicon open stapler. The other two was Euro-Surgical.

But if you look at the data in regards to the stapler applied, there was no difference in the post-operative air leaks.

But it's the same general thoracic surgeon. We went through this before the 10 investigators of our standard techniques. There is no buttress materials applied and so, for like -- the only lung volume reduction patient in this whole series was actually put in after lung volume reductions, when they had to go back for an air leak is when they used this sealant, and that was the same across every institution.

CHAIR BIRNBACH: Mr. Melkerson.

MR. MELKERSON: Just a couple procedural things to keep in mind during your questioning. The sponsor made mention of a comparison to another approved product. This PMA has to stand on its own, so your question should be related to the data provided in this PMA and how it was compared.

One other comment on the use of

Heimlich valve slide, there was data presented that was not presented to FDA. Just as a note of comment, we raise the question, and it will be part of your deliberations anyway, so just to note that.

CHAIR BIRNBACH: Thank you. Any other questions from the panel? Dr. Domino.

DR. DOMINO: I'm wondering about, since your study numbers are fairly small, what incidents of renal insufficiency after thoracotomies and lung resections are in general.

Is there any literature in the thoracic surgery literature that could provide an answer beyond the 58 patients in your control group versus your hundred-some in your experimental group?

DR. WALSH: Thank you. That's a good point. I think all of us who practice thoracic surgery recognize that transom bump in creatinine because of the relative hypovolemic state that we keep our patients

in, to avoid the problems of pulmonary edmeia is quite common. Five to 15 percent of patients will have a bump.

We certainly -- it's not uncommon to see creantinines that will go up by several points in the post-operative period.

So, we vetted this list very -- in a detailed manner and we could only find one patient that really, at that 20 day mark, had a bump in creatinine that would not be expected, based on either their pre-renal conditions or standard post-operative management issues.

CHAIR BIRNBACH: Dr. Jeevanandam.

DR. JEEVANANDAM: I think you've shown that, at least intra-operatively and in the recovery room, you have less air leaks using the sealant.

But I was interested to note that the length of stay, whether you use an air leak -- whether you use sealant or not really different, the amount of total time that chest

tubes were present, which presumably is a surrogate marker for how long an air leak was present, was not different, and you're really not showing any type of clinical benefit, in terms of stopping these air leaks.

So, I guess my question is, is there a clinical -- you have shown that you can stop an air leak. Is there any clinical benefit to stopping an air leak, at least in the study?

DR. CERFOLIO: I think you know that any study that has 10 surgeons involved with chest tube management is going to be difficult to show a sophistically significant difference on chest tube duration because there's always little differences.

When you look at hospital length of stay, we all know that we have patients whose chest tubes are out, air leaks are over on post-operative day three. They don't go home until post-operative day five because their mom can't get them, their daughter's shoes

aren't ready and multiple other reasons that we know of.

So, I think it's very difficult to show that. But I think if you look at the data, there was a reduced length of stay and you go back and look at the data, there was less length of stay, and the Heimlich valves, which you would think would be something to get people to out of the hospital quicker, some surgeons may have watched patients on a Heimlich valve for a day, where others didn't.

So, I think the data does show that there's clinical benefit to this product. It does get the tubes out quicker. It does get the patient out of the hospital quicker.

CHAIR BIRNBACH: Dr. Ries.

DR. RIES: I have two questions. One is a design question regarding the randomization. Since there were concerns about the between center differences and experience, it appears that the randomization was not site specific, the two to one

randomization, is that true? It was site specific?

DR. WALSH: No, it was site specific.

DR. RIES: Because the data suggested it really was -- it appeared to be a little bit off from a two to one randomization per site. Was that just random? But it was -- the assignment was by site?

DR. WALSH: Right, each -- and it's been a few years, but we would randomize intra-operatively. They'd go get a card from, I think it was pharmacy at that point, and the randomization was done at that point.

DR. RIES: By site?

DR. WALSH: Yes.

DR. RIES: Okay, and the second question is related to the first question, about since the surgeon was both applying the sealant and counting the leaks, any thoughts about why there appeared to be significantly more multiple air leaks on the -- in the

sealant group?

DR. WALSH: Well, I think it's because it looks like our sealant group, it just happened with the randomization, that the sealant group were -- ended up having more extended resections. I think there were re-do operations on the sealant side.

So, it just happened that there were more. We kind of -- the randomization actually put the sealant in a more favorable group of patients that we had to deal with, as far as leaks, and that's the way it worked out, larger tears in the lung and more leaks.

CHAIR BIRNBACH: Dr. LoCicero.

DR. LOCIERO: I have two questions, one for Dr. Parks. You stated that the product had an average gel time of 13 seconds, but in your performance objectives, you stated that you needed acceptable strength within two minutes. When did it reach acceptable strength?

DR. PARKS: It reached acceptable

strength in a range of one to two minutes.

DR. LOCIERO: Okay, thank you, and for the surgeons, this study was approved in 2000. Can you tell me the period of time that the patients were enrolled and the end of the study, the time of the end of the study?

DR. MILLER: The end of the study was 15 months.

DR. LOCIERO: So, it was finished in 2002?

DR. MILLER: Late 2001.

CHAIR BIRNBACH: Are there any other questions from the panel? Dr. Stoller.

DR. STOLLER: A question about the renal status. Recognizing that many factors may impact renal function post-operatively, do you have data about the actual volume management, the intra-operative volume I&O and the post-operative course in the ICU, in terms of net in and out?

DR. CERFOLIO: No, we really don't have data on that. But if you look at these

patient's serum creatinine, you'll see that I think the people who look at the study were very, very cautious because I would consider bumps in creatinine's from 1.2 to 1.8 or 2, almost normal. But here, they were called adverse events.

So, we don't have data of how much volume they got in the OR or how much volume they got afterwards. But if you look at the changes in the creatinine, there really was no difference between the sealant and control groups.

CHAIR BIRNBACH: Dr. Lillard.

DR. LILLARD: This question is regarding any attempt to look at any associated health disparities with intra-operative air leaks. In particular, I was interested to know the distribution of ethnicity or number of minority subjects in your study.

DR. PARKS: Across the spectrum of studies, in regards to minorities, it was less

than five percent at each center. To look at that statistically, there is no difference from that.

DR. LILLARD: And it's also in regards to -- one of the pre-clinical studies, you showed a hyper-sensitive response in rabbits. I was wondering what the hyper-sensitivity metric was in the clinical study.

DR. PARKS: We first began with the premise that the reactions that we saw were in guinea pigs. The reactions were anaphylaxis type 100 hyper-sensitivity, and so, we brought that up as a consideration n the clinical trial and we were assured that it was possible, during the induction of anesthesia or during the time of operation, that anaphylaxis, if it did occur, could be monitored.

As far as the type four hyper-sensitivity reaction, because this was a delayed reaction, we had to depend upon subsequent follow up in the patient at one

month and part of that was designed. Part of our design was to include the immune studies that we did.

CHAIR BIRNBACH: Dr. Normand.

DR. NORMAND: I'm still trying to understand the design, just because I don't know this subject matter area that well, and I think it's a question for Dr. Miller.

But let me state something, and if you could correct me if I'm wrong, in terms of my understanding.

So, a patient undergoes surgery. The number of leaks is counted, then the patient is either randomized to the sealant or control group. Please help me there with that one.

DR. MILLER: What occurred is, after the patient underwent the procedure, either a lobectomy, bi-lobectomy, what occurred at that point, we measured the number of air leaks, the quantity of air leaks at that time.

DR. NORMAND: Yes.

DR. MILLER: And then we applied standard techniques to repair that.

DR. NORMAND: Yes, okay.

DR. MILLER: Okay, then after that time, then they were randomized --

DR. NORMAND: So, could I stop you there?

DR. MILLER: Yes.

DR. NORMAND: After that time, when are the number of air leaks counted? So, you go under the standard procedure and then they're randomized and then you count how many air leaks there are?

DR. MILLER: Yes, afterwards, you count.

DR. NORMAND: Okay. So, they're randomized -- and I'm sorry to everybody for not following, but I need to understand it in my head.

So, there's a standard procedure, air leaks are then -- air leaks are determined and then there's something done to --