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MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
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(202) 546-6666

PARTICIPANTS

Paul A. Bunn, M.D., Chairperson (a.m.)
David R. Parkinson, M.D., Chairperson (p.m.)
Stephen Pollitt, P.A.-C, Executive Secretary

VOTING MEMBERS

Arlene Forastiere, M.D.
Richard Gelber, Ph.D.
James N. Ingle, M.D.
James Krook, M.D.
Judith Ochs, M.D.
Robert Ozols, M.D., Ph.D.
Sandra Swain, M.D.

Patricia Abbitt, M.D.
Michael D. Devous, Sr., Ph.D.
Arnold Malcolm, M.D.
Barry Siegel, M.D.
Marilyn J. Siegel, M.D.

CONSUMER REPRESENTATIVE

E. Carolyn Beaman, M.H.S.

PATIENT REPRESENTATIVE

Barbara Sortino

FDA (a.m.)
Robert Delap, M.D., Ph.D.
Lydia Larson, Pharm.D.
Alison Martin, M.D.
Robert Temple, M.D.

(p.m.)
Paul Botstein, M.D.
Ira Berkower
Patricia Keegan, M.D.
George Mills, M.D.
Jay Siegel, M.D.

C O N T E N T S

P R O C E E D I N G S

OPENING STATEMENTS

MR. POLLITT: My name is Steve Pollitt. I am the Executive Secretary of this Committee and I would like to welcome you to the 48th Meeting of the Oncologic Drugs Advisory Committee Meeting. At this time, I would like to introduce Dr. Paul Bunn who is the Chairman of the Committee.

CHAIRMAN BUNN: Thank you very much. I think we will have a few introductions and then we will actually go around the table and introduce ourselves. As hopefully everyone knows, the ODAC has a patient representative at every meeting. This morning, I would like to welcome Barbara Sortino who is here as the Patient Representative serving on the Committee for this session.

There is a new ODAC member who is a voting Consumer Representative, Carolyn Beaman. Carolyn Beaman is a permanent member of the Committee and we welcome you, also. Perhaps, we will just go around quickly and introduce ourselves. Even though I have introduced you, why don't you just say your name again and we will go this way.

MS. SORTINO: My name is Barbara Sortino. I am a lung-cancer survivor. I am here representing patients.

MS. BEAMAN: I am Carolyn Beaman. I am the Consumer Representative. I am a five-year breast-cancer

survivor.

DR. KROOK: I am Jim Krook from Duluth, Minnesota, medical oncologist.

DR. OZOLS: Bob Ozols from the Fox Chase Cancer Center in Philadelphia, medical oncologist.

DR. SWAIN: Sandra Swain, medical oncologist from Bethesda, Maryland.

DR. BUNN: I am Paul Bunn. I am a medical oncologist from the University of Colorado.

MR. POLLITT: Steve Pollitt. I am the Executive Secretary for the Committee.

DR. OCHS: Judy Ochs, now pediatrics and medical oncology, Little Rock, Arkansas.

DR. FORASTIERE: Arlene Forastiere, medical oncologist at Johns Hopkins, Baltimore.

DR. GELBER: Rich Gelber, biostatistician from Boston.

DR. DELAP: Bob Delap, Oncology Division, FDA.

DR. TEMPLE: Bob Temple. I am Associate Center Director for Medical Policy.

DR. JUSTICE: Robert Justice, Division of Oncology, FDA.

DR. LARSON: Lydia Larson, Division of Oncology, FDA.

DR. MARTIN: Alison Martin, medical oncologist,

FDA.

MR. POLLITT: I will now read the conflict-of-interest statement for this meeting.

The following announcement addresses conflict-of-interest issues associated with this meeting and is made a part of the record to preclude even the appearance of a conflict.

Based on the submitted agenda and information provided by the participants, the Agency has determined that all reported interests and firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 USC 208(b)3, full waivers have been granted to Dr. Robert Ozols, Dr. Marilyn Siegel, and Dr. Barry Siegel. The waivers permit them to participate fully in the discussions and voting concerning NR-LU-10 Fab. A copy of those waiver statements may be obtained by submitting a written request to FDA's Freedom of Information, Room 12A-30, of the Parklawn Building.

In addition, we would like to note that Dr. Ozols and his employer, the Fox Chase Cancer Center, have interests in the manufacture of a competing product, a sterile aerosol talc, which are unrelated to the firm's competing product. Although these interests do not

constitute a financial interest in the particular matter or in the competing product within the meaning of 18 USC Section 208, they could create the appearance of a conflict. However, it has been determined, notwithstanding those interests, that it is in the Agency's best interest to have Dr. Ozols participate in the Committee's discussions concerning sterile aerosol talc. He will, however, be excluded from any vote related to this product.

Further, during the discussions of NR-LU-10, Dr. Paul Bunn will step down as chairman. He will participate in the discussions concerning NR-LU-Fab, however, he will be excluded from any vote related to the product. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interests of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. I would also ask that anyone who does ask questions or come up to speak, please speak into a microphone, state your name first and who you represent, and if you have any financial interests in the product being discussed before the Committee.

Thank you.

Dr. Bunn.

OPEN PUBLIC HEARING

CHAIRMAN BUNN: Thank you very much.

We now turn to the open public hearing, and we have had one request, from Peggy McCarthy, to speak before us all.

Peggy, if you want to use this microphone, that will be great.

MS. PEGGY McCARTHY

MS. McCARTHY: I am Peggy McCarthy. I am Acting Executive Director of the Alliance for Lung Cancer Advocacy, Support and Education.

This group, ALCASE, is the only organization that supports, advocates, and educates people with lung cancer. It was founded in 1979 by a lung cancer survivor, Mort Liebling, who started a group called Spirit and Breath, after he had received his diagnosis of lung cancer and was very discouraged when his physician told him, after Mort complained of not feeling very well after his surgery and his therapy, his physician said, well, Mort, you are either going to die or you will eventually feel better, and Mort went out and found ways to make himself feel better, primarily through the use of exercise. He helped to learn to re-breathe after losing a lot of his lung tissue, and he

started an organization that he shared with other people.

We found out about it a number of years ago and got to be friends with Mort, and prior to his passing away two years ago, he asked my business if we would take over the organization, make sure it continued.

We changed the name to ALCASE, as I mentioned, and I am very pleased to be here representing the lung cancer survivors who work with us.

During the first half of the century, lung cancer was a very rare disease. According to epidemiologist, E.L. Wynder, a patient who presented with lung cancer in a clinic or a hospital became a teaching case for practicing physicians and physicians in training. Today, however, lung cancer kills more people than any other type of cancer. In fact, each year, it kills more women than does breast cancer.

Tobacco was identified as a major carcinogen in the first Surgeon General's report published January 11, 1964, which linked smoking and lung cancer. Epidemiological research over the past 40 to 50 years has revealed that tobacco smoke is associated with 80 to 90 percent of all lung cancers. Of course, other complicating risk factors can be having a genetic predisposition for the disease and exposure to other carcinogens, such as asbestos, radon, and arsenic, to name a few.

The increase in incidence is attributed to the increase in smoking that occurred during World War I and World War II when cigarettes were distributed to soldiers. The subsequent and ever-increasing advertising campaigns by cigarette manufacturers also contributes to this increase.

Today, the incidence of lung cancer is decreasing in men but increasing in women. Deaths from lung cancer in women have increased more than 400 percent in the last 30 years. Although overall, smoking has decreased among women in the last decade, teenage smoking rates have not declined appreciably since 1984, and, in fact, the incidence of smoking in young adult women and teenagers is increasing.

A 1994 report by Dr. Joycelyn Elders, the Surgeon General at that time, published in the American Journal of Public Health stated that, among daily smokers, 71 percent started smoking by the age of 18. We believe that the increase in lung cancer incidence in women can be attributed to cigarette advertising which exploits the adolescent and woman's concerns about body image, popularity, success, and fashion.

Despite the increasing prevalence of lung cancer, early diagnosis is difficult. Many people are asymptomatic until the disease has progressed significantly. The symptoms may be vague or can be attributed to other physical problems.

By the time the disease has been diagnosed, it is usually too advanced to be cured. There are many stories of people whose lung cancers are misdiagnosed thereby delaying treatment for months and even years. I would like to tell you a few of these stories. These are case histories based on people who have called in to ALCASE.

For example, there was a CPA from New York. She was in her early forties. She called us back in 1994. She had been treated for a year for back pain with analgesics and heat by her family practice physician. She after a year decided to consult a chiropractor because her pain wasn't getting any better. The chiropractor did an x-ray and found lung cancer. She was diagnosed with Stage 3 non-small cell lung cancer and died this past year.

Another woman, 39 years of age, called us recently. She had been suffering from bronchitis and a sinus infection all last winter, and was diagnosed with many, many different diagnostic steps including an MRI of her head to look at the sinuses.

She improved, was treated with antibiotics, improved somewhat, and decided to take a road trip. During her trip, she tripped and fell, and went to a hospital emergency room where they x-rayed her for possible broken ribs. She was diagnosed with Stage 3 non-small cell lung cancer.

A third woman, age 58, and her husband, age 68, had scheduled physical exams by the same physician. The doctor prescribed a chest x-ray for the man, and not for the woman. Later she was given a colonoscopy and was diagnosed via that with metastatic lung cancer.

These are many stories like these. Because lung cancer has historically been a man's disease, physicians forget to include it in the differential diagnosis for their female patients.

While lung cancer is no longer an old man's disease, neither is it an old woman's disease. More and more people in their 30's, 40's, and 50's are being diagnosed with lung cancer every year. It is imperative that health care professionals be educated about the changes in lung cancer's epidemiological profile.

Improving diagnostic procedures can become a part of that education. The May 1994 edition of a patient and family guide published by the American Lung Association stated that, "There is no benefit from yearly chest x-rays with sputum cytology ... and that screening has not shown to decrease the lung cancer death rate. In cases where lung cancer was detected in its earlier stages, the data have not shown any decrease in mortality."

This bleak outlook can become part of the physician's beliefs about the efficacy of early detection

and aggressive proactive treatments. Yet, it cannot be denied that a cure is possible when tumors localized in a resectable site are surgically removed before they have metastasized.

The American Cancer Society's Facts and Figures for 1995 states, however, that although the five-year survival rate for lung cancer is only 13 percent, it rises to 47 percent for cases detected when the disease is still localized. However, only 15 percent of lung cancers are diagnosed in Stage 1 and 2.

In this light, we believe that the issue here is not only treatment efficacy based on the current average stage of tumor at diagnosis, the issue is promoting and providing earlier diagnosis and improved diagnostic techniques.

While it is true that the chest x-ray can miss a tumor in its earliest stages and sputum cytology may yield individual cells in numbers that are too small to be seen on an x-ray, they are useful diagnostics and it is important to make these and other tools available to all persons with lung cancer risk factors.

We must educate the health care community to reclaim the scientific heritage of their craft by approaching patients with an open and investigative mind. Then, we must provide the tools to make that investigative

process fruitful and rewarding.

Finally, we must launch a whole-hearted and vigorous campaign to combat the effect of cigarette advertising, especially on our young women and men. And we must not be afraid to tackle the difficult task of eliminating the use of cigarettes in our culture.

I and the members of the Alliance for Lung Cancer Support, Education, and Advocacy, also known as ALCASE, thank you for this opportunity to speak. I am very glad to be here.

CHAIRMAN BUNN: Thank you very much.

Are there any questions or comments from Committee members?

[No response.]

CHAIRMAN BUNN: Since I am interested in this topic, I will give my points of view.

From the Surgeon General's report in 1964 until 1991, cigarette consumption as measured by the percentage of adults who smoke went down, and over the last three years, the data are that cigarette consumption is no longer declining in the United States and more than 25 percent of the adult population continues to smoke.

It is probably no accident that in the last 10 years, cigarette advertising expenditures have gone from $2 billion a year to $7 billion a year. Not only are they the

largest advertisers in the world, but they probably equal everything else advertised in the world.

A couple of points of good news. Even though the cure rate is only 13 percent in the United States, shortly after the Surgeon General's report came out, it was 4 or 5 percent, and it is now 13 percent as you mentioned. In Europe, the cure rate for lung cancer is still only 4 or 5 percent. So we seem to be doing something which may be somewhat hard to identify.

We appreciate hearing from you. There has been some controversy over whether the Committee is interested in hearing from consumers, and I can assure you that we are. We are also, as has been mentioned many times before, interested in approving safe and efficacious drugs which will improve the situation of cancer patients in our country.

NDA 20-587 STERILE AEROSOL TALC

CHAIRMAN BUNN: So without further comment, then, we will turn to NDA 20-587 sterile aerosol talc, and the presentation will be given by Bryan Corporation.

MR. FRANK ABRANO

MR. ABRANO: My name is Frank Abrano and I hold the position of Chief Executive Officer of Bryan Corporation, which is a small, privately-owned medical device company located outside of Boston. I am honored

today to have the opportunity to present Sclerosol, a sterile aerosol talc for use in malignant pleural effusion.

I will begin by providing some background information on Bryan Corporation. Bryan Corporation was established in 1985, develops and promotes technology in the field of diagnostic and therapeutic endoscopy.

This company began with the introduction of the modified Dumon-Harrell Yag Laser Rigid Bronchoscope which remains the number one bronchoscope in the world today.

Following this product, Bryan Corporation introduced the first Baggish Continuous Flow Hysteroscope in the United States in 1988. This system was marketed by Weck Surgical under a license agreement with Bryan Corporation.

After working with Dr. Dumon and his colleagues in Marseille, France, for a number of years, we realized that the development of an aerosol talc addressed significant clinical needs in the management of malignant pleural effusion.

This is Bryan Corporation's first New Drug Application. This is an unusual submission since it is based on a literature search.

It gives me great pleasure to introduce to you today Dr. John Beamis, the head of the Section of Pulmonary and Critical Care Medicine at Lahey-Hitchcock Clinic in Burlington, Massachusetts. Dr. Beamis was one of the first

individuals to assist Bryan Corporation in pioneering the Dumon tracheobronchial stents. Today, Dr. Beamis will present the clinical overview to Sclerosol sterile talc.

Thank you.

DR. JOHN BEAMIS

DR. BEAMIS: Thank you, Frank.

[Slide.]

Malignant pleural effusion is a condition that occurs in many cancer patients. One estimate is that there are 200,000 cases per year in the United States. This I think is just an estimate from Dr. Light's book on pleural disease. It is the second most common cause of pleural effusion next to congestive heart failure, and it is the most common cause of exudate of pleural effusions.

[Slide.]

Lung cancer is the most common cause of malignant pleural effusion followed by breast cancer, lymphomas, and a number of other malignancies that can metastasize to the lung or to the pleural space, producing a malignant pleural effusion.

[Slide.]

Most patients with malignant pleural effusions are symptomatic, and although these patients are usually considered incurable because of the fact that they have studding of their pleural cavity or certainly unresectable

disease, these patients do need palliation for the effusions because they do produce symptoms primarily of dyspnea, some chest pain, and usually, because of the dyspnea and the extent of their cancers, they have significant systemic symptoms.

[Slide.]

There are a number of treatment options for malignant pleural effusions. Some small effusions can simply be observed, at least for a number of weeks, sometimes a number of months, although usually they eventually become symptomatic.

Simple thoracentesis and removing the fluid occasionally suffices for therapy. Systemic therapy would certainly be ideal. It certainly is helpful in many patients with breast cancer who receive hormonal therapy or chemotherapy, but in most patients with lung cancer, systemic therapy does not control their effusion.

The last therapy that talc has been used for, for a number of years, is pleurodesis or pleural sclerosis.

[Slide.]

The indications for pleurodesis for malignant pleural effusions are symptomatic patients. Usually, one should document that the patient's symptoms are improved by removing the fluid. So every patient should have a standard thoracentesis, removal of the fluid, and then a follow-up to

assure that there has been relief of symptoms.

One has to rule out trapped lung or bronchial obstruction. It is most important that the lung re-expands after the fluid is removed, so that pleural synthesis can be achieved. Some authors feel that if a pH is very low, lower than 7.2, that the chance of success of pleural sclerosis is quite low. That hasn't been our experience, but that is mentioned in the literature.

[Slide.]

The options for pleurodesis over the years have included agents to produce inflammation and fibrosis of the pleural surfaces. Tetracycline for many years, from probably the mid-seventies until several years ago, was by far the most commonly used agent, but intravenous tetracycline, which is used through chest tubes, is no longer available, so that other treatments have been used.

Doxycycline and minocycline have been used by a number of institutions since then. They probably work as well as tetracycline did, but there have not been good long-term studies on these.

Bleomycin, a chemotherapeutic agent, has been used for pleurodesis for a number of years, probably producing similar results to tetracycline. One concern from many clinicians has been the expense of this medication.

Most studies in the literature show that these

agents work approximately 70 to 75, 80 percent of the time, but rarely approach success rates over 80 percent.

Talc has been available since the 1930's for various indications to produce pleural synthesis. It has been used either as a slurry, where it is suspended in saline, or by insufflation.

In the literature, there are a number of series of the use of talc for pleural sclerosis. Many of these have been reported in the briefing documents that you have been given. Many of these studies do show that the success rate of talc for pleurodesis is over 90 percent, and in some studies, approaches 100 percent.

[Slide.]

The advantages of using thoracoscopy for pleurodesis is that one can achieve a rapid total drainage of the pleural effusion, and this is most important to achieve full lung expansion and adherence of the visceral and parietal pleura.

One can also inspect the pleural space, do any biopsies that might be indicated. Visual placement of the chest tube I think is very important. In the thoracoscopy cases that we have done and placed the chest tube visually, you can assure that it is in the proper position going up in the posterior gutter. Extra holes can be put in the chest tube, again to make sure that the pleural cavity is drained

after suction is applied.

One can then confirm talc distribution if talc is aerosolized or placed inside the cavity.

[Slide.]

For years, USP talc has been used in an atomizer, which I will show in a minute, to insufflate talc into the pleural cavity. It is very inexpensive. There are multiple suppliers around the country evidently. It is supplied non-sterily to hospitals, so that one must sterilize this and package this locally.

That has been a problem in a number of institutions in that there is no good standard on how to sterilize this bulk talc, and one requires an insufflator to do this. So the pharmacies must sterilize it, they must prepare it and package it, and then store it in their institution.

[Slide.]

This is the type of insufflator that has been used through a thoracoscope to blow in insufflated talc. The talc is usually placed in this either glass or plastic container, and then there is an air bulb syringe that would blow the talc through a thoracoscope.

[Slide.]

There are several methods to sterilize talc, dry heat, ethylene oxide, and gamma irradiation, and most

hospitals have these two available to them, and there is some debate about the exact temperature that should be used. One author recommended this 130 degrees centigrade for six hours. Some people recommend 12 hours. So the problem has been the standardization of this.

Ethylene oxide also was used for some time. I think the last I read it was going out of vogue. Gamma irradiation may not be available for most hospitals.

[Slide.]

The Sclerosol agent sterilized talc that we are discussing today is a can of 4 grams of Luzenac talc. This is from France. It is a very fine asbestos-free talc powder of very fine particle size. It is sterilized by gamma irradiation, and it is in an aerosol canister that has a propellant.

The talc is delivered through a catheter that comes out of the container at a fairly fast rate.

[Slide.]

This just shows the container that we have used, a sterile aerosolized talc, the plastic catheter that comes off here, and the talc can then be delivered through a thoracoscope.

[Slide.]

The technique that we have been using for approximately a year now involves thoracoscopy performed by

a pulmonologist in a procedure room. This is not done in the operating room. It is done under local anesthesia with intravenous sedation.

We usually have the patient come in, in the morning. Every patient has already had an established diagnosis and has agreed to this procedure. We do a thoracentesis of 3- to 500 cc's, and then just the opposite of what we have been taught for many years, we actually try to induce a pneumothorax.

We have the patient take about 10 deep breaths, and they will suck air into the pleural cavity. We then send the patient to Radiology where we confirm that they have a pneumothorax and that they have a large air space, so that we can safely put in the thoracoscope.

Then, in the afternoons we have been doing the thoracoscopy in the bronchoscopy room, I.V. sedation, topical lidocaine, pretty much similar to the type of anesthesia you would be using to put in a chest tube, being at the bedside, possibly a little bit more of this.

We drain the remainder of the fluid. If we need to, we obtain a biopsy. We then place the chest tube under direct vision, so we are sure that it is not in a fissure, that it is not overlying the diaphragm, and we have been using two cans of the Sclerosol, which is a total of 8 grams.

Essentially, every patient has been discharged after two to three days of drainage with this.

[Slide.]

This just shows the pneumothorax that has been induced in the outpatient clinic in a patient that we did. You can maybe see a little pleural thickening where there was metastatic disease to the pleural surface.

This is a very safe procedure, putting a thoracoscope in this type of a cavity, much different from the video-assisted thoracic surgery that is done in the operating room.

[Slide.]

This just shows the talc that is going through the thoracoscope. Here is what is bringing this in.

[Slide.]

This may not show up too well, but this is a patient who proved to have a mesothelioma, but this is an adhesion to the chest wall. The lung is adhesed up here, but certainly it is a large cavity that we could spray talc out into. We usually don't try to cut these adhesions at this point.

[Slide.]

This shows the talc after it has been sprayed in. You can see it has coated the area quite well. Some of this powder is so fine that you really can't see it too well on

the surface. It does concentrate in the areas probably where that plastic catheter was aimed at.

[Slide.]

This just shows again the fine coating of the pleural cavity by the talc.

[Slide.]

There aren't papers or a series on Sclerosol. It is mentioned in one paper by Colt and Dumon, who had an article in Chest in 1994, describing the development of this spray canister. In their article, they mention that they did treat 12 patients with malignant pleural effusions, and 11 out of 12 were successful. No specific follow-up is given. There were no complications although 30 percent of their patients did have a low grade fever.

We have recently submitted an abstract for the American Thoracic Society annual meeting in May on the first 11 patients that we did. Ten of the 11 were successful. The one patient required -- I think it probably would have been successful. We became impatient after five days of drainage and put some extra doxycycline in, and then his drainage stopped and he has done fine since then.

We had no complications of the procedure. Again, we noted transient fever in some of the patients in follow-up.

[Slide.]

I haven't reviewed all the papers and the literature that was submitted with this application. All of them concern the use of the standard USP talc, which has been available for years.

I think some of these questions probably have been answered, talc versus other pleural sclerosants. In general, in the papers and the literature, the success of talc is 90 percent or more, approaches, in some series it has been 100 percent successful.

Most of the other sclerosants in the series give you success rates anywhere from 70 to 80 percent, sometimes even lower than that. So I think most clinicians and the literature supports the fact that talc is probably the best agent for pleural sclerosis.

The problem has been getting talc into the pleural cavity. It does require a procedure. Thoracoscopy, I think is an ideal way to apply this to the pleural cavity, but it is a procedure that may not be available to a number of institutions.

There is still some question of whether the talc can be put in as a slurry or whether it has to be sprayed in as a scope versus tube. There is, I think, an ongoing study, a multicenter study, looking at this. I have certainly not seen any data one way or the other.

Again, with talc, there is always the question how

much to use, and I think that has not been settled. People say anywhere from 2 to 8 grams of talc. I don't think there is a correct amount at this point in time.

We tried to visually coat the pleural cavity as best we can. In our experience, it has taken two cans of the Sclerosol.

Whether this should be used in benign disease is a question. Certainly, classically, USP talc has been used for many years to produce pleural synthesis in patients with recurrent pneumothorax. We are not talking about that today, but it certainly has been used for a long time for that indication.

Are there any long-term effects of this? This has been studied primarily in patients who were treated for benign disease with pneumothorax. There are papers in the literature with 30-year follow-ups showing that talc pleurodesis does not cause significant restrictive lung disease, and now that we can be sure that there is no asbestos fibers in the talc, I think the concern about inducing mesothelioma, other malignancies, is not there also.

[Photograph.]

I don't know if you can see this. I didn't have a slide, but this is the snowstorm effect that takes place when you put this talc in the cavity. When you blow the

talc into the pleural cavity, it produces almost like a snowstorm effect and that the talc distributes very finely throughout the entire pleural cavity and deposits there.

I will be glad to take any questions.

CHAIRMAN BUNN: I think we will hold questions until you are finished.

Do you have other speakers?

DR. BEAMIS: No.

CHAIRMAN BUNN: So you are not going to review any of the literature studies? We will have questions then.

DR. BEAMIS: I will be glad to go over some of the articles that are in the briefing documents.

CHAIRMAN BUNN: Dr. Krook?

DR. KROOK: Being an internist at heart and working with chest physicians who don't necessarily enter into the OR, have you put in the aerosol talc on -- I guess I will use the word oncology units -- we presently use the slurry, but have you put the aerosol talc through just the chest tube, or has it all been under a thoracoscope?

DR. BEAMIS: We haven't put it through a chest tube, no. Our colleagues in France have said that you can do this, but I think if the chest tube has a significant amount of humidity in it or fluid, I am afraid that the talc would congeal inside the chest tube.

It possibly could be done, but we haven't studied

that.

DR. KROOK: I would anticipate the response rate or the decrease of fluid would be less, but on the other side of the coin, there is a cost issue, and it is less costly to do that. It will be interesting what happens here.

DR. BEAMIS: We have done it in the procedure room, not in the operating room.

CHAIRMAN BUNN: You mentioned that the goal of this is to relieve patients' symptoms, and when you say that the success rate is 90 percent, and in your own series, 10 out of 11, is the success rate the absence of pleural effusion or is it relief of symptoms? What evidence do you have that the patients feel symptomatically better after this treatment?

DR. BEAMIS: Well, we have done a thoracentesis before the treatment to know that removing the fluid has improved their symptoms of dyspnea, so that we wouldn't do this on someone who isn't improved with thoracentesis.

Sometimes patients have lymphangiectic disease or the lung involvement, so that even if you take the fluid out, you don't palliate their dyspnea.

The follow-up that we have done has been both symptomatic and radiographic. We have had patients come back at monthly intervals. Certainly, if you can keep the

fluid out, the symptoms are relieved. The main symptom is dyspnea, and I don't think there is any question if you can keep their fluid controlled, the dyspnea is relieved.

CHAIRMAN BUNN: Let me be more succinct. When you say 10 out of 11 cases, does that mean the patient has not had a recurrence?

DR. BEAMIS: I would say both. That is symptomatic and radiographic improvement, radiographic control of the fluid and symptomatic improvement in dyspnea.

CHAIRMAN BUNN: When you were talking to this company about developing something new, you mentioned that tetracycline was pretty cheap and was removed from the market. Why doesn't the company make tetracycline, would that be cheaper than talc?

DR. BEAMIS: I have never quite figured out why tetracycline was removed from the market. I think it has to do with the availability of products to make the tetracycline. It was made by one of the large pharmaceutical companies worldwide, and they just stopped making it.

CHAIRMAN BUNN: When you were talking about costs there, as Dr. Krook just mentioned, doing these procedures, whether it is VATS or thoracoscopy, putting the person in the hospital for three or four days is pretty expensive.

Do you have any comparators of both costs and

efficacy compared to, for example, draining some effusion in outpatient, putting something in as an outpatient compared to, you know, your procedure that you presented here?

DR. BEAMIS: I don't have that. I think the standard in my career has been to bring patients into the hospital, put a chest tube in, drain them for several days or more until the drainage decreases to the classic number has been 150 cc's per day, and then a pleural sclerosant is inserted into the chest tube, and then you drain them again for another X number of days until you get to that magic 150 cc's.

That, in my experience, usually is anywhere from a seven- to a ten-day hospitalization. Using this technique, there is no up-front hospitalization. The patients come in the same day, and they are in the hospital two to three days.

So I think compared to the standard tetracycline/chest tube approach, this is a much short hospitalization. I know now there is interest in especially the interventional radiology field to put a tube in a patient, send them home with a drainage until the drainage decreases, and then have them come in, and quote, "put something in."

I have heard anecdotal reports of that. I know it is done in some institutions. I am not aware of the results

of that or the costs.

DR. KROOK: There are two interesting comments. Since I live in the managed care world in Minnesota, we now are an intelligent people putting chest tubes in and sending them home the same day, and letting them manage at home. It is happening.

DR. BEAMIS: It is happening with pneumothorax.

DR. KROOK: It is happening in malignant pleural effusions also, and that is why I brought up the delivery system. So there is other things that come into play at least in the --

DR. BEAMIS: I guess I am not sure I would want to be sent home draining 5- or 600 cc's of fluid.

DR. KROOK: I hear you, but it's happening.

DR. BEAMIS: I know, but that doesn't mean it is the right way to do it.

DR. KROOK: Right. The second issue is I think there is two things here that are of interest. One is the substance which you used talc. Paul already brought up you could have probably blown bleomycin in there, you probably could have put mustard in the situation, and you chose talc probably for reasons you can say.

But the other is, as I said, the delivery system. It's different than what has been used before, so there is really two things that are together here, and it fits.

DR. BEAMIS: It is still an old technique. I mean in recent years, video thoracoscopy has become more popularized, but it is still a very old technique.

CHAIRMAN BUNN: Dr. Forastiere?

DP. FORASTIERE: I was wondering if you could say how many of those 10 success patients did not have reaccumulation of the fluid, say, within a three-month period.

DR. BEAMIS: None of them had fluid at the end of a month, all the ones that did well. By the end of three months, some of them we haven't had follow-up on. We haven't had to admit anyone for more fluid management. They have died of other aspects of their disease or have moved to other areas.

So we don't have at this point complete three- and six-month follow-up, but I know that at one month, none of the patients had reaccumulation of fluid, and we haven't had to re-treat patients for fluid management.

DR. FORASTIERE: So the symptomatic improvement --

DR. BEAMIS: That's right, but these patients were at the late stages of their cancer, so they may be dyspneic for other reasons three months after we do this procedure.

DR. FORASTIERE: One of the concerns or the problems with the chest tube aspect of it, from my understanding, is the distribution of the tetracycline or

whatever the slurry is, whatever you put in there, but this, it would seem, then, it would have this advantage from looking at the pictures of broader and perhaps even distribution on the surfaces.

DR. BEAMIS: I think so. There has always been that concern about moving the patient, especially, if there are adhesions, if you put something into the chest tube, is it well distributed, is the slurry -- I have seen CT scans of patients who have had talc slurry, and it all seems to be congealed at the base of the lung rather than distributed.

DR. FORASTIERE: So you think that is what you would attribute the higher success rate that you have?

DR. BEAMIS: I think so. Talc is an excellent sclerosant, and it seems that you can distribute it very well with this technique.

DR. FORASTIERE: Thank you.

CHAIRMAN BUNN: Dr. Gelber.

DR. GELBER: We are going to be asked to take information from the literature to judge the safety and effectiveness of this agent.

DR. BEAMIS: I didn't hear the first part.

DR. GELBER: We are being asked on the Committee to take information from the literature --

DR. BEAMIS: Yes.

DR. GELBER: -- to judge the safety and

effectiveness of this agent, and you have told us about your series of 11 patients and describing 10 as being successful.

It is still not exactly clear to me how you have defined success, but I wonder if you can help us to understand, in the papers that you have reviewed, whether consistent definitions of success have been applied, and whether the definitions for success rate through the literature might match yours, and if you can give us some insight into what success might mean.

DR. BEAMIS: I think most of the papers in the literature that I have seen, success has been evaluated at 30 and 90 days, primarily based on the chest film, the lack of reaccumulation of fluid.

Some of the studies also talk about control of dyspnea, but most of the studies have been based on the fact that the fluid doesn't come back radiographically.

DR. GELBER: Is there, in general, a time frame within which the fluid does not come back or it does come back?

DR. BEAMIS: I think if it hasn't come back by 90 days, it is unlikely that it is going to come back in that space. If you just did a thoracentesis on a patient without a pleural sclerosant, it invariably comes back within 30 days.

So I think if you can go 30 and 60, 90 days

without reaccumulation of fluid, I think you can attribute that very realistically to your therapy.

DR. GELBER: Is there any limited follow-up that you need for the patients?

DR. BEAMIS: In the literature, a number of the patients have died within the first few weeks, usually of their primary disease. So I don't think you could say that those patients were necessarily a success of the therapy. I think you would have to follow a patient for 30 days.

DR. GELBER: Just a few more?

CHAIRMAN BUNN: Let me just make one comment. This Committee recommended that the FDA approve bleomycin a year or so ago, and the studies there were based on the efficacy objective was a 30-day chest x-ray not showing a recurrence of the pleural effusion. That was the primary endpoint of the study which we accepted.

That study was purported to also show as a secondary objective a 90-day chest x-ray, and it was reported to this Committee that this agent reduced recurrence rate at 90 days, as well.

However, the 90-day data were not statistically valid in my recollection primarily because so many patients had dropped out, not because of recurrent pleural effusion, but because these are sick patients, and the median survival is often only three or four months. So many of the patients

had had progressive disease elsewhere, and had dropped off the study.

But the majority of what we were presented and the majority of things in the literature used absence of recurrence at 30 days and a chest x-ray as the primary study endpoints.

There is a national trial going on, and I think you alluded to it, and I believe the primary endpoint is also 30-day chest x-ray.

DR. BEAMIS: Pleurodesis, insufflation versus slurry?

CHAIRMAN BUNN: Dr. Dresler, do you want to tell us about the national study that is going on?

DR. DRESLER: It is a Phase III randomized trial looking at thoracoscopic talc versus insufflated talc, and there are several endpoints to it, but the main therapeutic one is looking at 30 days, but we are following the patients out for six months in order to see if we can't capture the three months or six months.

CHAIRMAN BUNN: Is it using this product?

DR. DRESLER: No, it is not. It was initially written that it could use the product, but because of some difficulty in obtaining the drug, there is many questions that come up that are pertinent to the study, and you need to, once the patient is randomized to go to the operating

room, they need to do it within 24 hours, so therefore, it is difficult to get access to the drug within those 24 hours because of current restrictions.

CHAIRMAN BUNN: Because it is not an approved drug yet.

DR. DRESLER: Right.

DR. BEAMIS: The best study in the ones that we submitted was a study by Hartman, et al., University of Indiana, and they were not concurrent randomization, but they did compare talc versus bleomycin and tetracycline. Their endpoint was at 30 days and at 90 days.

Talc was 97 percent successful based on the chest x-ray at 30 days. Bleomycin was 64 percent. In their study, tetracycline was quite low, only 33 percent.

DR. GELBER: Are the 11 patients you just reported, all of the patients that you attempted the procedure in?

DR. BEAMIS: Yes.

DR. GELBER: No dropouts from that number in your series?

DR. BEAMIS: No.

DR. GELBER: You also reported to us two additional studies, your own and another one that are not in our literature review.

Are you aware of any other people who might have

done investigations of this agent, that for one reason or another did not report out their results?

DR. BEAMIS: I am not aware. I think there will be some reported later on by the FDA group, but I am not aware of any other studies, and frankly, the paper by Colt and Dumon from Chest, I had thought that they were just describing the technique. I happened to take another look at it last week, and I saw they had mentioned the number of patients in there, but they don't mention a lot about these patients. They just said they treated 12 patients, and they were all successful.

DR. GELBER: Twelve is about the average number in most of the studies that are reported, so 12 is not an insignificant number when doing an individual study.

DR. BEAMIS: I think you do 12 patients, and you write a paper, I guess.

DR. GELBER: That is apparently what has been happening, yes.

CHAIRMAN BUNN: Just to clarify, the particular product, those two studies that he presented were with this particular product. The other studies in the literature was something almost identical, but they weren't necessarily sterilized with the gamma irradiation by this company, and they weren't necessarily in this particular type of can. They could have been insufflated with the old style thing

that he showed there.

DR. GELBER: I see. So the data that we have reviewed are with a different product.

DR. BEAMIS: That's right.

DR. GELBER: But supposedly the same --

CHAIRMAN BUNN: More or less the same product, just minor differences, right.

DR. GELBER: So the additional information that you have just shown us might be even more important.

CHAIRMAN BUNN: It is with this particular product, right.

DR. GELBER: For this particular product.

DR. SWAIN: In the Colt study and your study, were any of the patients breast cancer patients who received systemic treatment also at the same time?

DR. BEAMIS: We did have some breast cancer patients. I don't know about the Colt study. We had two breast cancer patients. They had failed systemic therapy already.

CHAIRMAN BUNN: Could I ask the president of the company a couple of questions?

This product you get from some mine in France, and it is stated that there is no asbestos in here. We are pretty naive on the Committee here, we don't know much about manufacturing, and so on, but how do you know that there is

not asbestos in there, and how do you know that what the shovel digs out of the mine is the same from one canister to another?

MR. ABRANO: First of all, it is an interesting question, but Talc Luzenac probably has the purest mine in the world located in France. It is well known. They have a U.S. distribution office here in Denver, Colorado.

The talc that is made for this procedure, the particle size is very well regulated, and it has been chemically tested for asbestos-free in Colorado through their office and also Talc Luzenac in Europe. They are the largest supplier of talc in the world.

I have never personally visited the mine, but I understand from people who are in the business, have indicated that their mine is very pure.

CHAIRMAN BUNN: So someplace, though, somebody is testing it for asbestos and purity.

MR. ABRANO: Yes, it is done in France, and also there is a certain number that is attached to this talc, and this particular talc is also used in food processing in the United States. So I would presume that the testing of the asbestos has been regulated by the FDA since it is used in food.

CHAIRMAN BUNN: Obviously, a concern would be that this could cause mesothelioma or some other pleural disease.

There wasn't much on the long-term side effects other than it could be an issue.

Are you aware of any long-term complications from the use of this, either another malignancy or infections, empyema?

MR. ABRANO: I am not aware of any infections, and it has been used in Europe for years in an aerosol container, and we have asked about any clinical papers indicating any irregularities at all.

DR. OCHS: Could you talk about the eligibility of the patients to get the talc? Is this primarily a palliative approach in Europe?

DR. BEAMIS: Oh, yes, it is definitely a palliative approach. Talc is not a chemotherapeutic agent. People that have died after talc pleurodesis, that have had post-mortem examinations, you can demonstrate that there are tumor cells still within the pleural cavity, within the area that is fibrosed.

So this is purely palliation. Certainly, if there are other therapies that are available to the patient, we would encourage them to have that, but many of the patients with breast cancer have already failed systemic therapy. The lung cancer patients, in general, they have failed other therapies, too, or they just don't work as well. This is purely local therapy for palliation.

DR. OCHS: I think that needs to be clearly stated because I saw in most of the studies, you have elderly patients, but from personal experience, having had a teenager with a pleural effusion that was given talc, who turned out to be a newly diagnosed lymphoma patient, and certainly in teenagers and young adults, where highly curable lymphomas oftentimes the presenting symptom will be a pleural effusion. I think that needs to be very clearly understood.

DR. BEAMIS: I agree it is palliation. In some ways that is one advantage of the thoracoscopy in that you can be assured of the diagnosis. Patients often present with a pleural effusion. If you do a thoracentesis, you might get endocarcinoma cells and just stop there, but we have had two of our series had that diagnosis, and on thoracoscopy proved to have mesothelioma.

So I think the systemic therapy is much different in endocarcinoma of the lung versus mesothelioma, so I think it is important for one to know what the diagnosis is and to make sure that they have benefitted from appropriate therapy for that primary disease.

CHAIRMAN BUNN: I am going to ask you a question that the FDA usually asks us. We have to approve or recommend approval or disapproval based on whether a drug is safe and efficacious, and we are supposed to determine

whether it is safe and efficacious based on some study that is deemed to be an adequate and well-controlled study.

For your own information, historical control can be sufficient or well controlled, but in your own view, you have obviously read these papers, obviously, they range in size and quality considerably, do you in your own opinion believe that some of these trials are adequate, well-controlled trials?

DR. BEAMIS: I think Hartman's trial is the best. Some of the others I would say probably adequate. Hartman's, I think is very good. Again, it is based on historical controls.

I guess in my own mind I do feel that talc has stood the test of time. I do feel that it is the best agent. The question of delivery and availability of thoracoscopy or getting into the pleural spaces will remain even if this product is approved.

I think the safety issue has been, in all these series, I think pretty well proven over the years. Many patients have fever. It appears not to be related to infection.

Although empyema is a problem, and it has been a problem with the talc that is available over the years, I know before we started using this agent, we had some USP talc that was sterilized in our institution, and it had a

number -- over a six-month period -- a number of empyemas that we could never absolutely prove it was from the talc, but when we stopped using our home-sterilized talc, the empyemas didn't happen.

So I think there is always a question of sterility of the agent, and it is very localized, there are no standards, there appears to be no systemic distribution of the talc when it is put in the pleural cavity.

There have been some animal studies that have shown talc in other organs, but I think as far as damage to other organs of malignancy, restrictive lung disease, all these safety issues, I think have been pretty well shown in these studies.

DR. GELBER: Thank you for the answer to that. That was very helpful. I wonder what aspect of the Hartman study in particular, if you have any ideas you can give us, that selected that one as the one that you would say is the most adequately controlled.

DR. BEAMIS: I think it had the largest numbers, for one, and it is a well-respected institution. They had had experience in all of the various areas. They were good at thoracoscopy. I think they did the technique well. I happen to know one of the authors. I am pretty sure -- but I think the study was done correctly, having talked to them about this, I think primarily it is because it has such

large numbers compared to other studies. It is more than 12 patients.

CHAIRMAN BUNN: If there are no other questions, thank you very much.

We will go on to the FDA presentation by Lydia Larson.

FDA PRESENTATION

DR. LYDIA LARSON

[Slide.]

DR. LARSON: Good morning. I will be presenting the review on NDA No. 20-587, Sclerosol, which is sterile aerosol talc. The sponsor is Bryan Corporation.

[Slide.]

The proposed indication for Sclerosol is for the treatment of malignant pleural effusions secondary to malignancies having spread to the pleural space.

[Slide.]

What I would like to do is take a moment and just go over the trilaminate structure of talc. It has alternating silicate and magnesium sheets, silicate and magnesium, and then silicate again. And it acts as a lubricant due to its planar properties, as you can see across the difference crystals.

Now, cation impurities can result from cation substitutions in the magnesium position. As I mentioned

earlier, this where your magnesium is positioned in the crystalline structure.

These cation substitutions can consist of calcium, aluminum or iron. Now, other contamination, for instance, asbestos, can occur depending on where the product is mined.

[Slide.]

Talc is documented in the literature as early as 1935, when Bethune reported the first use of talc to create pleural adhesions. Then, in the fifties, there was documented use in England, as well as Europe, of talc being used as a pleural sclerosing agent via poudrage, which is insufflation or slurry.

In the sixties, talc (poudrage) was reported in the U.S. as effective management of malignant pleural effusions, however, it was used sporadically at that time, and that was mainly due to the fact that tetracycline was available then.

Then, injectable tetracycline no longer became available, and there was increased use of video-assisted thoracoscopy, both for diagnosing and treating pleural diseases, and so poudrage became more viable, which led to the increased use of talc.

[Slide.]

There is no approved talc product for the treatment of malignant pleural effusions, in fact, USP

standards at this time do not require that talc be asbestos-free or sterile. They are moving toward international harmonization with the British, European, and Japanese pharmacopeia.

In October of '93, the FDA Centers for Devices and Drugs determined that talc could be approved for the treatment of malignant pleural effusions if certain conditions were met, mainly that it be asbestos-free and sterile.

In March of '94, as a result of this, CDER did send out to all talc distributors a letter inviting them to submit an NDA, and Bryan Corporation was one of the few companies that did submit an NDA.

Now, the Federal Food and Cosmetic Act does allow a literature-based NDA, so the decision was made that it would be acceptable, Bryan's NDA would be acceptable for filing, however, it is subject to the criteria of adequate and well-controlled trials or studies.

[Slide.]

As I mentioned, this NDA is literature based, and the three databases that the sponsor used were three of the largest known today, namely, Medline, Biosis, and Embase. Searched parameters were malignant pleural effusions, talc pleurodesis, and chemical pleurodesis, and their results were nine controlled trials (6 articles and 3 abstracts),

consisting of talc compared to chest tube only concurrent control, that was one study; five active concurrent controls, and three historical controls.

So the Agency verified the search and added the next three largest databases, which are Cancerlit, International Pharmaceutical Abstracts, and Derwent Drug File, and found an additional three controlled trials, however, they are abstracts.

They consisted of talc compared to active concurrent control, that is two studies, and one study is a historical control.

So as you see it here, we have 12 studies, of which 6 are articles and 6 are abstracts. However, one of the abstracts that the sponsor submitted was an abstract by Hartman in 1992, and that was a preliminary report of Hartman's 1993 article. Therefore, we took it out. In fact, that study was reported at the 72nd annual meeting of the American Association of Thoracic Surgery in Los Angeles, California, back in April of 1992.

So when you see this presentation, you are going to notice that Hartman's abstract is not going to be included, and that is why.

[Slide.]

What I am going to do now is go over the articles first, and then I will move on to the abstracts.

This is the study design of the concurrent control articles, and I just wanted to orient you to these tables, because we are going to be seeing quite a few, and they are all set up the same.

On the lefthand column, you will find the author and patient numbers per arm, study design, whether stratification did take place, treatment received and dose, and the tumor type if it was reported.

I did want to state ahead of time that in all these articles except for one -- and I will get into that later -- a single dose was administered, whether it be the control arm or the talc arm.

Now, in all four of these articles, they all four were prospective and randomized. Two of the articles did stratify according to the presence or the absence of metastases requiring systemic chemotherapy.

The treatment received was via poudrage in three of the articles, and one was via slurry, and the tumor type in three of the articles was breast cancer, and in one of the articles, in Sorensen's '84 article, it was a variety of tumors, which included ovarian, prostate, mesothelioma, breast, GI, and lung.

Now, in Sorensen's article, this was the chest tube drainage with talc compared to chest tube drainage alone, and they did control for the chest tube drainage time

equally in both arms, which was 72 hours.

I also wanted to mention that the tumor type in Sorensen's was reported in both arms together, so there was no way of separating tumor types.

In Hamed's article, '89, actually, one patient received bleomycin in one lung and one talc in the other, and then there were two patients that received bilateral therapy.

I also wanted to quickly go over the doses of the control arms. In Fentiman's '86 article, tetracycline was administered at 500 milligrams of slurry. In Fentiman's '83 article, mustine was administered at 15 milligrams. In Hamed's '89 article, bleomycin was administered at 1 milligram per kilogram.

[Slide.]

This particular slide is a characteristics of success across the trials. So you have a number of evaluable patients per number entered, definition of evaluable patients, definition of success, method of evaluating success, success in evaluable patients, the results, an intent to treat analysis -- this is the Agency's analysis -- response duration, and symptom relief.

In Sorensen's '84 article, definition of evaluable patients was these patients, their lungs had to re-expand by 72 hours, otherwise, they were no longer considered

evaluable. As you can see, definition of success throughout these four trials was no fluid reaccumulation on all follow-ups. Follow-up time did vary, though, anywhere from three months to 12 months, and in Hamed's, they did say on all follow-ups.

Method of evaluating success across the four trials was by chest x-ray, with three of them identifying it at one-month interval, and then two articles did evaluate success every three months after that.

As far as success in evaluable patients are concerned, in the talc arm, we had a range of anywhere from 90 to 100 percent, and in the controls, the range was anywhere from 33 to 58 percent.

Now, if we were to apply an intent-to-treat analysis, the results would have ranged anywhere from 61 to 78 percent in the talc arm, and 39 to 43 percent in the control arms. As you see here, we were not able to apply an intent-to-treat analysis in this particular study, Hamed's '89 study. The reason for that is that once they did report their patients, after that, their success rate was reported as procedures, and there was no way of assessing how many patients actually did experience success. So an intent-to-treat analysis was not possible at that time from that point on.

Response duration was, in Sorensen's trial, until

death in both arms with 10-month median duration, 12 months in Fentiman's '86 trial, 6 months in Fentiman's '83 trial in both arms or until death, and it was not provided in Hamed's '89 article.

Symptom relief was described in Sorensen's '84 trial. It was 9 out of 9 in the chest tube and talc arm, and chest tube only arm experienced 6 out of 7, and those are evaluables or rather success patients. Symptom relief for the talc arm was described as relief of dyspnea, and in the control arm, they defined it as subjective improvement, but they didn't describe it any further.

You have a small fraction here in Hamed's '89 article, and basically, that is to remind me to tell you that 2 of the patients in the bleomycin group, 2 of the patients that failed on bleomycin went on to receive talc, and 1 out of the 2 did experience relief of symptoms, however, they didn't describe it any further than that.

[Slide.]

On this slide are historical-controls articles. In addition to the possible publication biases, the controls are historical in nature and further bias can be introduced. In Adler's study, '67, the study was retrospective in nature with a historical review group. They weren't really historical controls. The medication that was used, the sclerosing agent that was used, was a variety of agents to

include thiotepa, nitrogen mustard, radioactive phosphate, radioactive gold, quinacrine.

As you can see in both studies, they did administer talc via poudrage, and there was a variety of tumor in both studies, tumor types, that were actually accepted onto the study.

In Adler's study, the tumor type in the talc arm consisted of mesothelioma, bronchogenic carcinoma, and breast. In the historical review group, the tumor type consisted of breast, lung, lymphoma, and ovarian.

I did want to mention that they did compare age, tumor type, response, chest tube drainage time, also pleural fluid, amount of pleural fluid drained, but they made no conclusions and no comparisons beyond that.

In that particular study, the patients were from a previous multicenter study that had taken place at the investigator's institution, which was Buffalo General Hospital, and also another institution, which was Roswell Park Memorial Institute.

Basically, the objective of this study was to introduce a new aerosolized unit of talc, and they actually reported experience with four patients in that particular study.

Now, in Hartman's '93 article, this was a prospective nonrandomized study, and the patients that

participated were from a multicenter study, but it was unclear if the principal investigator's institution was one of them.

The dose administered in the control arm consisted of either bleomycin or tetracycline at 60 units or 1 gram respectively, and the tumor type consisted of lung, breast, or ovarian in the talc arm, and they just stated that in the control arm, the tumor type was the same.

[Slide.]

In Hartman's trial, there were some patient number discrepancies. They had higher success rates at 90 days versus 30, and didn't further describe that, but I wanted to -- excuse me, let me jump back a moment.

They evaluated their patients at 30 days and at 90 days, and that is why you have two different figures here, and also they went ahead and reported success rates at both time points for talc, as well as bleomycin, as well as tetracycline.

Definition of success was defined in Hartman's article as no fluid reaccumulation, and the method of assessing success was via chest x-ray at one month and then every three months after that. Response duration was not reported in either trial.

[Slide.]

Now, there is much less information in these

studies because they are abstracts. Remember I mentioned earlier that all of the studies administered one dose. There was one study, Muir's '87 study, where talc was compared to doxycycline, where they administered more than one dose of the control drug, and it was slurry, repeated lavage drainage at 20 milligrams per kilogram.

They actually did this until "pleural drainage was at a minimum," and they didn't describe it any further. However, four of the studies were prospective in nature, three were randomized, and in Jones '89 study, the patients were allocated to the tetracycline arm if they were identified as a high operative risk patient.

Poudrage was the method of administering talc in all four of the active concurrent control studies. Tumor type was identified in one. In Lantos' study, it is uncertain whether this study was prospective or retrospective in nature, however, they did have a control to compare talc to.

[Slide.]

Evaluables were described in two studies as survival greater than or equal to one month post-procedure. In Boutin's '85 study, the patients had to survive for six months, and in Jones', they did not describe what an evaluable patient was, but as you can see, success in the talc arms in these four studies ranged anywhere from 92 to

100 percent, and in the controls, it ranged anywhere from 53 to 95 percent.

Success was defined in two studies. Method of evaluating success was described in one, response duration described in one study, and symptom relief was not identified in any of these four abstracts.

[Slide.]

In Lantos' study, '94, it was unclear whether these were actually patient numbers or cases, because they used cases and patients interchangeably throughout the entire abstract, but as you can see, success in the talc arm was 96 percent, and in the controls being oxytetracycline and doxycycline, of 87 and 92, respectively.

[Slide.]

There were also 24 noncomparator studies that were submitted by the sponsor, and this is the results of efficacy regarding these 24 studies. Total patient numbers were 1,756, which included 1,548 malignant pleural effusion patients. There were also some benign pleural effusion patients, pneumothorax patients, and one study, there was no way of separating patients out. They reported them as benign pleural effusion, pneumothorax, or other, to include empyema or chylothorax patients.

Response data per procedure, there were 1,535 evaluable procedures of which, as you can see, there was a

90 percent success rate in all the reported malignant pleural effusion patients, and a 93 percent success rate in a study where malignant pleural effusion and benign pleural effusion, I was unable to separate the two out.

Definition of success was provided in 9 studies, and there was no reaccumulation of pleural fluid for a minimum period of 30 to 90 days.

I did want to mention one thing. I did say that there were 24 articles, however, 3 articles were taken out because there were 3 articles that were a series of articles, so 2 were taken out for fear of double counting, and they did report that it was a series of articles, so we left 1 in, and 2 were taken out, and then 1 article we had to take out because patient numbers were reported as greater than 40, success rate was reported as greater than 100 percent. So that particular article was not counted in the final analysis.

[Slide.]

Now, we have no way of assessing the completeness of reporting. This is a summary of safety from the published literature, and this is to include controlled, as well as noncomparator studies.

As you can see, fever and pain were the most frequently reported adverse events. About 23 percent of the patients did experience fever and pain. Following were

adverse events including infection in nature, respiratory disorders, and as you can see, the range is anywhere from 1 to 0.09 percent.

[Slide.]

This is the continuation of the previous slide. Also, some of the adverse events that were reported were cardiac in nature, and then there were some that we went ahead and put under Other. As you can see, the range in those, the reporting range was 0.2 percent to 0.09 percent.

[Slide.]

What I wanted to do was focus on the serious of life-threatening toxicities that were described. This is from controlled and uncontrolled trials. There were four reported cases of adult respiratory distress syndrome and two were fatal. They were at a dose of 10 grams, and it was delivered as a slurry.

Four cases of pulmonary embolism were reported, and these patients had an underlying malignancy, one resulted in fatality. There were three cases of myocardial infarction. One was fatal. This was in a patient with severe cardiac disease, that died about three months after receiving talc pleurodesis. The patient had received quinacrine first and then talc bilaterally within a few days of one another.

There were two cases of asystole reported, and

this was while under general anesthesia with complete resuscitation.

[Slide.]

As far as clinical experience with Bryan Corporation's talc, you have already heard Dr. Beamis' presentation, and I don't want to bore you with the results of Colt and Dumon's study, because Dr. Beamis was very thorough in describing it.

While this particular NDA has been undergoing review, Bryan Corporation has made their product available through individual patient INDs, and I am going to go ahead and describe those results at this time.

The Agency, in order to gain more experience with Bryan's product, went ahead and collected data on these individual INDs.

[Slide.]

There were 69 individual patient INDs that were issued for malignant pleural effusion from May 18, 1995 to October 22nd of this year, and that is when we censored the data, so that we could have a one-month follow-up.

Out of those 69, we actually received results on 38 patients, so we got 38 patient results back, and 3 were lost to follow-up, there were 7 deaths, and 3 failures due to no lung re-expansion.

So out of those 38, we had 30-day follow-up on 25

patients, 21 of which had no recurrence, 1 is unknown, and 3 patients had recurrence. So then out of those 21 patients, we received 12, 60-day follow-up forms back, 2 deaths, 1 recurrence, and 9 no recurrence, and then out of those 9, we received 5, 90-day follow-up forms back, 4 no recurrences, and 1 recurrence.

The dose that was used in these individual INDs was 1 to 2 cans, which would be 4 to 8 grams.

[Slide.]

In conclusion, there are both strengths and weaknesses to this NDA. The weaknesses are that it is literature-based, therefore, there could be publication bias, there was incomplete data, and it was difficult to maintain quality assurance.

Sample sizes were small, and in many situations, there was no way to tell the source or the purity of the talc that was used. There was variability and unspecified dose of talc, and as you know, achieving pleural synthesis is procedure-dependent and may impact on adverse experiences, as well as success.

I want to go back to variability of the dose. What I did very quickly was I summarized the doses that were used in the controlled and uncontrolled trials, and what I am going to do is go over the controls first.

There were four studies that actually reported a

dose in the control trials. Two reported a dose of 5 milliliters, did not provide a concentration. One specified a dose of 3 to 10 grams, and one study they used 10 grams.

Then, in the noncomparator studies, there were 10 that reported a dose of talc. Seven studies reported using 1 to 5 grams, three studies reported using 10 to 10 1/2 grams. As I mentioned earlier, in our experience, the individual patient INDs, it was anywhere from 4 to 8 grams.

Now, as far as the strengths are concerned, we did have four prospective randomized trials that were reported. There was a response definition in those four, with objective measure via chest x-ray.

There was consistency of results over time, institution, and despite different comparator arms. Sclerosol is asbestos-free and it is sterile, therefore, this would be an option for treatment. And it appears from the preclinical data and the clinical experience today that talc is not systemically absorbed.

Are there any questions?

CHAIRMAN BUNN: Questions? Dr. Krook.

DR. KROOK: I really don't have any. I think it is a nice review, and I thank you.

CHAIRMAN BUNN: Dr. Ingle?

DR. INGLE: Obviously, the Agency has considered the heterogeneity of talc issue. The two randomized

clinical trials of talc that are ongoing at the present time, the two intergroup studies, as I remember in seeing those studies, there is a variety of talc preparations that are permissible for those studies.

One assumes that the findings from those studies will be applicable to talc in general, I guess the principle all talc is created "approximately" equal, is that a reasonable statement, that the clinical trials that are ongoing will, in fact, relate to this product?

DR. LARSON: I am not certain of that. Dr. Martin or Dr. Justice?

DR. MARTIN: Since we are using the body of literature that has used a variety of talc to support a particular product, that by extension, we would have to assume that the variety that is being used in the two intergroup studies could also be applied.

CHAIRMAN BUNN: Would the FDA recommend to the people doing those studies if this product should get approved, that perhaps this product should be incorporated into those studies?

DR. JUSTICE: We have suggested that already.

CHAIRMAN BUNN: It would seem reasonable.

It is interesting that there are so many abstracts that haven't been published, and these abstracts were largely reported 10 years ago or so.

Do you have any idea what happened to these abstracts, why they weren't published?

DR. LARSON: As I said earlier, our literature base, when we did our search, we actually used six of the largest literature bases that we know of today, we came up with about 400 articles, and this is it.

CHAIRMAN BUNN: I personally, I mean it might have been interesting to call them, but I mean I personally wouldn't view these abstracts as is, I would rule them out as being adequate and well controlled, because they have not been peer reviewed.

DR. GELBER: Could I make a comment on that?

CHAIRMAN BUNN: Yes.

DR. GELBER: It relates to one of the things you mentioned, which is publication bias, and it was an interesting example looking at the studies that were reviewed, that the largest difference was in the historically controlled, and the next largest were the randomized trials that were able to be published, that editors decided were important enough, and if you look at the abstracts that haven't been published that we saw, the differences were less remarkable.

So there might be an example right here of the tendency to be as an example of publication bias, and one of the reasons not to push those abstracts forward is they

weren't as interesting as the ones that the editors decided to accept, so people lost enthusiasm for publishing. That, by definition, is publication bias.

Your point about the question of going to the authors of the abstracts, and even the published reports, to find out do they have information about other series that were done, or what other information to corroborate what is already in the literature, I think would be a pretty trivial thing to at least start to try to do, and get some more information about some of the studies that were inadequately reported.

CHAIRMAN BUNN: Dr. Ozols.

DR. OZOLS: Of the 69 individual patient INDs, were those done out of many institutions? The collection rate on that data is pretty low. About half of them you received the forms back.

DR. LARSON: You mean as far as the response rate that we got back?

DR. OZOLS: Right, returned forms.

DR. LARSON: We were rather disappointed also. It was only 55 percent of what we actually did send out.

DR. OZOLS: How did people know about the availability, how representative are these 69 patients?

DR. LARSON: I am going to defer that question to Dr. Martin.

DR. MARTIN: I am not sure how they knew about it. I assume they called Bryan Corporation first and then they contacted us to issue an IND.

That 55 percent of the forms that were returned was despite numerous phone calls by our project manager, Debbie Catterson, who called them repeatedly and asked for the forms with chest x-rays. So I would say that probably without that diligence, we would have gotten 10 percent of the forms, even though initially, when we issued the IND, we sent them the forms and asked them to sign to show that they would follow through with all of the 90-day forms.

CHAIRMAN BUNN: But that is not unusual, right, for treatment IND. Does the company want to say how people found out about these treatment INDs, did you make this known in some way or somehow people just found out?

MR. ABRANO: I would believe that people became aware of the talc through the article that was published by Dr. Dumon and Dr. Colt, and it has certainly been word of mouth. I mean we receive a lot of calls daily waiting for, you know, inquiring about the approval or where we stand with the talc.

DR. OZOLS: But this is not just one or two institutions, these 69 patients are throughout the country?

MR. ABRANO: Yes, they were throughout the country. They are at various institutions, and if they did

one institution at first, they were using the same IND, but that was eliminated, and if they called in again, they had to use a new IND.

DR. MARTIN: It represented, to my recollection, at least 20 different places, oftentimes private practice and occasionally some tertiary referral centers from the intergroup studies.

CHAIRMAN BUNN: That was quite a new review that you did. It obviously took a lot of work. This might not be fair, but you are going to ask us whether we think any of these are adequate. So I will take the liberty of making a little editorial comment, and then asking you a question.

Certainly, Dr. Sorensen's article was prospectively randomized, gave a dose, gave a definition of efficacy, reported data on that efficacy, which included both chest x-ray and symptom relief.

Certainly, Dr. Hartman's article also gave a dose, had a definition of efficacy, reported the efficacy at various time points.

Would you consider those particular articles to be adequate?

DR. LARSON: Slide No. 7, please.

CHAIRMAN BUNN: You anticipated my question.

DR. LARSON: This is an opinion.

CHAIRMAN BUNN: That is what I am asking for.

DR. LARSON: These, in our opinion, are what we thought were adequate and well-controlled trials, the reasons being, number one, they stated an objective, mainly to prove talc superiority in the treatment of malignant pleural effusion; number two, these described their trial design, and in Sorensen's, it was rather nice, because they went ahead and also controlled for chest tube drainage time equally in both arms.

Stratification did take place in two of the studies, so they did attempt at stratifying patients, and the tumor type was also described. I realize that the dose was not given, but it was available in enough of the studies, we felt, where it actually wouldn't make a difference in these particular four studies.

They also described the treatment that was actually given as far as talc is concerned and the control arms.

CHAIRMAN BUNN: Well, you seem to have gotten some questions on this. Dr. Temple.

DR. TEMPLE: The thing that you can't tell in the literature usually is what happened to all the patients, or you often can't tell. In a certain sense, the limited data we got from the IND is better in that respect, because we discovered that a number of patients died, therefore, they probably weren't in the list of people who were evaluated,

and some of them were lost to follow-up, and they probably weren't included. Usually, the literature is not so good at that.

Do you have any impression from your review of the studies whether that is addressed in them? Can you, for example, tell how many people were given the therapy and then how many patients they actually had data on or lived long enough to reach the 30-day endpoint, and things like that? That is just one element of whether a study is well controlled.

DR. LARSON: Yes, in these particular four studies, they did provide information on how many patients were evaluable per patient center, and if I may veer off just for a moment also, they also defined evaluable patients, defined success and method of evaluating success, and reported success in those four studies.

Even though Hamed's trial did report procedures, they did report something there, and they attempted at providing information regarding response duration. Also, three of the studies, we were able to apply an intent to treat analysis.

CHAIRMAN BUNN: Dr. Gelber.

DR. GELBER: I have a comment and then a question. The comment is thank you very much for an excellent review. I must say that if the Committee decides to vote approval,

that it would be largely based on your efforts and the efforts of the Agency, and this is another example of where the Agency is not the bad guy in terms of the drug approval process.

I also have to say that I am paid to be here by the FDA.

[Laughter.]

DR. GELBER: The question relates to your next to the last slide, and it is more something I am curious about, because you did show the individual patient INDs.

DR. LARSON: Oh, yes, the flow chart?

DR. GELBER: The flow chart.

DR. LARSON: No. 19, please.

[Slide.]

DR. GELBER: Now, admittedly, there is a lot of missing data there, but if these were the data we were to look at, what would the success rate be?

CHAIRMAN BUNN: Thirty days, 21 out of 24.

DR. LARSON: Thirty days.

DR. GELBER: Twenty-one out of 25.

CHAIRMAN BUNN: Twenty-one of 24, or 21 of 25, depending on --

DR. INGLE: The issue here is the 55 percent of the forms returned. Is that a reflection of the drug, is it a reflection of the FDA? My question is this. It seems

strange to me, if I had used an agent under IND, and the FDA called me a couple of times, I think I would respond, and this seems fairly casual, for 45 percent of the patients, for you not to have any forms.

Now, I think you have to have your denominator be the 69 patients. So I would like the FDA's help on that question, is this a reflection of the drug or what?

DR. TEMPLE: You fundamentally can't know the answer to that. I mean some people are more in awe of us than others.

[Laughter.]

DR. TEMPLE: We are grateful for your attitude, and wish it were more widely shared.

I don't think it is safe to assume that there was a lack of success in those. I mean the most conservative impression would be, okay, the denominator is 69, and there are 21 no recurrences, so the success rate is 33, but you would know that that was almost surely an underestimate, but it is one way of describing an conservative analysis.

But my guess is that failure to report has more to do with how busy people are.

CHAIRMAN BUNN: I asked Alison about this before, and this is typical, and I can just tell, you know, from my own institution, this comes up a fair amount. In the cancer center, the data managers are asked to do this, and then

they complain, and they say no one is giving us any money to get these chest x-rays and fill out these forms, and why are we doing this.

You say you are doing this because you have an obligation to do it, do it, but I can guess that many places, they don't have a cancer center director telling them that they have to do this, and they had better do it or they are not going to have a job, you know, there is not a lot of incentive to return the data and get the chest x-rays, and you are not getting paid.

I would guess this is actually pretty good data collection.

DR. MARTIN: Also, we had another methodologic problem, which is oftentimes it was a thoracic surgeon or a pulmonary doctor doing the procedure, and they released care shortly after that procedure, and then we had to track down the primary caregiver.

DR. GELBER: Even beyond that, I mean if you take the 38 as the denominator, then, who do you consider successes, what do you do with the 7 deaths, are the 3 no lung re-expansion, failures of the procedure, and then the final issue is do you stop at 30 days or do you want to look at recurrences beyond that point, failure to maintain.

DR. JUSTICE: I don't think we have enough data to answer the question precisely, but I think, at least in the

literature, early deaths from disease are not considered failures, they may be considered inevaluable.

If you were going to be consistent with the literature --

CHAIRMAN BUNN: If you were doing it time to recurrence, those people would be censored.

DR. GELBER: The point is, in fact, that intent to treat is for one issue, and as you said, dropping out the patients who died early, as long as it is recognized that the success percentages are conditional percentages in terms of the usefulness of the therapy, then, at least if that is stated up-front, those are where the 90 to 100 come from.

It doesn't seem to me from the literature that 90 to 100 percent of the patients for whom you tried this procedure were successfully treated with it.

DR. DELAP: The only other thing I would add is please look at the data at the top, that it is from 5-18-95 to 10-22-95. This is a fairly recent innovation on our part, and it is quite likely that we will get some further forms returned on some of those patients, particularly for the longer periods of follow-up where many of the patients probably aren't even out that long yet.

CHAIRMAN BUNN: I think it is worth pointing out for the public who are here that oftentimes there is a misperception also that experimental agents or

investigational agents are not available to the public, and oftentimes these agents are available to the public through this mechanism, which is often used to provide drugs to people, and it is a lot of work for the FDA and the people that do it, but it makes these agents available, and people should be aware that the consumer does often have access to agents even before they are approved by the FDA with the FDA's concurrence and with a lot of work by the FDA.

Are there any other questions?

What is the sense of the Committee? Do you want to go to the questions or do you want to take a five-minute break? Go to the questions? Okay.

DR. TEMPLE: I just want to say a couple of words about the use of literature. I think actually he has covered much of this.

As people probably remember, we have expressed a lot of interest in getting new uses of drugs into the label where possible, and have said that we are at least prepared to look at the literature as a basis for those reviews. We have never said that that is always going to win, but we have said we would take a look.

While this isn't a new use exactly, it is a sort of validation of an established use, a lot of the situation is the same.

The first question is why it is an issue. Most

physicians learn about things from literature and trust it, believe in peer review, and it is sort of the major method of communication. Why would we be so skeptical? The answer is the literature is usually very incomplete with respect to details and methodology, with respect to what happened to patients, who is included, who is not, and those kinds of things, and we learn this every day when we compare the reports of studies with what we see, and we have many instances in which there are a significant disparity.

So we have a fairly strong, I would describe it as experience-based preference for access to underlying data, and we are aware of publication bias. Nonetheless, despite all that, we certainly legally can, and on a number of conspicuous occasions have, relied primarily or even entirely on a literature-derived database for approval.

Some of the examples are fairly conspicuous. The approval of secretin for diagnosis of pancreatic function was actually based entirely on the literature with no raw data at all. The literature was absolutely fast. Secretin was the first hormone, and people were sort of excited about it. There were well over a thousand publications describing what it did in animals and humans, and the approval was based entirely on that.

The approval of propranolol for the treatment of angina was actually based on the literature also. There

were data submitted to us, but they were crumby, and the better data were in the publications. There were probably 20 controlled trials showing the effectiveness, so there was a certain mass to it.

A controversial approval some years ago of imipramine for the treatment of enuresis in children was entirely based on the literature. The approval of nitroprusside for treatment of bad hypertension included a 22-patient multicenter study, and a lot of vast literature showing that nitroprusside lowered blood pressure.

Recently, actually, an important approval of coumadin for use in the post-infarction setting was at least partly based on a paper published in Hong Kong actually.

It is worth thinking about what makes literature persuasive versus what makes it unpersuasive. One critical element is redundancy. When you can't check the actual data, a great deal of consistency, including no exceptions, is, relatively speaking, reassuring, and in certain instances, data without a control group, but where you feel you know what the natural history of the disease is reasonably well can add to the accumulated sense.

It also helps to have access to some data. On a number of occasions we have relied primarily on the literature and pursued one or more studies to reassure ourselves that you could do that. So actually, to a degree,

even the small data we are getting from the INDs is probably helpful.

It is easier to believe in data that shows a very robust effect. I mean 90 and 100 percent response rates are more persuasive than 20 percent response rates.

It also helps if the measurements are not too exotic and seem like the sorts of things people can reasonably well do without a great deal of quality control. So that is probably a favorable situation here.

But I agree in a sense with what Rick Gelber says, is you should maybe trust abstracts more because they are not subject to publication bias. On the other hand, you know so little about what is in them, that I guess they fail my test for being able to rely on.

But in the end, it is a judgment that has to be made that doesn't have terribly precise rules. It is a feeling you get, and I guess I should add that we have been able, where this was critical, to get the records even from the fairly distant past.

So that needs to be kept in mind as an option if the data were otherwise almost persuasive, but not quite, you can do that. There is a fair amount of difficulty, and it certainly has not always been considered necessary, but it is a possibility, and we have gone back 15 years sometimes to find data. We have not always been pleased

with the results, but we have done that.

Anyway, there is no legal bar to doing so, and this does represent something of a model for us. As you all know too well, there is a great many uses of drugs in oncology that aren't in the label.

One possibility for getting them in there is a robust published database. I think when we have looked, it hasn't been as robust as we have hoped most of the time, but it is a possibility we need to consider.

CHAIRMAN BUNN: You left out -- I don't know what the FDA has done with this recently, but this Committee did hear another literature-based application for the same indication, and the size of the studies and quality of the data was probably quite similar, since it was the same indication and it was pretty similar, and we did in that instance, as a committee, recommend approval.

DR. TEMPLE: We had access to one of the studies there. That is a small, perhaps important advantage.

CHAIRMAN BUNN: Yes. I think also the Committee, of course, is very aware in this changing health care environment that more and more managed care companies love to not pay for drugs on some basis, and even though we believe in the literature there is adequate reasons to use a particular drug, that may not be good enough for them. That, in my own experience, seems to be an increasing

popular way for insurance companies to try to save money, and if that continues, we may see more of these, and it is probably reasonable if that happens, that we do.

DR. TEMPLE: But we have been encouraging people to at least take a crack at it, how to interpret them and what we will eventually do still remains to be seen, but at a minimum it is worth a try, and if the worst outcome is that one of the studies has to be looked at more closely, that is still a considerable decrease in effort compared to starting from scratch.

DR. GELBER: Just a quick point of clarification. Is this product approved for other purposes, then? Are we talking about expanding a --

DR. TEMPLE: No. This is the first human drug application for talc. It is a new molecular entity in our terms.

COMMITTEE DELIBERATION

CHAIRMAN BUNN: We will turn to the questions. There is a little bit of a preamble, but since we have set ourselves up, the first question which the FDA has asked the advisers to provide their advice on is: Which, if any, of the clinical trials, which we have just had reviewed, are adequate and well controlled?

Dr. Krook.

DR. KROOK: I think it has already been stated

from what was presented by the FDA, the four trials which were on the first slide, particularly the Sorensen trial, although it be small, was controlled, and I think those are the four that we have to accept as perhaps adequate and reasonable controlled. I guess that is my use of the words, and I would recommend to the Committee that this question be answered yes, that there are trials that are.

CHAIRMAN BUNN: I will take a stab at this as the other reviewer. Sometimes we have a question of what is statistically relevant and what is clinically relevant, and they are not always necessarily the same.

Oftentimes, in a particular clinical trial, the statistical question that is being asked is, is one treatment significantly better than another, and I suspect that sometimes the statistical answer to whether some of the trials are adequate is no.

On the other hand, as Dr. Temple was pointing out, when you have something that is 90 percent effective all the time, if the comparator is effective 80 percent of the time, and those aren't statistically different, does that mean the product isn't any good or the study isn't adequate to show efficacy.

Of course, you get into the comparability issue, and obviously, none of these trials are statistically adequate to show comparability even if they are not

statistically adequate to show superiority.

On the other hand, my own view is that these studies are adequate for the question being asked, both in terms of showing efficacy and safety. So I concur with Dr. Krook.

DR. KROOK: One more comment which I hear our thoracic people say, is that the chest tube alone, the first trial has a chest tube arm alone although it is small, is that that does control some without the talc.

CHAIRMAN BUNN: Does anyone, Dr. Gelber, since I have made a distinction between clinically relevant and statistically relevant --

DR. GELBER: I would change really one thing you said, Paul, when you said sometimes there are issues of discussion between clinical and statistical. I would say very often or quite frequently that is the case.

But I don't think necessarily that the issue is so much statistical versus clinical for me here. It is more the issue that Bob Temple brought out, that we are really being asked to answer a question that is clear in the regulations, of the submitted clinical trials, which ones of the individual clinical trials are adequate and controlled, and yet in Bob's very nice remarks, he used phrases like a certain mass of the literature, a consistency, accumulated evidence, and things like that, that are not present from a

single individual trial.

So I think we are caught, as we are very often on the Committee, between addressing the issue of single, adequate, well-controlled trial that can be used. I think that any one of the four studies that you mentioned, if we only had one, there would be serious questions as to whether that trial was adequate and well controlled even from a clinical perspective.

Seeing the literature, seeing the four together, seeing the supportive evidence, it is a certain mass of the literature that we are voting on, but we have to answer this question here about individual trials, and I think that is really the dilemma we are in.

CHAIRMAN BUNN: Dr. Temple.

DR. TEMPLE: I may not have been quite clear. The presumption is that you are only talking about literature trials that on their face appear to be well controlled. The question then is, okay, there are a number of trials that appear to be well controlled, should I believe this, and the burden is greater, from our point of view anyway, than if we actually have the data in hand.

With the data, we can be reasonably certain that what is said is what happened. In the literature, you never can actually do that directly, you have to take a fair amount on faith, and experience tells you that some of the

areas that you have to take on faith are disposition of patients and a bunch of stuff like that.

So the presumption is -- there is a sort of first step, which says are these by design and apparent reporting well-controlled trials, and then collectively, does this make a persuasive case, but sort of going in presumption is that they have to look like well-controlled trials including historically controlled trials, or you don't even think about it.

DR. GELBER: Can I just follow up on that with one short phrase, which is I am less concerned about the aspect of the well controlled in the four studies that have been mentioned. I mean these were randomized prospective studies. I am more concerned about the issue of adequate for getting the information that we need as individual trials.

Specifically, the Hartman report was mentioned as the one that would be important because of its sample size, but I would have problems indicating that as a well-controlled study because of the lack of understanding that I had with respect to the control groups and how they were assembled, and so on.

So you have the sample size adequacy in one study, but that is not what I would consider well controlled, but the four that were mentioned, I would consider to be well

controlled by design, but not really, or on the margin of adequate as individual trials for demonstrating what we want to show.

CHAIRMAN BUNN: Actually, the Hartman trial, I actually sort of think it is adequate and well controlled, not because of the control group in the study, but because of historical controls, just looking at the 39 patients and comparing them to historical.

DR. GELBER: Almost as a single-arm, Phase II trial of effectiveness.

CHAIRMAN BUNN: Right.

Dr. Ingle.

DR. INGLE: Just one other requirement about how much faith we put in the literature. Clearly, peer-reviewed literature is essential. There are numerous publications which are clearly sponsored by pharmaceutical firms or that appear in the pseudo-literature, but if a study has stood peer review, for instance, in one case, at a national meeting and then showed up in the peer-reviewed literature, I think that gives us much more, that is a requirement to put any store in the quality of the study.

CHAIRMAN BUNN: We are being too kind to these studies, because all of us would wish that some of the studies had been a bit differently, the stratification, the diseases studied, the dose, there is a number of issues in

these studies that make them somewhat less than ideal.

But on the other hand, we do recognize that being short of breath to the point where you can't walk is not pleasant for patients, and we all know that an effusion goes away, the people feel better, and we all know that taking a chest x-ray and showing there is no effusion is a fairly simple matter, and I think we are all biased by that, as well, or influenced by that.

DR. TEMPLE: Some of the questions one would often ask about things about stratification tend to go away when the response rates are 90 percent plus. I mean stratify it all you want, but 90 percent is 90 percent.

The controls, the no-treatment controls fairly consistently come out in the 40 to 50 percent range, so there obviously is a nonaccumulation rate of 30 days even if you don't do anything, but that is a fairly large difference. You know, if it were 60-50 or something like that, I don't think we would be here.

CHAIRMAN BUNN: Well, I think we would actually. If this worked 90 percent of the time, and they were asking us to approve it, it wouldn't matter if there is something else, 80 percent effective. It is just is this 90 percent effective.

DR. TEMPLE: Well, if it was 90 and no treatment at all was 80 --

CHAIRMAN BUNN: Oh, well, yes.

DR. TEMPLE: Other than drainage.

CHAIRMAN BUNN: Yes.

DR. TEMPLE: Okay.

CHAIRMAN BUNN: So we have a motion that the answer to Question 1 is that there are adequate and well-controlled trials, and they were identified by the FDA, and we concur that these are adequate and well-controlled studies. That was seconded.

Is there any further discussion?

[No response.]

CHAIRMAN BUNN: All in favor?

[Show of hands.]

CHAIRMAN BUNN: Dr. Ozols can't vote, so we have seven in favor against one abstained, one abstention, 7-0-1.

DR. GELBER: Just an explanation on that is, as a group, I would say that there is evidence, but, as phrased, it asks for individual trials, and I have a problem with that.

CHAIRMAN BUNN: The second question: Do the identified trial(s) provide substantial evidence for efficacy in the treatment of malignant pleural effusions? We have somewhat beat this up, but Dr. Krook.

DR. KROOK: I would make the motion that the identified trials using talc does provide substantial

evidence of efficiency in the treatment of malignant pleural effusions.

CHAIRMAN BUNN: Thank you for not putting a negative in there, which we always gets these double negatives that confuse all of us.

I agree. I think, again, it is the mass of the data. Every article essentially is showing something close to a 90 percent efficacy rate, and I do view that as efficacious.

I will also note that the surgeons will continue to do this, because they believe it works whether we vote for this or not, but obviously, our surgical colleagues believe it works as well.

DR. SWAIN: I would just like to make one comment. I am a little concerned about using the numbers 90 to 100 percent efficacious. When you look at the intent to treat, and you really read these papers, I think that is overstating it.

CHAIRMAN BUNN: Yes. If you censored patients, it might be close to 90 percent, but certainly a lot of people, this is a bad disease, and a lot of people die of other causes, and so on.

Dr. Ingle.

DR. INGLE: I would just like to support what Dr. Swain said. Clearly, the two current randomized studies are

very important.

CHAIRMAN BUNN: Right.

Any other discussion?

[No response.]

CHAIRMAN BUNN: All in favor of Dr. Krook's motion?

[Show of hands.]

CHAIRMAN BUNN: Eight. Opposed? Zero. Abstained? Zero. 8-0-0.

The third question: Is the safety profile of a single administration of 4 to 8 grams of talc acceptable?

Dr. Krook.

DR. KROOK: Again, I would make the motion that the safety profile of a single administration of 4 to 8 grams is acceptable.

The only comment I will have, as I reviewed the literature, there were a couple of 10-gram doses which there appeared as it went above 8, to be problems, as I remember the data. So I think that 8 is the top.

CHAIRMAN BUNN: There were I think two fatalities.

DR. KROOK: Right. Whether they are related or not --

CHAIRMAN BUNN: Yes. Obviously, the serious side effects were quite uncommon, and one of the things that wasn't pointed out was most of those side effects were

probably due to the procedure, either the VATS or the thoracoscopy and the anesthesia really rather than the agent itself, and I think actually I would ask -- it was commented on that infections were pretty uncommon, empyema, a little less than 1 percent, but we heard from the company that as far as they knew, there weren't any infectious complications from their product.

Alison, do you know, in those treatment INDs, were there any infectious complications?

DR. MARTIN: The only serious complication that was reported to us was intubation for a couple of days due to re-expansion and pulmonary edema. We had no other serious ADRs reported.

CHAIRMAN BUNN: So I second Dr. Krook's motion that this is sufficiently safe.

Is there other discussion about safety?

DR. GELBER: Just one more question. Again, it is an estimation of how safe, because it was pretty clear that there is likely to be a lot of under-reporting in the large series of uncontrolled studies.

So if your denominator is over 1,000, that is being reported, then, your incidence of things is going to be quite low. I just wonder, taking a number out of those series, is reasonable or should be modified by the potential to miss things.

But overall, in terms of I guess serious complications, there didn't seem to be anything reported.

CHAIRMAN BUNN: Some of the randomized trials, I think should help also in sorting out complication rates from procedures, as well as from the agent. Once again, if one procedure has a lower incidence of side effects, that would be important, but it is really not the issue here.

Any other discussion?

[No response.]

CHAIRMAN BUNN: All in favor of Dr. Krook's motion that the safety profile is acceptable?

[Show of hands.]

CHAIRMAN BUNN: Eight. Opposed? Zero. Abstained? Zero. 8-0-0.

Question 4 is: Is Sclerosol approvable for the treatment of malignant pleural effusions?

Dr. Krook.

DR. KROOK: I guess my comments here is that I think aerosol talc is what we have seen or talc as it is, is approvable. I think when we talk about Sclerosol, that there is also a delivery system involved here, and I am not sure we are asking -- maybe I am wrong, maybe FDA is asking us to approve the delivery system also.

So my comment here is that I believe aerosol talc is approvable for the treatment of malignant pleural

effusions rather than the brand name, although I have to turn to my colleagues and say what are they asking.

I mean the studies are talc. We have a 12 -- am I correct -- a 12-person study using Sclerosol.

CHAIRMAN BUNN: A 12 and an 11.

DR. KROOK: A 12 and an 11.

CHAIRMAN BUNN: A published 12 and an abstract 11.

DR. KROOK: And we have, if I am also correct, we have the 69 individual INDs. That is my problem with that question, and so if I were to be asked, I would say sterile aerosol talc is approvable for malignant pleural effusions. I am changing the question.

CHAIRMAN BUNN: Dr. Temple, do you want to comment on this?

DR. TEMPLE: We understand. We will have to reach a judgment about -- well, you could help us on this -- about how likely it is that any form that delivers -- I mean sometimes with aerosols and things like that, you worry about the spray pattern and things like that.

That seems less of a problem here than in many cases, because you are sort of doing it under visualization, but your point is certainly noted. I think we have to take that into account.

We have certainly been thinking, though, that aerosol data in general would be applicable to this product.

CHAIRMAN BUNN: I just say actually, though, in the company's presentation, you know, I think oftentimes a picture is worth a thousand words, and the advantage of that spray is that you can really say whether you have coated the pleura or not, and I think that is a little bit easier to control, so that I think it probably is easier to get a fairly uniform distribution over the pleural surface with that applicator.

The real difference from what you are saying is, is the applicator reasonable, and we don't have a lot of data. Twenty-three cases isn't a lot, but, you know, I was impressed by the pictures, that you were able to get a pretty uniform distribution over the pleura with that particular applicator.

It wouldn't dissuade me from some other applicator being acceptable, but I am fairly convinced that that applicator seems fairly reasonable based on the pictures.

DR. GELBER: Just remember, we only saw one picture of one instance. So, again, I agree with your point that to make it more generic, those are the data we saw, and to encourage review of the data that are coming in on the particular product.

CHAIRMAN BUNN: We don't usually let the companies talk, but, Dr. Beamis, do you want to make a comment about whether you think that picture that you showed is fairly

representative of the type of uniformity of distribution you can get with this applicator, and especially compared to some other applicator?

DR. BEAMIS: We haven't used other applicators with the Sclerosol. I have been to Marseille and seen other people do talc applications with the powdered talc, USP talc, and I think either applicator can do a good job.

The visual confirmation, I think is very important, and all of our cases have been visually confirmed. We tape each case, we are not the best photographer through thoracoscope, but --

CHAIRMAN BUNN: Obviously show you the best pictures, but in other words, you think that usually, things are pretty much like those pictures that you showed us?

DR. BEAMIS: That's right, yes.

CHAIRMAN BUNN: Dr. Ozols.

DR. OZOLS: I guess the problem of patient safety, I think we should consider. I mean if we are talking about not approving this particular product, other than USP, which again raises the problems of individual pharmacies having to sterilize it, and so forth, and it seems to me you are caught in a bind if you just sort of approve it generically, but there is no sort of approved other substitute.

DR. TEMPLE: But we have to deal with an application for a particular product. Our current approval

won't be generic, even if your advice is, we will have to interpret it.

CHAIRMAN BUNN: I don't know Robert's Rules of Orders, but I would like to propose an amendment. I would like to say that Sclerosol (sterile aerosol talc) is approvable for the treatment of malignant pleural effusions.

We can have a discussion on that amendment and vote on it.

DR. OCHS: Would you say palliative treatment rather than treatment? Treatment rather implies, and it really isn't, it's a palliative treatment.

CHAIRMAN BUNN: Sure.

So we have a proposal to amend this to add the word Sclerosol and to add the word palliative.

DR. KROOK: I guess my question again -- turning to Bob Temple over here -- does that change it for you? I mean instead of "sterile aerosol talc" or "sterile talc," however you want, put the word Sclerosol? It's a brand name.

DR. TEMPLE: Well, it is the particular product that we are reviewing. I think we are content either way. We understand. We understand what you are saying.

DR. KROOK: Then, I accept the amendment.

CHAIRMAN BUNN: We will just vote on the amendment then.

Any other discussion?

DR. TEMPLE: I guess before we leave that too quickly, our probable assumption is that the ability to visualize it won't interfere, the results won't be worse that way than with methods that didn't give you as much control.

So I would say that you should know our attitude as reflecting that.

CHAIRMAN BUNN: I think that this agent is most likely in the community going to be used via VATS or thoracoscopy, and I think it is unlikely that people are going to put this in through a thoracentesis, and it is really, be definition, almost we are approving the combination of thoracoscopy and VATS with this. But I think that is fine. I can't imagine anybody giving this via a thoracentesis. Physically, it wouldn't go in there.

I mean almost by definition, you are giving it in a manner where you can see where it goes. I mean that is just the way the techniques are done now.

So we have a vote on the amendment, which is to make the motion be Sclerosol (sterile aerosol talc) is approvable for the palliative treatment of malignant pleural effusions.

All in favor of the amendment?

[Show of hands.]

CHAIRMAN BUNN: That is 8 to zero.

Now we will vote on the motion then. The motion is that Sclerosol (sterile aerosol talc) is approvable for the palliative treatment of malignant pleural effusions.

All in favor?

[Show of hands.]

CHAIRMAN BUNN: Dr. Gelber?

DR. GELBER: It just seems that the amendment and the motion are exactly the same.

CHAIRMAN BUNN: They are. So it is 8 to 0, 8 in favor, zero abstained, zero against.

Question 5. Does ODAC have advice for the FDA regarding the acceptability of literature-based NDAs for cancer therapeutics? For example:

a. What types of patient populations/clinical indications could be considered as appropriate for a literature-based NDA?

b. What types of products could be considered, e.g., cytotoxic, hormonal, supportive care?

c. What should be required regarding the quality and the quantity of data?

Since I have put Dr. Krook on the line, I will go first on this. We have had some discussion of this already. I think that literature-based NDAs are reasonable for cancer therapeutics. I think if the changes in health care

continue to increase the number of denials by insurance companies, particularly for approved products for nonapproved indications, that this might become more important. Actually, I personally hope that it isn't.

Historically, most insurers have relied on physician expertise and the literature, and I think it is an unfortunate thing where insurers are not relying on physician expertise or the literature. If that becomes an increasing problem, I hope that we will see increasing literature-based NDAs, but I hope that doesn't happen. I think that is a step backwards for health care in the United States.

I personally believe that all types of products listed here, cytotoxic, hormonal, supportive care, could be considered. Regarding the quality and the quantity of the data, obviously, the better the quality, the more the quantity, the better. I would point out that this Committee has gone on record as saying that randomized trials are often easier to interpret than Phase II trials.

The cooperative group randomized trials often have fairly good quality monitoring and quality assurance built into the studies, both from an audit point of view and from a statistical design point of view, and generally, I think most people on the Committee feel that randomized studies from cooperative groups are generally quite useful, but

obviously, since we approved this without cooperative group randomized trials, there are other ways with bulk of evidence that can be used.

Dr. Krook.

DR. KROOK: My only thing to add, Paul, is I think that under 5(b), supportive care or palliative care I guess I may change that to, maybe there is a fourth one, palliative care, as Dr. Ochs has brought up, what we went through today, the malignant pleural effusion certainly falls into that, and I suppose supportive care can fall into nausea questions, which aren't palliative care. I think that particularly through literature-based NDAs.

I have a little more difficulty with cytotoxic. I think you have got a little bit more commonly through a literature. You have to have some controlled trials when you increase the toxicity without a gain.

That is my only comment. I am saying the same about quality and quantity as you are.

CHAIRMAN BUNN: Dr. Ingle.

DR. INGLE: This has already been mentioned. For literature to be acceptable, there have to be strong assurances of peer review and the minimizing of conflict of interest, which can come from many sources.

CHAIRMAN BUNN: There is a lot of debate going on in the community. I have been involved in some of this from

the insurers about what is standard treatment, and I personally don't believe that the FDA should be the final common denominator on what is adequate peer review of the literature, and I think if every, you know, every indication for every drug has to come back to the FDA for consideration of is the literature adequate, again, I believe that is a huge step backwards.

I believe that there are sensible people who should be in the community, who can make those judgments without bringing every indication for every approved drug to this Committee and to the FDA, but again, that is my own bias. I think in certain instances, like this, this is very useful, but I don't think every drug for every indication should come here for a review of the literature.

DR. GELBER: I just wanted to add also that the entire literature should be presented including abstracts to allow the Committee to look at those data, as well, especially because of the tendency not to publish abstracts that are not as exciting as what is appearing --

CHAIRMAN BUNN: Again, I think we commend the FDA for making sure that these literature searches are completely thorough and as unbiased as possible.

DR. GELBER: And one last point is efforts that could track down additional studies should be pursued and the fact that arms-length literature by itself probably

would not be as persuasive as having some of the additional information, for example, that was presented, the supportive information about a consistency throughout, I think is very important to a literature-based NDA.

CHAIRMAN BUNN: Dr. Temple.

DR. TEMPLE: Despite what some people think, we don't think FDA-approved labeling ought to be the sole determinant of practice either. At least part of the reason for that is that sometimes you do things even before there is decent evidence in support of them, and that is just one of the exigencies of being out there.

I think our concern is that we don't want to put things in the label as if they met a standard when they haven't. So we are very sympathetic to the idea that there is a real problem that insurers are not paying for things that doctors think are important, but our immediate question is what standard can we use to put things into labeling that deserve to be there without compromising.

As this Committee pointed out repeatedly, there have been many instances where close review of the actual cases, where effectiveness depended on individual cases, often revealed differences between one interpretation and another, and for better or worse, peer review doesn't solve that problem, because the peer reviewer rarely has access to case reports. I have done my share of that, and you are