

# TRANSCRIPT OF PROCEEDINGS

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

OBSTETRICS AND GYNECOLOGY DEVICES PANEL  
62nd MEETING

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Pages 1 thru 271

Gaithersburg, Maryland  
January 25, 2000

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VOL

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

OBSTETRICS AND GYNECOLOGY DEVICES PANEL

62<sup>nd</sup> MEETING

Tuesday, January 25, 2000

9:00 A.M.

Gaithersburg Holiday Inn  
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.  
507 C Street, N.E.  
Washington, D.C. 20002  
(202) 546-6666

ATTENDEES

Panel Members

Jorge Blanco, M.D. (Panel Chair)

Sandra Carson, M.D.

Donald Chatman, M.D.

Ralph D'Agostino, Ph.D.

Subir Roy, M.D.

Nancy Sharts-Hopko, Ph.D.

Gerald Shirk, M.D.

Industry Representative

Ray Silkaitis, Ph.D.

Consumer Representative

Diony Young

Executive Secretary

Elisa Harvey, D.V.M., Ph.D.

FDA Participants

Mike Diamond, M.D.

Dave Segerson

Daniel Schultz, M.D.

## AGENDA

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

2                    DR. BLANCO: I call the meeting to order. This is  
3 the 62nd meeting of the Obstetrics and Gynecology Devices  
4 Panel, and I want to remind the audience that there is a  
5 sign-in sheet at the entrance by the door, if you would  
6 please sign in, so that we have a listing of who is in the  
7 audience and who participated.

8                    We will have some time for open public hearing so  
9 that you can make some comments to the panel. That time  
10 will be at some point in the morning. We may have to change  
11 the schedule, the agenda little bit this morning because of  
12 the weather and people getting here or not getting here, but  
13 you will have your opportunity.

14                    Let me remind you, though, that you must be  
15 recognized by the Chair, you must come to the mike. At the  
16 time that you come to the mike, please state your full name,  
17 any affiliation, and also give any information whether you  
18 have any conflict of interest, including any support of  
19 travel, per diem, research support or any other relationship  
20 with any company that may have any dealings with this  
21 particular product or with the Food and Drug Administration.

22                    At this time I would like to begin with having the  
23 individuals on the panel introduce themselves, and if we  
24 will begin from the right-hand side this time?

25                    \*\* I am Dave Segerson, Associate Division

1 Director in the Center for Devices and Radiological Health.

2 DR. CHATMAN: I am Donald Chatman, obstetrician-  
3 gynecologist, Northwestern University.

4 DR. D'AGOSTINO: Ralph D'Agostino, Boston  
5 University, biostatistician.

6 DR. SHIRK: Jerry Shirk, clinical associate  
7 professor, OB/GYN, and private practice, Cedar Rapids, Iowa.

8 DR. HARVEY: Elisa Harvey from the Center for  
9 Devices and Radiological Health. I'm the Executive  
10 Secretary to the OB/GYN Devices Panel.

11 DR. BLANCO: I am Jorge, George, Blanco, an  
12 obstetrician-gynecologist with the University of Florida.

13 DR. ROY: Subir Roy, professor, OB/GYN, University  
14 of Southern California.

15 DR. CARSON: Sandra Carson, professor of OB/GYN,  
16 Baylor College of Medicine.

17 DR. SHARTS-HOPKO: Nancy Sharts-Hopko, professor  
18 of maternal-infant-women's health nursing at Villanova  
19 University.

20 MS. YOUNG: Diony Young. I'm the consumer member  
21 on the panel from Geneseo, New York, and I am editor of the  
22 journal Birth.

23 DR. SILKAITIS: My name is Ray Silkaitis. I'm a  
24 registered pharmacist and I have a doctorate in  
25 pharmacology. I have about 25 years of experience in

1 preclinical and clinical research. I'm the industry rep on  
2 loan to this panel.

3 DR. BLANCO: Welcome, everyone, this morning. I'd  
4 like to make the audience aware that the FDA press contact  
5 is Dave Segerson, sitting at the end. If you need any  
6 information for the press, contact him.

7 At this point I'll turn the meeting over to Dr.  
8 Harvey to read some necessary statements.

9 DR. HARVEY: Thank you, Dr. Blanco. I just wanted  
10 to read the conflict of interest statement for our January  
11 25th, 2000 meeting of the OB/GYN Devices Panel. The  
12 following announcement addresses conflict of interest issues  
13 associated with this meeting, and is made a part of the  
14 record to preclude even the appearance of an impropriety.

15 To determine if any conflict existed, the agency  
16 reviewed the submitted agenda and all financial interests  
17 reported by the committee participants. The conflict of  
18 interest statutes prohibit special government employees from  
19 participating in matters that could affect their or their  
20 employers' financial interests. However, the agency has  
21 determined that participation of certain members and  
22 consultants, the need for whose services outweighs the  
23 potential conflict of interest involved, is in the best  
24 interest of the government.

25 A waiver is on file for Dr. Donald Chatman for his

1 interest in firms that could potentially be affected by the  
2 panel's deliberations. The waivers permit him to  
3 participate fully in today's session. A copy of this waiver  
4 may be obtained from the agency's Freedom of Information  
5 Office, Room 12A-15 of the Parklawn Building.

6 We would like to note for the record that the  
7 agency took into consideration certain matters regarding  
8 Drs. Sandra Carson, Ralph D'Agostino, and Subir Roy. These  
9 individuals reported past or current interest in firms at  
10 issue, but in matters not related to the topics for today's  
11 session. Therefore, the agency has determined that they may  
12 participate fully in the deliberations.

13 The agency would also like to note for the record  
14 that Dr. Alan DeCherney, who is a guest speaker today, has  
15 reported a personal financial interest with the firm at  
16 issue. Dr. Steven Schwaitzberg, who is also a guest speaker  
17 today, has reported a personal financial interest and a  
18 current consulting relationship with the firm at issue.

19 In the event that the discussions involve any  
20 other products or firms not already on the agenda, for which  
21 an FDA participant has a financial interest, the participant  
22 should excuse him or herself from such involvement, and the  
23 exclusion will be noted for the record.

24 With respect to all other participants, we ask in  
25 the interest of fairness that all persons making statements

1 or presentations disclose any current or previous financial  
2 involvement with any firm whose products they may wish to  
3 comment upon.

4 A few other announcements. We have no  
5 transcriptionist today, so the only document we will have on  
6 record at this point will be the video, and there are fliers  
7 at the back of the room for information on getting a video  
8 of today's meeting.

9 I also want to make a note to the record that we  
10 have changed our October panel meeting date from Monday and  
11 Tuesday, October 9th and 10th, to Tuesday and Wednesday,  
12 October 10th and 11th, because October 9th is a Federal  
13 holiday.

14 One last note. I want to point out for the panel  
15 what their folder contents are. You should have a copy in  
16 your folder of the agenda; the panel roster for today, which  
17 is not current anymore because of some last-minute changes  
18 due to weather; discussion questions; copies of my  
19 presentation and Dr. Mitchell's presentation; copies of Dr.  
20 Schwaitzberg and Dr. DeCherney's notes for today's  
21 presentations; and you should have presentations from two  
22 parties who will be giving open public hearing  
23 presentations, Dr. Burns from Genzyme on behalf of a group  
24 of adhesion barrier sponsors, Dr. Wiseman for the  
25 International Adhesions Society. We also have two letters

1 to the panel which I believe we will have our industry  
2 representative, Dr. Silkaitis, read into the record, from  
3 Drs. Wexner and Ellis.

4 Okay. Dr. Blanco?

5 DR. BLANCO: All right. Thank you, Dr. Harvey.

6 Now we will go ahead and start with the  
7 proceedings, and the first item on the agenda is a  
8 postmarket activities presentation by Tom Gross, Director,  
9 Division of Postmarket Surveillance.

10 MR. GROSS: Good morning. I am Tom Gross,  
11 Director of the Division of Postmarket Surveillance here at  
12 CDRH. Now, how do I get that to work? It's all set up. Do  
13 I use this?

14 Good morning. I would like to take a few minutes  
15 of your time today to talk to you about postmarket  
16 evaluation at CDRH. We in the Office of Surveillance and  
17 Biometrics think it's important that the advisory panels are  
18 aware of postmarket programs and activities, since they may  
19 directly relate to your deliberations about product safety  
20 and effectiveness.

21 The objectives of this presentation are threefold:  
22 One, to describe a few of the key methods of device  
23 postmarket evaluation; two, to present challenges in better  
24 accomplishing postmarket evaluation; and, three, to describe  
25 the pivotal role that the advisory panel can play in this

1 arena.

2           This slide, entitled "From Design to  
3 Obsolescence," makes three key points. One, it depicts the  
4 natural history of medical devices from design to lab bench  
5 testing, clinical testing, FDA review and, importantly,  
6 postmarket evaluation. Secondly, it shows the continual  
7 feedback loops throughout the process, leading to continual  
8 product improvements; and we feel that postmarket  
9 evaluation--whoops. Are we expecting a call? Sorry for  
10 that. We feel that postmarket evaluation has an important  
11 part to play in this process of continual product  
12 improvement.

13           The rest of this talk will focus on three key  
14 programs: the MDR program, Section 522, known as Postmarket  
15 Surveillance Studies; and our post-approval or conditional  
16 approvals program. And the third point that this slide  
17 makes is that the clinical community, and importantly the  
18 advisory panel, can have a key role to play in this process  
19 of continual product improvement. Next slide.

20           Now, as we all know, once products are let on the  
21 marketplace, questions may arise in the postmarket period,  
22 and they can be varied. There can be concerns about a  
23 product's long-term safety; about the performance of the  
24 device as used in community practice, as it moves outside  
25 the narrow confines of clinical trials. There may be

1 concerns about effects of changes in user setting, such as  
2 moving from professional to home use; concerns about effects  
3 of changes in technology; and, lastly, concerns about  
4 adverse events or unusual patterns of adverse events.

5           Now let's focus on some of the postmarket  
6 evaluation programs that may help address some of these  
7 questions, beginning with the Medical Device Reporting  
8 program or MDR. Now MDR is a nationwide passive  
9 surveillance system of voluntary and mandatory reporting.  
10 Voluntary reporting began in 1973; mandatory reporting of  
11 manufacturers and importers began in 1984.

12           Currently, manufacturers must report deaths and  
13 serious injuries to the FDA if the device caused or  
14 contributed to the event. They also have to report  
15 malfunctions. User facilities, importantly including  
16 hospitals and nursing homes, have to report deaths to the  
17 FDA and serious injuries to the manufacturer. Next slide.

18           Now, all told, since its inception in 1973 we have  
19 received a little more than 1 million total reports.  
20 Beginning in the early '90s, we receive about 100,000  
21 adverse event reports per year. These reports are submitted  
22 on standardized forms. They capture device specifics such  
23 as brand name and model number; capture event descriptions,  
24 pertinent dates and patient characteristics.

25           Now unfortunately these reports often have very

1 limited information. Even basic information on age and  
2 gender may be missing from a large number of reports.  
3 Nonetheless, they do provide us critical signals upon which  
4 we take action.

5           What are some of those actions? Well, based on  
6 MDR reports, we may have a directed inspection of  
7 manufacturer's or user facilities. It may occasionally lead  
8 to product injunctions or seizures; product recalls, as in  
9 the recent case of a pelvic floor stimulator and problems  
10 with electrical shorting. It may lead to nationwide patient  
11 and/or physician notification, as in the case of the Public  
12 Health Advisory in 1998 on the use of vacuum assist delivery  
13 devices and its association with neonatal injury; and  
14 occasionally it may lead to additional postmarket studies.

15           Now CDRH has two authorities upon which to order  
16 postmarket studies. Section 522 under FDAMA is entitled the  
17 Postmarket Surveillance Authority, and our post-approval or  
18 conditions of approval authority is under the PMA  
19 regulation.

20           Now section 522 was originally mandated in SMMA  
21 1990 and was changed significantly in FDAMA 1997. The 1990  
22 version had categories and lists of device, the  
23 manufacturers of which were required to do postmarket  
24 studies on regardless of whether there were pertinent public  
25 health questions to address. That requirement was dropped

1 in the FDAMA '97 version. However, FDA retains its  
2 discretionary authority for imposing postmarket study  
3 requirements if there are pertinent public health questions  
4 that need to be addressed.

5 The post-approval or conditions of approval  
6 authority is reserved for PMA products. The 522 authority  
7 extends our coverage to Class II or III 510(k) products  
8 whose failure may present a significant public health  
9 problem. Now, both authorities are seen as a complement to  
10 our premarket efforts.

11 Now, in implementing the FDAMA version of 522, we  
12 published criteria in the form of guidance to help guide our  
13 considerations on when to impose postmarket study  
14 requirements. The first criterion is that there has to be a  
15 critical public health question. It may arise from a for  
16 cause reason such an adverse event report. It may arise  
17 from concerns about new or expanded conditions of use,  
18 moving say from professional to home use; or concern, safety  
19 concerns about the evolution of a product's technology.

20 The second criterion is that we need to give  
21 consideration to other postmarket strategies prior to  
22 imposing a postmarket study requirement. There may be other  
23 strategies, such as inspections, that are better suited to  
24 address the public health question of interest.

25 Thirdly, the studies have to be practical and

1 feasible to conduct. Can you recruit interested physicians?  
2 Can you recruit sufficient numbers of patients? Can we do  
3 this in a timely fashion? And a related question is, how  
4 will the data be used? Can it be captured in a timely  
5 manner? Because for rapidly evolving technologies, we may  
6 receive the data and by the time we receive it, it may be  
7 considered obsolete. And, lastly, in an age of limited  
8 resources, we have to consider the priority of these  
9 postmarket studies.

10 Now, once we decide to impose a postmarket study,  
11 there are obviously a host of design approaches that may be  
12 chosen. We would obviously choose or hope to choose that  
13 design approach that best fits the public health question of  
14 interest, and that design approach that is least burdensome  
15 for addressing that public health question. And there  
16 listed are a series of different approaches, starting from  
17 least burdensome, meaning a detailed review of complaint  
18 history and literature, all the way up to more sophisticated  
19 and complex designs such as case control studies, and rarely  
20 we would impose randomized trials.

21 Now, in conducting these postmarket studies, we  
22 have experienced a number of frustrations. I have alluded  
23 to the fact referring to rapidly evolving technologies may  
24 make studies obsolete, and we have got to be mindful of that  
25 before we engage companies in these studies. There may be

1 lack of acceptance from the industry. The industry may see  
2 these discretionary studies as the bearer of bad news, and  
3 we have to change that paradigm and make it worthwhile for  
4 industry to participate. There may be lack of interest in  
5 the clinical community. Physicians may not be interested in  
6 studying mature technologies. And lastly, of course, we  
7 need to be careful that there is a clearly specified public  
8 health question.

9           Now, what is the challenge to the advisory panel,  
10 and really a challenge to us all? In considering postmarket  
11 studies, whether conditional approval or 522, we need to  
12 ensure that they are of primary importance, that they are  
13 practical, feasible, can be done in a timely fashion. There  
14 has to be a clearly specified public health question. And  
15 we need to know the clinical or regulatory relevance of  
16 addressing the issue. Are the data to be collected to  
17 assure us that what's happening in the postmarket period is  
18 no different than what was happening premarket? Are they  
19 there to address residual questions, or are they there to  
20 capture adverse events?

21           This is the last slide, and it is just a brief  
22 overview of the future of MDR and postmarket surveillance.  
23 With regard to medical device reporting, we are tending to  
24 move away from individual reporting of well characterized,  
25 well known events, opting for summary reporting, which is a

1 tabular summary of these events.

2 We are moving away from universal hospital and  
3 nursing home reporting, to reporting based on a cadre of  
4 hospitals that are well trained, hoping for more timely and  
5 higher quality reports. We are moving into the electronic  
6 age and having these reports submitted electronically as  
7 opposed to hard copy. We are integrating our efforts with  
8 the quality systems regulation, in particular analysis of  
9 transit reports. And, on the international scene, we are  
10 currently exchanging adverse reports of interest between  
11 international regulatory authorities.

12 Now, with regard to postmarket surveillance, I  
13 have alluded to the wide variety of design approaches that  
14 are available to answer public health questions. We need to  
15 have more collaboration with industry and with the clinical  
16 community, and also access to more pertinent data sources  
17 such as registries.

18 That concludes my talk. Thank you very much, and  
19 I hope you get out of here safely.

20 DR. BLANCO: Thank you.

21 DR. HARVEY: Thank you very much, Tom, for making  
22 it here today.

23 DR. BLANCO: All right. We are going to alter the  
24 agenda a little bit. We have two guest speaker  
25 presentations that were going to occur a little bit later in

1 the morning. Dr. Schwaitzberg has made it onto the panel.

2           Unfortunately, Dr. DeCherney, who is the other  
3 presenter, is at Dulles and the weather is preventing him  
4 from making it from Dulles Airport here. However, we are  
5 going to have him present, give his presentation on the  
6 speaker phone, if we can arrange that. So he came halfway  
7 across the country or full way across the country to talk  
8 into the telephone to us and give us his speech. I think we  
9 should commend him for that.

10           And so we are going to go ahead and do Dr.  
11 DeCherney's presentation first and then Dr. Schwaitzberg's  
12 presentation. Dr. Harvey, do we have Dr. DeCherney on the  
13 line?

14           DR. HARVEY: Is this mike working? Okay, Mike,  
15 Dr. Diamond, is calling him now, and he will call back in  
16 here on this phone, theoretically.

17           DR. BLANCO: Okay.

18           DR. HARVEY: We appreciate everybody's patience  
19 today. Things are not exactly as usual.

20           DR. BLANCO: While we're waiting for Dr.  
21 DeCherney, if there's anyone besides the two individuals who  
22 Dr. Harvey already announced have registered to present, to  
23 make presentations during the open public hearing portion of  
24 this meeting, I would ask you to register so that we go  
25 ahead and have your name and place you in some sort of

1 order, if you are interested in speaking during that portion  
2 of the program.

3 Does the hotel know that he's going to? I mean,  
4 maybe they have this phone blocked. I guess not. They  
5 called in before.

6 DR. HARVEY: Dr. DeCherney?

7 DR. DeCHERNEY: Yes.

8 DR. HARVEY: This is Dr. Harvey here, the  
9 Executive Secretary for the panel. We very much appreciate  
10 your taking this extra effort here.

11 You probably will not be able to hear the  
12 deliberations or comments from the panel, but we'll try to  
13 relay those to you. But what we would like to hear from you  
14 are any comments you can make about the guidance itself,  
15 adhesions, GYN models for clinical evaluation adhesions, and  
16 so forth. So I'll let you have the floor here. We have a  
17 mike on your phone, so everyone should be able to hear what  
18 you're saying.

19 DR. DeCHERNEY: Okay. I read over the guidelines,  
20 and actually I think that the guidelines are pretty good as  
21 written. I think they address surrogate endpoints and real  
22 endpoints adequately. So what I'll do is, I'll just  
23 describe my slide and tell you what the point of that slide  
24 was.

25 The first slide is a picture of a bare lateral

1 pelvic sidewall, such showing how an adhesion is formed and  
2 how it's set up for adhesions. The second slide is Curtis-  
3 Fitzhugh, just another form of adhesion, an area of  
4 adhesions.

5 The next is a study, and it's going to be a little  
6 bit hard for me to quote from the study, but--

7 DR. HARVEY: Dr. DeCherney?

8 DR. DeCHERNEY: Yes?

9 DR. HARVEY: Could you speak up a little bit more?

10 DR. DeCHERNEY: Okay. How's that?

11 DR. HARVEY: Thank you. That's a little bit  
12 better.

13 DR. DeCHERNEY: Okay. It's going to be a little  
14 hard for me to quote the study, so what I'll do is, I'll  
15 dictate the references for the slides when I get back to  
16 L.A., if I ever do.

17 So this is a study looking at C-sections, and  
18 looking at fecundity after C-sections, and it turns out that  
19 fecundity is decreased by about a third after a C-section,  
20 so patients that have C-sections are more likely to have  
21 secondary infertility, and that is based on adhesion  
22 formation. At least that's the supposition.

23 Next is just a study that Dr. Grainger, one of our  
24 fellows, put together, looking at the adhesion rate after  
25 certain procedures, the highest procedure being myomectomy

1 with almost a 60 percent adhesion rate, and the last being  
2 just a tubal, a distal tubal--

3           The next slide is a study that Winston did at  
4 Hammersmith, and we actually repeated at Yale, that showed  
5 that patients that had previous surgery represented 73  
6 percent of the patients that we operated on for adhesions,  
7 and those that had infection only represented 27 percent,  
8 which was counted and the counts are intuitive because we  
9 thought actually that it would be the opposite, all building  
10 a case for the fact that the major cause of peritubal and  
11 abdominal adhesions is a result of previous surgery, not the  
12 result of infection.

13           The next slide just looks at the complications  
14 from adhesions, including pelvic pain, infertility, and  
15 bowel obstruction. And, in fact, 54 to 74 percent of small  
16 bowel obstruction is due to adhesions. This is--well, I'll  
17 have to dictate the references because they're too small.

18           I then have two slides just looking at peritubal  
19 adhesions, first fimbrial agglutination, which is a form of  
20 adhesion, and a drawing of the tube covered, covered with  
21 adhesions.

22           The next slide addresses the important factor of  
23 de novo versus reformation adhesions. About 40 percent of  
24 patients that undergo pelvic surgery develop de novo  
25 adhesions, and about 90 percent of reformation adhesions, if

1 some adjunctive therapy is not used, there is a reformation  
2 of those adhesions.

3           And the next slide is a compendium slide of six  
4 studies that demonstrate the reformation of adhesions. One  
5 is myself and Dr. Mezzer; the paper by Dr. Diamond; the  
6 paper by Daniel Treadway; a paper of Kemper's, demonstrating  
7 the reformation. And, in fact, in my lecture about  
8 adhesions this is where I mention that adjunctive therapy,  
9 although not perfect, can cut down the reformation adhesions  
10 to 50 percent from 90 percent, and it can cut down the de  
11 novo adhesions from 40 percent to 20 percent. Although not  
12 a perfect endpoint, it certainly is an improvement, and most  
13 of the studies are able to demonstrate that.

14           The next two slides just look at adhesions after  
15 seven days and after a year, showing the collagenous,  
16 gelatinous adhesions, and then of course the well formed  
17 vascular adhesions after a year. And this leads into a  
18 study that Jensen did a number of years ago in Australia,  
19 where he did third-look laparoscopies. And what he was able  
20 to show is that the adhesions for these 10 patients went  
21 down dramatically after the second look; after the second-  
22 look operative laparoscopy, found by a third-look  
23 assessment.

24           Then just a slide on foreign bodies. I might add  
25 here that there is no study that shows that pregnancy rates

1 are increased after the second-look laparoscopy, so although  
2 the cosmetic effect is good, it doesn't seem to impact on  
3 fertility.

4 The next is foreign bodies, and I have a picture  
5 of a titanium clip, just to stress the importance of foreign  
6 bodies in adhesion formation.

7 And then I address laparoscopy versus laparotomy  
8 as far as adhesions are concerned. I look at a number of  
9 procedures, adhesiolysis, ovarian surgery, myomectomy,  
10 demonstrating that there really is no difference whether the  
11 procedure is done laparoscopically or by laparotomy.

12 The next looks at outcome after adhesiolysis, and  
13 this is a study by Cassidy, a study by Dynan, a study by  
14 Farandi, and an old study by Francin showing that pregnancy  
15 rates are about 50 percent after adhesiolysis.

16 The next two slides demonstrate a very well done  
17 study years ago looking at Hyscon, and this was a study that  
18 I'm sure you are all familiar with, where 200 cc's of Hyscon  
19 and 200 cc's of saline were placed in the abdomen, and  
20 demonstrating--and a second-look laparoscopy after two to  
21 four months, but demonstrating that it was very effective,  
22 Hyscon, in preventing colon adhesions but pretty ineffective  
23 in preventing lateral pelvic sidewall, i.e., ovarian  
24 adhesions. And I use this mainly to show that this is the  
25 kind of study that's well designed, and really it gives an

1 answer, not necessarily an answer you want, but it certainly  
2 gives the answer that we're interested in.

3           Then I look at--then I have two other studies.  
4 These are Interceed studies. One looks--one is Takiba,  
5 looking at prevention of adhesions, and that looks at an  
6 Interceed group versus a control group; and the next is a  
7 pelvic pain laparoscopy study which I cannot read. It's in  
8 the American Journal but I cannot read the reference. It's  
9 too small or my eyes are too bad.

10           But, basically, these demonstrate studies where  
11 the diagnosis--one, the diagnosis was made on second-look  
12 laparoscopy; and the other is the assessment of a surrogate  
13 endpoint, helping pain. Both give important information,  
14 one direct and one inferential.

15           Next is just the application of Interceed through  
16 the laparoscope, demonstrating how important it is to apply  
17 Interceed--

18           DR. HARVEY: Dr. DeCherney, we're losing you  
19 again. Speak up. Thanks.

20           DR. DeCHERNEY: Showing the importance of being  
21 able to apply the barrier, or whatever the substance is,  
22 through a laparoscopic approach. Since this is an important  
23 feature, this is how most of it is performed.

24           And then I have another looking at that pain  
25 assessment, with the very important finding in this study of

1 the recurrence of pain. Pain I think is a bad way to  
2 measure adhesion formation, because the original results  
3 might be good but after a period of time about 70 percent of  
4 the patients have return of their pain, making this a poor  
5 surrogate endpoint.

6 And the last slide I have is just--I just want to  
7 take a look to review things--but the last slide I have is  
8 one of a peritubal cyst, and demonstrating many of the  
9 features about adhesion formation, the blood supply, the  
10 peritoneum, foreign body reaction, and the use of a barrier  
11 to prevent adhesions.

12 Now, just give me one minute to make sure that I  
13 covered everything I wanted to. Yes. So do you have any--I  
14 know that's a little sketchy, but do you have any questions  
15 for me at this time?

16 DR. HARVEY: We're going to poll the panel now,  
17 and I'll relay the questions to you if you can't hear them.

18 DR. DeCHERNEY: That's fine.

19 DR. BLANCO: All right. Does any of the panel  
20 members have any questions for Dr. DeCherney? Dr. Roy?

21 DR. ROY: Alan, I was wondering which surrogate  
22 markers you would then deem satisfactory for proper  
23 evaluation of the utility of any of these adhesion  
24 prevention modalities.

25 DR. HARVEY: Did you get that?

1 DR. DeCHERNEY: I heard it. Actually, I'm not--  
2 any of the surrogate markers are difficult to assess.  
3 Certainly pregnancy is multifactorial. Pelvic pain I  
4 mentioned because of the transient nature in 70 percent of  
5 the patients. Certainly bowel obstruction is extremely  
6 difficult, as you know, and after a year's period of time if  
7 a patient doesn't develop a bowel obstruction, she is just  
8 as likely to develop that bowel obstruction 20 years down  
9 the line as she is two years from the original surgery.

10 I thought it was interesting in the guidelines,  
11 the study, the bowel motility. That was a creative way to  
12 look at but I'm not so sure that that has a lot of promise.  
13 I have no experience with it. It just sounds to me like the  
14 endpoints would be too vague.

15 So to me the only way to measure the effectiveness  
16 of this is to do second-look laparoscopies.

17 DR. BLANCO: All right. Any other questions from  
18 the panel? Dr. D'Agostino?

19 DR. D'AGOSTINO: This is Ralph D'Agostino. With  
20 regard to the--is this working?

21 DR. HARVEY: Can you hear Dr. D'Agostino, Dr.  
22 DeCherney?

23 DR. DeCHERNEY: So far, yes.

24 DR. HARVEY: Okay.

25 DR. D'AGOSTINO: With regard to the surrogate

1 endpoints, the examples you were giving, they seemed to be  
2 both surrogate and clinical endpoints in the same study. I  
3 mean, the question I guess that bothers a lot of people is  
4 the surrogate endpoint as a replacement.

5 Are you suggesting in the presentation that the  
6 surrogate endpoints ought to be carried along with clinical  
7 endpoints, or are you actually suggesting along the way that  
8 they get replaced, they are used as a replacement? And  
9 that's where the difficulty comes in, into the problem.

10 I don't know if I'm making myself clear that the--  
11 let me just say it again. If you're running surrogates  
12 along with clinical endpoints, then you can see how useful  
13 they are and so forth. If you're running surrogates as a  
14 replacement of the clinical endpoints, then you're in real  
15 trouble. And which is the discussion that you're picking up  
16 on, and what is sort of the advice you're giving us in terms  
17 of later deliberations?

18 DR. DeCHERNEY: Well, I think this is--actually,  
19 to me it's confusing, because the surrogate endpoints are  
20 really the real endpoints, and they're really not in the  
21 traditional sense the surrogate endpoints. They're the  
22 easier, easier to assess endpoints.

23 So although there is kind of a confusion I think  
24 as far as clinical versus surrogate endpoints, I think  
25 you're better off looking at clinical endpoints versus real

1 endpoints, real endpoints being the exact observation of the  
2 changes in the anatomy based on--based on doing the use of  
3 adjunctive therapy to prevent adhesions. Because the  
4 clinical--to me the clinical endpoints are really the  
5 surrogate endpoints here because they're really--they're  
6 secondary endpoints, they're not primary endpoints, and  
7 they're so difficult.

8 I mean, I'm very troubled about using pregnancy as  
9 an endpoint because it has been used for many years, dates  
10 back to the time when Dr. Horn did this. So pregnancy is  
11 so multifactorial that even if the thing we're trying to  
12 achieve is pregnancy and that's the real endpoint, it's  
13 difficult to assess the cause and effect, and I use IVF is  
14 an example of that.

15 DR. D'AGOSTINO: Thank you.

16 DR. BLANCO: Sandra?

17 DR. CARSON: I just wanted to make sure I  
18 understood what you were saying. Are you saying that if a  
19 patient's pregnancy rate increases, she has no bowel  
20 obstruction, and she is pain-free, then it doesn't really  
21 matter what her adhesion score is?

22 DR. DeCHERNEY: Well, to be truthful, yes, I would  
23 say that, because you're really looking at the adhesion,  
24 you're looking at the prevention of adhesions. And if she's  
25 fortunate enough to get pregnant, it just might mean that

1 she has tons of adhesions but just not in the right place,  
2 and your therapy was not effective. On the other hand, her  
3 pelvis might be perfectly clean as far as adhesion formation  
4 after your surgery is completed, and she doesn't go on to  
5 get pregnant, and that shouldn't be used to judge the use of  
6 the substance that you're evaluating, basically.

7           So although it sounds kind of dumb to say, "Well,  
8 everything went great. Do you mean to tell me it didn't  
9 work?" I have to say that I would say that, because I think  
10 that's the problem with evaluating adhesion formation.

11           DR. ROY: Alan, this is Subir. Can you answer a  
12 slightly different question? In terms of adhesion scores or  
13 adhesion schematics, as to where the degree and extent of  
14 adhesions, can we be confident that the AFS classification,  
15 with or without modification, is a suitable tool to use, and  
16 particularly if one is to take the so-called average score?

17           DR. DeCHERNEY: Well, I have--you know as well as  
18 I do that there are inherent problems in these scoring  
19 systems. The best example for that to me is the ASRM and  
20 the scoring system, where when one went back--went back and  
21 looked at that, it was fairly non-predictive of outcome.  
22 And then of course they redid it and there is a second tier,  
23 a second level of adhesion--I'm sorry, of endometriosis  
24 scoring.

25           But this is the best that we have. I think that

1 it's okay. It is descriptive. Just two other comments  
2 about description. To me, the most valuable thing is an  
3 operative note or a narrative that really describes what the  
4 adhesions are like, and then scoring the patient at that  
5 point but also having that piece of information so that you  
6 can go back and kind of evaluate the subtleties of any  
7 scoring system.

8           So I would endorse the ASRM and the scoring  
9 system. I think it's fine. It does talk about density of  
10 adhesions, it does talk about location of adhesions, so as  
11 far as I'm concerned, I don't have much in the way of  
12 improvement that--improvement.

13           But the last thing is, although some people are  
14 high on videotaping results, I find this less helpful than a  
15 good narrative. And what people do, if they videotape their  
16 surgery, they are less likely to give you a good narrative.  
17 Actually, as you all know, the camera flies around. It's  
18 never in an area that you want to be in for long enough, and  
19 just as you begin to focus on an area, the person moves the  
20 endoscope.

21           So I know it sounds wrong to say because they  
22 should be complementary, a good videotape and a good  
23 narrative, I think people don't do a good narrative if they  
24 feel that the videotape will compensate for that, and I  
25 think that's a problem. But the bottom line answer to your

1 question is, I think the ASRM scoring system is okay. I  
2 couldn't think, I can't think of a way to improve it.

3 MR. : Let me just ask for clarification  
4 on one small point there, Alan. What about the average  
5 adhesion score? Do you think that has clinical utility, and  
6 that it correlates with potential clinical outcomes?

7 DR. DeCHERNEY: No, you know, I don't think so,  
8 because it's the same thing. You're adding different  
9 parameters to come up with an average score, and I think  
10 it's better to use, as most of the studies have done,  
11 location, looking at location, looking at the area that the  
12 adhesions have reoccurred and if 50 percent of the surface  
13 is covered with adhesions instead of 100 percent. So the  
14 average score I think is something that can be reported, but  
15 I would feel skeptical of a study if I read a study that  
16 only reported the average score, because there's too much  
17 hidden, could be hidden in that average, in that average  
18 score.

19 MR. : Let me ask you another question,  
20 because I'm still a little uncertain about when you're  
21 talking about surrogate endpoints and actual endpoints,  
22 exactly what your recommendation would be for the importance  
23 of each. I wonder if you would go over that a little bit?

24 I mean, it would seem that to some extent it  
25 depends on what the product claim is, as to which endpoint

1 might want to be picked, and the product manufacturer or the  
2 sponsor needs to be aware that such a thing as pregnancy is  
3 going to have multifactorial factors or other factors  
4 besides the adhesions that may prevent pregnancy, and  
5 they're going to have to deal with that if that's the  
6 endpoint that they seek to eventually be able to use for  
7 their indication. Could you elaborate a little bit on that?

8 DR. DeCHERNEY: I don't get the point. You mean  
9 as far as advertising and the ends?

10 MR. : No, I don't--I guess my question  
11 is, I don't get what you are recommending to be used as  
12 endpoints, and I want you to clarify that a little bit for  
13 me. In other words, what--

14 DR. DeCHERNEY: I would be unhappy if only  
15 clinical endpoints were used. I don't think that that gives  
16 us very good information as far as a product is concerned.

17 MR. : Meaning pregnancy, pain,  
18 obstruction--

19 DR. DeCHERNEY: --clinical versus--a clinical and  
20 surrogate endpoint, to me the clinical endpoints are too  
21 multifactorial to make--to endorse the agent.

22 MR. : So you would use some measure of  
23 adhesion, actual looking and quantitating in some form the  
24 adhesions?

25 DR. DeCHERNEY: Yes. Certainly in the beginning

1 of an evaluation of a product, I would demand that kind of  
2 evaluation. The others, I think just look at bowel  
3 obstruction. It could take up to 20 years until you had a  
4 true picture of how effective this was in preventing bowel  
5 adhesion. Let's say you used an adjuvant in hysterectomy to  
6 cover the cuff. When you were finished, you wouldn't have a  
7 good picture, if you used bowel obstruction, for many, many  
8 years, and in fact a very false impression, because say  
9 after five years the bowel obstruction rate was 2 percent  
10 and then it turns out to be 20 percent down the line. So  
11 that--I think that the clinical endpoints are not  
12 --I mean, maybe I'm taking too hard a stand, but I think  
13 that clinical endpoints are difficult to make a judgment as  
14 to the effects of these agents.

15 MR. : Thank you.

16 DR. DeCHERNEY: Are you trying to talk me into  
17 clinical endpoints?

18 MR. : No, not at all. I just was--I was  
19 unclear because I thought what you said, well, if you get  
20 pregnant then you're successful, so I thought you had first  
21 said clinical endpoints should not be used and then you were  
22 sort of implying, well, but if you have successful clinical  
23 endpoints, then that's of some merit. And you have made it  
24 clear that that's not your position, that you have to do a  
25 second-look laparoscopy and look at actual adhesion

1 information and some sort of quantitation in order to see  
2 whether you have some effect from the product, which I think  
3 is just clearer now for me.

4 DR. DeCHERNEY: Okay.

5 MR. : Alan, one other point. If one  
6 performs gynecological laparotomy surgery and the second  
7 look only looks at the pelvis or the gynecological  
8 structures, in your mind do you think that any reduction in  
9 adhesions should translate to the presumption that that  
10 compound is also effective intra-abdominally, that is, in  
11 the upper abdomen, in reducing adhesions?

12 DR. DeCHERNEY: I would be satisfied with that. I  
13 mean, years ago Dr. Diamond and I looked at that. There  
14 were a number of panels looking at that. It showed that  
15 there was--there wasn't good correlation. I mean, I don't  
16 know the proper term but it was--actually it was, I would  
17 say that abdominal adhesions were directly proportional to  
18 the pelvic adhesions, but not in a one-to-one ratio.

19 So if a patient didn't have any--you did  
20 gynecologic surgery and she had minimal pelvic adhesions  
21 afterwards, I would feel fairly confident to say that she  
22 had very little in the way bowel surgery. Of course, a lot  
23 has to do with the motility of the bowel, and the fact that  
24 we do very little to the bowel when we operate on patients,  
25 hopefully.

1 MR. : I think the question was more  
2 directed as, if a sponsor develops a study for preventing  
3 gynecologic adhesions and they demonstrated that by whatever  
4 the accepted methodology is, can you expand that  
5 automatically into also being able to claim that you should  
6 have a lower rate of upper abdominal adhesions from use of  
7 the product?

8 DR. DeCHERNEY: I would say yes. I would, based  
9 on my experience, I would say that that would be a fair  
10 assumption.

11 MS. : Just to go back once again about  
12 the endpoints, do you recommend, would your recommendation  
13 be to look solely at an anatomical--

14 DR. DeCHERNEY: Hold on one minute, because  
15 they're blasting something. I don't know.

16 MS. : Would your recommendation be to  
17 use solely an anatomical endpoint such as adhesion score,  
18 without any clinical endpoint? To take this to the extreme,  
19 if a product totally prevents adhesion reformation, however,  
20 none of the clinical endpoints are improved, then what use  
21 is it?

22 DR. DeCHERNEY: Well, okay. Let's say you do--you  
23 have a product and you evaluate it, and you do it--you look  
24 at 100 infertility patients, you do a second-look  
25 laparoscopy, and there is no adhesion. The pelvis is

1 perfectly clean, the tubes are open. And if none of them  
2 get pregnant, sure, I'd say that the product worked.

3 I mean, that's extreme, you're not going to have  
4 anything like that, but I would say that the product was  
5 effective because, you know, it's not going to make the  
6 patient pregnant. And if that happens, I think that that  
7 would be a fair statement to say, that if that patient's  
8 pelvis was totally clean, had absolutely no adhesions  
9 anywhere, I would say that the product was successful even  
10 if nobody got pregnant.

11 This is easy for me to say. I'm steps away.  
12 These are not my studies, and these are very difficult  
13 studies to do because it's second-look laparoscopy. So I  
14 have the advantage to take that purist approach.

15 DR. BLANCO: All right. We have a few more  
16 questions.

17 DR. CHATMAN: Alan, this is Donald Chatman. The  
18 functional endpoints are obviously not practical to use  
19 here, but there has to be some kind of temporal or some kind  
20 of time endpoint. What are you recommending in that area,  
21 in terms of evaluating any of these anti-adhesion products?

22 DR. DeCHERNEY: Hold one for one more minute.

23 DR. BLANCO: I'm sorry. Would you repeat that  
24 answer?

25 DR. HARVEY: He said hold on a minute.

1 DR. BLANCO: I guess everybody else heard it but  
2 me.

3 DR. HARVEY: Are you there, Dr. DeCherney?

4 MS. : Maybe his plane has left?

5 DR. HARVEY: Are you back?

6 DR. DeCHERNEY: I'm back.

7 DR. HARVEY: Okay. Dr. Chatman.

8 DR. CHATMAN: Again, just in terms of evaluating  
9 these anti-adhesion products, what sort of temporal endpoint  
10 would you recommend that we use?

11 DR. DeCHERNEY: Well, I, for lack of more  
12 information, my feeling is that, based on some of the  
13 studies that we've done over time, that these adhesions  
14 reform rather quickly, and therefore you can reevaluate  
15 these people two to four months down the line and find a  
16 valid answer. I don't think that much would be gained by  
17 laparoscoping these patients later on.

18 Dr. Mezzner and I did that many years ago. We  
19 laparoscoped patients two to four months after the surgery  
20 and then a year later, and this was a select group, and you  
21 had all the problems with clinical studies, but it turned  
22 out that these--that there was nothing gained as far as  
23 information and evaluation of the patients' adhesions by  
24 waiting more than that two-to-four month period of time. So  
25 I would still attest to that as being a valid time.

1 DR. BLANCO: Any other questions for the panel?

2 DR. DeCHERNEY: Do I have any questions?

3 DR. BLANCO: No, I--okay.

4 DR. DeCHERNEY: Okay. Do you want me to--are we  
5 though?

6 DR. HARVEY: Yes, we're here. If you want to stay  
7 on the line, you're absolutely welcome to do so, if you want  
8 to do that, and then pipe up if you're leaving. That's  
9 fine. If you want to leave us now, you know, that's okay,  
10 too.

11 DR. DeCHERNEY: I'll tell you what I'm going to  
12 do. I'll leave you now, and I'll check back in about an  
13 hour.

14 DR. HARVEY: Okay. Sounds good.

15 DR. DeCHERNEY: If there are any more questions  
16 then, and then I'll listen for a while then. Okay?

17 DR. HARVEY: Thanks very much.

18 DR. BLANCO: All right, Dr. DeCherney. We will  
19 now continue the presentation with Dr. Schwaitzberg,  
20 "General Surgical Aspects of Adhesion Barrier Studies."

21 DR. SCHWAI T ZBERG: Good morning. I would like to  
22 thank Dr. Harvey and her associates for the opportunity to  
23 have the floor.

24 Before I start, following Alan DeCherney is a  
25 tough act, but I do share one thing in common. We share the

1 same birthday, and that's coming up. And so every year Alan  
2 and I e-mail each other to remind each other that another  
3 birthday has passed.

4           What I would like to do is address the panel  
5 concerning general surgical aspects of the topic at hand.  
6 Next slide. The key points that I would like to address  
7 concern the guidance document. I will try not to make this  
8 a discussion too much about adhesions are an important  
9 topic, which is very tempting to do always, and I think I  
10 would like to discuss these topics in order and as they  
11 pertain to the guidance document, which I have in hand in  
12 case anybody wants to ask a specific question.

13           So the key points I would like to address are  
14 whether or not we need to assess infection potential, and at  
15 what stage of product development; the impact of malignancy  
16 potentiation from adjuvant products; whether there are good  
17 adhesions that we need to preserve; the use of surrogate  
18 endpoints; product labeling issues; how much efficacy is  
19 sufficient efficacy; adhesion reformations; then change, use  
20 just a little bit to talk about systems issues. Next slide,  
21 please.

22           My viewpoint of why I'm here today is listed in  
23 this slide. I have been working in this area since 1989.  
24 I've had the opportunity to participate and design  
25 preclinical studies, and I was in a position where I might

1 be amongst the first people in the world to apply a  
2 particular product in somebody's abdomen.

3           And when you contemplate it from that point of  
4 view, that's pretty scary. It's easy to do a follow-on  
5 study, it's easy to do the tenth study of another topic, but  
6 if you are going to be the first person to dump a new  
7 substance into somebody's abdomen, it's kind of scary, and I  
8 was very grateful to the sponsor to allow me to do a series  
9 of preclinical studies that would give me the confidence  
10 that what I was going to do was safe.

11           And I'd like to thank my previous chairman,  
12 Richard Cleveland, who's a heart surgeon, for teaching me  
13 something very important, and I'd like to start with an  
14 anecdote. Many, many years ago, he was a heart surgeon and  
15 he had a young boy with an infected chest. And they didn't  
16 know what to do, so they thought, "Well, maybe we ought to  
17 put some penicillin in the chest and clean up that  
18 infection," because it was the primary drug that was  
19 available.

20           Being the smart guy that he was, he said, "I'm not  
21 going to put anything into a patient that I haven't tried in  
22 the lab first." And I have taken that philosophy to heart,  
23 as the story unwinds. He put the penicillin in the chest of  
24 an animal, and the animal immediately fibrillated because of  
25 the potassium, a little thought that nobody had contemplated

1 as they suggested putting penicillin in the chest. And so  
2 my viewpoint since then, since the mid-eighties, is to  
3 follow what I call the Cleveland doctrine: I'm not trying  
4 it in people until I've seen that it's okay in some other  
5 model.

6 And having done that, the issues that I was  
7 concerned about in the late eighties are, will this make  
8 infection worse? I really wasn't so concerned about  
9 malignancy because I think we can isolate patients with  
10 cancer from clinical trials. I think we can isolate  
11 patients who are potentially pregnant from clinical trials.  
12 But there is no way to 100 percent guarantee that an  
13 infection won't occur; there is no way to 100 percent  
14 guarantee that we won't commit an injury during surgery and  
15 have a contaminated abdomen, even once some of these  
16 pretreatment things have been in effect.

17 So I--there was no precedent. There were no  
18 products. And I was very grateful to the sponsor for  
19 allowing me to take this tack and to show that infection  
20 studies are very important prior to placing these into the  
21 abdomen.

22 I had the opportunity then to participate in Phase  
23 II study design and Phase III study design, and I think my  
24 contribution was working out the method by which we could  
25 put laparoscopies through ileostomies and measure adhesions

1 to the abdominal wall in the Seprafilm trial, because we  
2 needed an endpoint in general surgery. We don't have second  
3 looks in general surgery, and studying adhesions in general  
4 surgery is an extremely difficult problem. We don't have a  
5 rationalization for putting this in. And I helped design a  
6 study for which I don't do surgery. I don't do J pouches,  
7 and so I basically blocked myself out of an exciting  
8 clinical trial, but was glad to see that it was successfully  
9 carried out.

10 I've had an opportunity to participate with many  
11 people in the room in developing their adhesion models and  
12 looking at their endpoints. I had the opportunity to attend  
13 a panel several years ago, and I'll get back to that.

14 From the clinical point of view, I sit as the vice  
15 chairman of the HIRC, and I worry about the issues of what  
16 do we put into our patients. I've spent years thinking  
17 about the ethical issues of surgical research and how they  
18 apply to the care of our patients. And most recently, as  
19 noted in my potential conflicts, I sit on a medical advisory  
20 board.

21 But I really earn my living doing surgery, and  
22 what I do mostly is laparoscopy, but if you're going to do  
23 work and publish in the field of adhesion, adhesion patients  
24 will find you. And adhesion patients, fortunately or  
25 unfortunately, depending on the case, have found me, and so

1 a good part of my clinical practice is evaluating patients  
2 with chronic abdominal pain, multiple laparotomies, partial  
3 bowel obstructions.

4           And, as such--next slide--I feel sort of like Cy  
5 Sperling. Not only am I an adhesion researcher, but I'm a  
6 user. My concern in all of this, and my interest in the  
7 last 10 years, is I am looking for--I need to grow some hair  
8 soon--but I need to find something for my patients. I have  
9 a collection of desperate patients out there, and I am  
10 vitally interested in helping them, and I have learned that  
11 surgery in and of itself is not the way and we are going to  
12 need adjunctive therapies. Next slide.

13           So what are the hazards? You know, I'm not a  
14 toxicologist, and I think that there are experts in  
15 toxicology, but as it applies to general surgery,  
16 infections, malignancy, and I worry about the prevention of  
17 good adhesions, and you can go back and look at some of the  
18 things we did looking at, well, what if we don't make a full  
19 anastomosis? What if we know there's a leak?

20           And so I cooked up this 90 percent anastomosis  
21 model, saying, well, we better be able to make sure that  
22 this stuff isn't so good that we prevent good adhesions from  
23 forming. And I think the bottom line is, at least for  
24 barriers, that the formation of adhesions to close leaks and  
25 fistulas is so strong that it is greater than the ability of

1 the barriers to prevent them. So unless we have a product  
2 that interferes with the way collagen is formed, barriers  
3 probably won't ultimately prevent what I call the good  
4 adhesions. Next slide.

5 But as we look at infection potential, there's a  
6 variety of ways that this can be manifested, and I think  
7 this is very relevant to the guidance document because  
8 different substances will have different impacts on the  
9 ability to cause infection. If you look at some of the  
10 substrates that are carbohydrates, they cause or enhance  
11 infection because they're food for the bacteria, and we have  
12 looked at that issue in some of the materials we have  
13 tested. And other devices will cause or potentiate  
14 infection because they serve as a foreign body effect..

15 So we have to, depending on the nature of the  
16 substrate, look at both of these. Do bacteria grow in the  
17 presence of this because it's food, or is there a  
18 significant foreign body effect? The problem with this,  
19 having tried to create animal models of infectivity and  
20 talked to other people that have, as well, is that this is  
21 tough work for the predictor of human disease.

22 I've spent 10 years trying to make models that  
23 have some relevance to human disease, and if you go back and  
24 you look at other diseases, things like, you know, IL-1-RA  
25 and some of these sepsis drugs, the models are great but

1 they didn't reflect clinical disease. And I think that's  
2 the real challenge: How do we create models that reflect  
3 clinical disease, so that you've done an animal study and  
4 it's meaningful in some way to the next step of the process?  
5 And I don't think we have a perfect answer.

6 One of the things that I would say is, is that the  
7 nature of bacteria in animals is different and that needs to  
8 be taken into account. The nature of how bacteria clear is  
9 a little bit different. And so these are guidelines, these  
10 are clues that they may be okay for clinical trial. In  
11 addition, I was concerned that antibiotic activity could be  
12 affected by products, and we did a variety of tests to look  
13 at and make sure that our antibiotics would be effective in  
14 the models we were studying. Next slide.

15 So the net results of this is that I strongly  
16 believe, as a clinician, as an advocate for the patient, as  
17 an IRC member, that these in vivo testings should be done  
18 and completed prior to the initiation of Phase I trials. I  
19 think we need to know that these will not hurt our patients,  
20 that we--in the presence of contamination, these studies  
21 should be done and completed before putting it into any of  
22 our patients.

23 Now, the problem with these animal models, and I  
24 think that we're on a moving target here, is that many of  
25 the studies concern mortality, LD-50 models, LD whatever

1 models. And I think, as you travel around the country and  
2 you talk to different ethicists in the field, that the use  
3 of mortality, what is known as the "feet up, feet down"  
4 approach to animal studies, is going away.

5           And I think that people are going to need to look  
6 into the future, that the use of mortality as an endpoint in  
7 animals is, in some geographic areas, of questionable  
8 efficacy and not allowed, and that sponsors should be  
9 encouraged to create models where this isn't a problem,  
10 whether these animals are autopsied and humanely sacrificed  
11 at 48 hours to look at some of the clinical endpoints. But  
12 I would strongly encourage the panel to consider and the  
13 manufacturers to consider the landscape of animal care, and  
14 that mortality studies, unless they are absolutely  
15 necessary, and I'm not sure they are necessary here, that we  
16 have to come up with more creative ways to perform these  
17 studies. Next slide.

18           In vitro testing I think is important as well, and  
19 I think that they should address the issue of whether  
20 bacterial growth is enhanced in the presence of a device.  
21 And I think these are relatively simple studies, these are  
22 straightforward studies. They're not particularly mind-  
23 boggling, expensive studies, and I think this is just some  
24 of the basic groundwork. And these are outlined in the  
25 guidance document, which reflects a lot of work and a lot of

1 thought and is a very good document in general. Next slide.

2 Well, malignancy potentiation is a tough one  
3 because it falls into many phases. One is, if you're doing  
4 a patient in a clinical trial and you find that they have  
5 cancer, they should just simply be excluded. They should  
6 not have the device put in. They should just be eliminated  
7 from the trial.

8 But what happens if you find that the patient had  
9 a malignancy after you have applied the device, whether it  
10 comes back in a biopsy, whether it wasn't apparent when you  
11 first put this in? And I think the answer is clear. I  
12 think they should be included in the intention to treat  
13 analysis. I think the sponsor should have the right to also  
14 analyze this patient separately to see if there's any  
15 particular effect, but there shouldn't be a penalty as long  
16 as the intent was to avoid putting these patients in in the  
17 first place.

18 The problem that we find is that cancer comes in  
19 two forms, the type that you can cure completely and you  
20 suspect that the barriers would have no impact, and the  
21 types of patients that have residual tumor, who are  
22 functionally immunosuppressed, and that this combination of  
23 infection potential and immunosuppression from malignancy  
24 would be a very tough nut to crack and make any sense out of  
25 the data, particularly in small numbers. So we should work

1 to avoid these patients. Next slide.

2 Now, there are clearly good adhesions, and I think  
3 that the sponsors are under the obligation to show that  
4 basic issues such as wound healing and potentially  
5 anastomosis healing are not affected in a preclinical model  
6 prior to Phase I studies, and there's a variety of ways to  
7 do that. The guidance document looks a histopathology, but  
8 you might suggest that some aspects of wound strength might  
9 even be more important.

10 Early wounds are kept closed by their sutures, but  
11 somewhere around the 10-day mark there is a crossover  
12 between healing and suture strength. And since most of  
13 these barriers are going to be in place for not an  
14 extraordinarily long time, but they're going to be in place  
15 for at least 10 days, knowing that the weakest time in an  
16 anastomosis or a wound is 10 days, I think we're going to  
17 absolutely need to know for sure that these have been looked  
18 at in preclinical models prior to initiating Phase I  
19 studies. Next slide, please.

20 Now really this is the heart of the matter, this  
21 slide. The purists, and having attended panel meetings, can  
22 use the fact that clinical endpoints are the only thing that  
23 really counts, and I would debate that. And Dr. Carson, as  
24 a double Baylor alumnus, I would agree with Dr. DeCherney:  
25 If you have an issue where the bowel obstruction rate

1 doesn't change, the pregnancy rate doesn't change, the  
2 abdominal score doesn't change, but the adhesions are gone,  
3 that in fact is a substantial clinical benefit.

4           Now, where is that a benefit? It's a benefit for  
5 all those patients that are going to have a second surgery.  
6 I'm doing a lot of reoperative surgery. In fact, I go  
7 through weeks at a time saying, "Please find me a patient  
8 with a virgin abdomen, because I don't think I could take  
9 another adhesion-filled, long laparotomy."

10           The absence of adhesions, the elimination of  
11 adhesions themselves, will reduce morbidity, mortality,  
12 hospital stay, subsequent complications, if in no other  
13 arena except the arena of second-look surgery, second  
14 reoperative laparotomy surgery. And so I think that the  
15 adhesions in and of themselves, the presence or absence of  
16 the adhesions, are a valid endpoint in which the sponsors  
17 and manufacturers can gain market approval.

18           I think we have been way too hung up on the  
19 clinical endpoints, because the adhesions in and of  
20 themselves have meaning, and that the endpoints that people  
21 have been looking for are multifactorial. And if we insist  
22 upon these endpoints, well, we might as well just pack up  
23 our bags and go home, because there is no good way to do a  
24 study. Unlike cancer, cancer is easy; five years, if you're  
25 cured, you're cured. Infections, the infection is good or

1 bad. Heart disease, we can measure your EF, we can measure  
2 your blood pressure.

3 But a five-year study in adhesions is nothing, and  
4 we just can't do 20-year studies, let's be serious, at least  
5 in the PMA process. And so I think that we're going to be  
6 forced to accept, for good, clear, rational reasons, that  
7 the endpoints of adhesions are the real endpoints. And I  
8 think Alan has got it completely right; we have got it  
9 completely backwards. The clinical endpoints are the  
10 surrogate endpoints. The adhesions, in and of themselves,  
11 are valid targets for our activity. So the realists say the  
12 surrogate endpoints, which I will now call the real  
13 endpoints, are really all that's available to us in a  
14 clinical trial. Next slide.

15 But you can't have your cake and eat it, too, and  
16 I think the manufacturers will have to limit their claims to  
17 that the adhesions are reduced. I don't think that they are  
18 going to be able to show pictures of patients with bowel  
19 obstructions that now have smiling faces, and patients in  
20 pain who now have Tylenol instead of Percocet. I think if  
21 we're going to take this approach, we're going to have to  
22 say that we are going to reduce adhesions. And if  
23 clinicians feel this is important, they'll use it, if it's  
24 safe. Next slide.

25 Now, this leads us to what can you claim and where

1 can you claim it? I think there's a couple of really  
2 interesting dilemmas in this regard. Next slide.

3           The first is laparoscopic versus open, and this  
4 will not be the last that we ever hear of this, and this is  
5 going to go around in circles for years to come. But there  
6 is no question that the extent of adhesions laparoscopically  
7 are different than the extent of adhesions done open. So  
8 the first thing you learn is, no study should have a mixed  
9 population of patients. There should be no mixed  
10 laparoscopic and open trials, because laparoscopy results in  
11 less de novo adhesions, and that has been shown over and  
12 over and over again.

13           And what it leads you to worry about is, well,  
14 then, maybe if we're doing a laparotomy, we're making more  
15 adhesions and they're harder to cure, and so can you extent  
16 laparoscopic data to laparotomy data? Well, is there any  
17 sufficient--is there any real basis to believe that the  
18 efficacy, if you can find it in one arena, will be  
19 nonexistent in the other?

20           And I think one of the key issues is, at least in  
21 laparoscopy, I think you have to show that there's no CO2  
22 effect. CO2 causes acidosis; acidosis may cause a chemical  
23 reaction in some of these products. So I think that that's  
24 one rational basis to worry. Is your product affected by  
25 changes in pH?

1           But in the absence of that and in the presence of  
2 good, rigorous, nonhuman data or in the presence of Phase IV  
3 data, I think that a claim to reduce adhesions is a claim to  
4 reduce adhesions, and I'll get back to what I think we can  
5 do to strengthen that approach. But I think if a  
6 manufacturer offers up a laparoscopic trial and shows that  
7 there is a reduction of adhesions, that this should not  
8 limit them from using it in laparotomy. Next slide.

9           Now, the next thing is, you do the study in the  
10 pelvis, and what do you say about the upper abdomen. Well,  
11 you could look at it from a variety of different  
12 standpoints. First of all, all these are peritonealized  
13 surfaces, and I think that there should be some data.

14           If you're going to do a pelvic study, you need to  
15 show in at least some non-human model that your results are  
16 generalizable, so that people can have some confidence.  
17 You've got to provide the panel some confidence that your  
18 results can be generalizable.

19           But I don't think you can segregate the abdomen  
20 into a pelvic compartment and an abdominal compartment  
21 because they're not two different compartments. The stuff  
22 from the abdomen drops down in the pelvis. Fortunately, we  
23 don't find the uterus up in the upper abdomen very often.  
24 I'm not sure what I would do if I found it there. But I  
25 think that we've made these issues just way too complex.

1 The peritonealized surfaces are the peritonealized surfaces.

2           Having said that, I do have one concern. We do a  
3 lot of our animal models in animals that stand on four legs,  
4 and yet we stand on two legs, and so I'm going to put in my  
5 bias, my plea, is that I think primate models are better  
6 than models of animals on four legs, because we stand up and  
7 these are the stresses; animals, the stresses are just  
8 oriented in a different area. And I believe, actually would  
9 enjoy the opportunity to show that maybe there are different  
10 patterns of adhesions.

11           But if you could show in a stand-up animal model  
12 that you product is generalizable to the up and down, and  
13 then do a clinical trial to prove that you had prevented  
14 adhesions, I think you have made your point. Next slide.

15           Sufficient efficacy, this is another tough  
16 question. You know, efficacy of some of these products that  
17 are currently in the market is in the twenties, 20-something  
18 percents, and that doesn't sound that great in some ways.  
19 And I think that the key thing is that this is sort of like  
20 cancer. This is a tough problem, and I believe that long-  
21 term strategies to adhesions may require multimodal therapy;  
22 that it's not just going to be this drug or this device or  
23 this barrier; that we are going to need to attack this  
24 problem using a multimodal approach.

25           And one of the things that became clear to me,

1 having sort of take this analogy from the cancer concern, is  
2 that there are some products out there that have limited  
3 efficacy against cancer, but combine them with other  
4 therapies and they become synergistically effective. And so  
5 I would make the plea that products of lowish--we all know  
6 what "lowish" is--but statistically significant adhesion  
7 reduction should be approved as long as they're safe,  
8 because this will allow for several things.

9           Number one, it will allow us to then do multimodal  
10 clinical trials, and I think that's going to be very  
11 important because I don't think this single mode therapy is  
12 the answer. Two, if the efficacy is too low, then this is  
13 America; the marketplace will decide. If they don't have a  
14 viable product because people don't think that 15 percent is  
15 good enough, well, it will sit on the shelf. And, thirdly,  
16 I think we've got to remember that patients are cared for  
17 one at a time, we are desperate for solutions, and that I  
18 think we have to have a little faith in our clinicians as  
19 well. Next slide.

20           So this is--I probably did too much of this, but  
21 this is the question sort of at hand. This is a woman that  
22 I operated on recently, and she has a de novo adhesion. She  
23 had a low incision. This is way up by the umbilicus. This  
24 is not in the operative site of trauma. This is, I think, a  
25 2(b) or something, and this is a de novo adhesion. But it's

1 a piece of bowel on a focal point. I looked at this  
2 adhesion and said, she's just a young woman, this is a  
3 potentially, across her lifetime, clinically significant  
4 adhesion, because you can torse on this single spot, and I  
5 was doing a lap hernia repair.

6 So I'm in a quandary. What do I do? Do I leave  
7 it there? She's not having a problem today, never had a  
8 problem, never had a bowel obstruction. I'm worried that  
9 she's going to torse on this, but what do I really have to  
10 offer this patient? Now I'm in the game of adhesion  
11 reformation, and I've got nothing to offer her, really, when  
12 it really comes down to it.

13 This is how a de novo adhesion becomes a  
14 clinically relevant adhesion. I wish this adhesion never  
15 occurred, even though she hasn't had a symptom from it. I  
16 couldn't decide--I mean, I did decide. I cut the adhesion  
17 back, got it out of the way. But I was worried that I was  
18 going to (a) make the situation worse, and that she would  
19 just rescar this; and frustrated that I didn't have  
20 something to offer her in this regard. Next slide.

21 And I think this is the most important issue by  
22 far, because we can dilly-dally about, you know, you've got  
23 to put it in 100 people to see a benefit in a couple, but in  
24 those of us who operate on patients who have adhesions,  
25 these are clinically significant adhesions. We're going to

1 cut them, and every time you cut an adhesion, you make the  
2 clinical situation potentially worse.

3 This is really where the most important progress  
4 over the next hopefully 5 or 10 or 20 years will be, and yet  
5 there is no good general surgery model to study this. And  
6 this is why I would implore the panel to not segregate the  
7 abdomen into abdominal and pelvic compartments. We don't  
8 have a gynecologic model. We are stuck.

9 The only way we're going to be able to study this  
10 as general surgeons are long-term, longitudinal, Phase IV  
11 trials in products that are given a chance as long as  
12 they're safe. And if I could come up with a--I have spent  
13 10 years trying to come up with a clinical study. It was  
14 easy to come up with the general surgery models for adhesion  
15 prevention. This is hard.

16 And so my solutions are not very good solutions.  
17 And I would hope that if we can show that products have some  
18 anti-adhesion activity, that if they're submitted to a  
19 rigorous model, and in my mind I think these are upright  
20 primate models, where we can do a much better job of  
21 simulating human surgery--I mean, I'm not talking pelvic  
22 sidewall models. I mean, I know this has been done. I'm  
23 not a big fan of pelvic sidewall for answering the tough  
24 questions. I think they're great screening studies. I  
25 think they tell you whether you've got a potential product.

1 But I want to do tough studies, and I like to see  
2 the manufacturers stand up and do tough studies, because  
3 even the most expensive animal model will be done more  
4 quickly for less cost than a bad human trial that is looking  
5 at many, many multifactorial situations.

6 And I think this is what adhesion problems have  
7 led us to. They're going to lead us to solutions that we  
8 would consider to be inappropriate. We would never do a  
9 drug study this way, we would never do a cancer trial this  
10 way, but we've got a tough problem here. We've got a  
11 different problem here, and it's an elegant problem and it's  
12 a fascinating problem, although adhesions on the surface  
13 seems kind of dry. But when you really get into it, it's  
14 one of the more elegant clinical problems that we can study.

15 And I think that if we're going to try to look at  
16 some of these things, I would hope that we would be able to  
17 get additional indications from well-done, rigorous primate  
18 models, and those are products that have already been  
19 approved for adhesion prevention. And then the other way of  
20 looking at this is long-term registries. Next slide.

21 It's a costly problem, \$1.7 billion. This is all  
22 Dr. Ellis' data. \$1.3 billion, and you suggest from this  
23 that the problem is becoming less important, it's .4 billion  
24 dollars less. But no, I think what this reflects is that we  
25 have become more efficient with our health care, because we

1 have more hospitalizations for less days, and this is the  
2 reflection of probably managed care on the problem. Next  
3 slide.

4 Well, this is the real face of adhesions. This is  
5 the real patient who gave me permission, in writing, to  
6 bring her picture to the panel today, and you could look at  
7 her story. I didn't do her first two operations. Maybe I'm  
8 just slower than her previous surgeons.

9 But her last enterolysis was 17 hours at the  
10 table; 17 hours on the table. Previous enterolysis, nine  
11 hours. And she's back, and I would do anything, anything,  
12 to not have to operate on her, because I've got nothing,  
13 nothing to offer her. And I have a collection of patients  
14 like this. This is Rosemary Sedacki, is her first name, and  
15 Rosemary isn't the only one.

16 And so my passion for taking care of these  
17 patients is multifactorial, and so when I came and looked  
18 and studied these problems, and I've spent years and year  
19 thinking about these problems and Alan has spent years and  
20 years thinking about these problems and we still don't have  
21 solutions.

22 When I had an opportunity to come to observe a  
23 panel meeting a few years ago, I was really very excited. I  
24 mean, I had been doing adhesion research for a couple of  
25 years, and I was coming to the federal government, and I'd

1 like to share my experience with you. Next slide.

2           So this is my crystal wonderland. I felt like  
3 Alice in Wonderland. So I went to the pre-panel meeting and  
4 listened to the presentations, and there were no major  
5 objections made to the efficacy of the particular product.  
6 it was plus/minus, but it was going to be recommended to go  
7 to panel.

8           And so that was February, and I didn't meet  
9 anybody on the panel because that's the pre-panel meeting.  
10 I came to the panel, and I went to the panel meeting and I  
11 was disappointed, quite frankly. I looked at the--I  
12 listened to the presentations, I talked about some of my  
13 research, and there was a potential conflict for industry,  
14 but I think that's okay, because anybody who has done any  
15 research has worked with somebody, somewhere. This is--  
16 there is just almost no pure basic research. Maybe there  
17 should be, if we don't want people--if you want an all-  
18 nonconflicted panel.

19           I listened to the two presentations, one from  
20 general surgery and one from gynecology, and was kind of  
21 disappointed. I thought I was going to meet the experts.  
22 And then the thing that was really amazing to me was that  
23 even though no objections were at the February pre-panel  
24 meeting, the statistician stood up and said, "I don't think  
25 the study is valid." I'm sitting there going, "Well, why

1 are we here, then? Why haven't these problems..."--I'm  
2 looking at this as a taxpayer, now. Next slide.

3 So forget about it as a clinician, I'm now a  
4 taxpayer, so I did my--I went home and did my homework, and  
5 I did a Medline, and everybody on the panel--notice, there's  
6 no names, this isn't personal, and this is just me as a  
7 taxpayer trying to wonder what the process is doing for me.  
8 And the two people in yellow are the ones that made the  
9 presentations. Six Medline items, 13 Medline items at the  
10 time, never participated in a clinical study, never done  
11 adhesion research. And I'm going as a taxpayer. Is this  
12 what I'm paying for? We're all taxpayers here. Is this  
13 what we're paying for?

14 There were several good people that belonged on  
15 the panel, some with some very good experience, but only one  
16 person that had ever studied adhesions or written a paper  
17 about it, and as a taxpayer I was disappointed.

18 I listened to the panel presentations, and they  
19 said, "I've reviewed the mountains of material they sent me.  
20 It took me a while because I'm not a good reader and I don't  
21 like to read that much." And I asked myself, as a taxpayer,  
22 "Why are you here? If you don't want to do this, why are  
23 you here?" And I was, frankly, I was disappointed. Next  
24 slide.

25 So what did I do. I wrote my Senator. I was in

1 Massachusetts. I wrote my Senator from the viewpoint of a  
2 taxpayer, a clinician, a potential patient some day, a  
3 researcher. And, you know, we live in America. This is a  
4 capitalistic society. We all have pension plans, I hope.  
5 And how would you feel if some company you invested in went  
6 down the tubes because they got kind of a superficial review  
7 on their product?

8 I'm not questioning the merits of the answers.  
9 This isn't about the answers. I have no financial interest  
10 in the product. I'm just trying to look at this from a lot  
11 of different views.

12 He wrote back, "We'll look into it." Notice, "he"  
13 is in quotes. I got a letter from the FDA: "There's no  
14 problem here." And then he wrote back to me: "See, there's  
15 no problem." So my response to all this is, grow up and get  
16 over it, and I did. And eagles were out at the time, and I  
17 clearly moved on. Next slide.

18 So, in summary, this is a tough problem and this  
19 is going to require unique solutions. Five year follow-ups  
20 are meaningless in this game if you want to look at clinical  
21 endpoints. Surrogate endpoints are all that's available.  
22 Adhesion reformation is the most important issue, and I  
23 think that we're going to need creative ways of looking at  
24 whether it's rational to allow labeling in this regard  
25 because, quite frankly--next slide--we need a high level of

1 commitment.

2           We need a level of commitment from the  
3 manufacturers that may be new to them. I think we're going  
4 to need to do aggressive and potentially long-term post  
5 marketing studies, and manufacturers that aren't in this for  
6 the long haul may be in the wrong field.

7           I think at the same time, as a taxpayer, I expect  
8 as Joe American Citizen that the FDA will provide expert  
9 analysis of these products. Because, quite frankly, what  
10 does the guy on the street think the FDA does? What do they  
11 think the panel, what do they think you guys are supposed to  
12 be doing? That is, protect us from the dangerous products,  
13 but make sure that the things that are going to be useful to  
14 us make it to market.

15           It's easy to say no. The safe position is always  
16 no. There's no risk in no. And even though we have an  
17 excellent process, we will send products to market and we'll  
18 take them off. There are antibiotics that come off. And  
19 we're never going to be perfect, but I think that the  
20 American citizen sort of thinks that they depend on you and  
21 they trust you to provide expert analysis, and that a  
22 similar commitment from the manufacturers will be necessary.  
23 Next slide.

24           This guidance document is going to have to last us  
25 for a while, and I think that one of the things that we have

1 to recognize is that, clinicians being what they are, most  
2 clinicians, if you look at the compassionate trials for some  
3 of these things, they are interested in adhesion  
4 reformation.

5           We need a way to get at labeling for adhesion  
6 reformation, because they're going to use it anyway, so  
7 we've got to get our heads out of the sand and say, all  
8 right, if you make it through Phase I and you have adhesion  
9 potential, how are we going to get it to the next stage  
10 where clinicians are really going to use it? We're just  
11 kidding ourselves. It's kind of silly. We approve it for  
12 one indication and they're using it for something else.  
13 We've got to get it into reality in this regard.

14           So this guidance document needs to be sufficiently  
15 robust, because to look at the creative ways of establishing  
16 the stated goals, whether it be for infection potential, or  
17 trying to prove the point that adhesions are prevented, or  
18 adhesion prevention is withdrawn. I think the guidance  
19 document needs to recognize that this field represents  
20 unique challenges that things like even cancer, heart  
21 disease and infection don't bring to the table; and that,  
22 finally, that we're going to have to hopefully allow  
23 solutions that we would have never considered acceptable in  
24 other arenas, acceptable to allow things to move forward as  
25 long as they are sufficiently safe to our patients.

1 I am very grateful to the floor. I'm very  
2 grateful to the floor, since the floor obviously knew that I  
3 have been critical of the process in some ways, and it's a  
4 credit to the institution to stand up there and have  
5 somebody who was disappointed, to let them have their say,  
6 and I am deeply appreciative. Thank you.

7 DR. BLANCO: Thank you, Dr. Schwaitzberg. I  
8 wonder if you would entertain a few questions?

9 DR. SCHWAITZBERG: Your turn. Fire back.

10 DR. BLANCO: Sandy?

11 DR. CARSON: You said at the very beginning that  
12 you don't have second looks in general surgery?

13 DR. SCHWAITZBERG: Very rarely. There's two  
14 exceptions. One is in, if you make a sigmoid colostomy for  
15 diverticulitis, and you go back and take it down. And the  
16 other obvious one is, for those patients who are getting J  
17 pouch, really a proctoscopy for ulcerative colitis; that  
18 opportunity to look at the abdomen in that model is very  
19 real.

20 Now, when I helped design the model, to get to  
21 your point, and I looked at this other model for pelvic, and  
22 there's the sidewall and there's the tubes and the ovaries  
23 and all these things, and I was going nuts because I said,  
24 "Well, let's try to do something more simple." The  
25 incision, the adhesions are there or they are not.

1           And the models for which some of these other  
2 products were proven, they don't get to interloop things.  
3 They just prove the point. Did you or did you not prevent  
4 adhesions to the incision, and is that important?  
5 Absolutely, it's important. People get holes in the bowel,  
6 way in the abdomen. So that's pretty much it for us.

7           DR. CARSON: Well, I'm a little confused. Why not  
8 just do a second-look laparoscopy like we do in gynecology?

9           DR. SCHWAITZBERG: Well, there's an ethical  
10 problem, so let me put on my HIRC cap. Surgery for research  
11 purposes, of no potential clinical benefit, doesn't fly  
12 through too many local IRBs.

13           DR. CARSON: Well, what's different about that and  
14 doing it for gynecologic surgery?

15           DR. SCHWAITZBERG: That's a good question. The  
16 general surgery arena doesn't have a mechanism by which it's  
17 commonly used. It's not the standard of care. See, one of  
18 the ways the gynecology arena has gotten through this is  
19 that there are varying standards of care in different  
20 pockets, and for some individuals it is their standard of  
21 care to go back, in their fertility practice, to go back and  
22 look at these adhesions. It's almost nowhere the standard  
23 of care in general surgery. It just simply is not  
24 considered valid.

25           DR. BLANCO: Any questions?

1 MR. : I have a question and it's  
2 different. Obviously, one of the first statements you made  
3 was the difference between surrogate types of outcomes and  
4 real outcomes.

5 Obviously, you know, this gets us into the realm  
6 of human experimentation, because obviously the adhesive  
7 things that you get, number one, aren't standardized if  
8 you're doing, you know, surgery on patients. Secondly, you  
9 know, you can't make standardized wounds and stuff like  
10 that. So that even if you go back and look at scoring  
11 adhesions and stuff like that, it's still not totally a  
12 scientific outcome that one can analyze very well  
13 statistically.

14 I mean, how do you, how would you suggest that we  
15 overcome this difference, so that what you're proposing  
16 basically on a second look or reevaluation of adhesions  
17 versus a surrogate, is one any more scientific than the  
18 other?

19 DR. SCHWAITZBERG: I think that's a fair question,  
20 and I think that the first answer, as I get to this, is that  
21 research is a specialty, and I think that you hit some of  
22 the issues right on the head. As clinicians we get very  
23 little training in research as a specialty.

24 And when I looked at this problem, going back, if  
25 you want to talk about the Seprafilm trial, I was interested

1 in--the primary goal was the presence or absence of any  
2 adhesion whatsoever, because that takes us out of scoring  
3 systems. Scoring systems have all kinds of problems. And,  
4 you know, we've looked at area, and I was very interested in  
5 just the linear aspects of the thing because I was trying to  
6 make it as simple as possible, as obvious as possible.

7           And one way that a product wins is the total  
8 presence or absence of any adhesion. I would think that  
9 most people would agree that's easy to score. It's there in  
10 any form; no, it's not. So that's one potential answer, and  
11 you can standardize some things. If you look at that trial,  
12 the use of omentectomy was standardized, the way the  
13 incisions were made, to the extent of humanly possible.

14           One of the things that amazes me, that any  
15 clinical trial is ultimately successful, because the amount  
16 of noise that's introduced when you're looking for the  
17 signal is so great. I mean, you hit the nail exactly on the  
18 head. That's why efficacies of 20 percent in a clinical  
19 trial really may mean that they're much more of a case than  
20 that, but the noise that's introduced is just amazing. And  
21 the people that do sepsis research are suffering from this,  
22 you know, signal-to-noise problem in the way the patients  
23 are cared for.

24           But that's why I propose that high level,  
25 rigorous, well done simulated surgery, primate research--and

1 these are survivable studies, these are not necessarily  
2 sacrifice studies--may give us some of the best clues as to  
3 how good a particular device is in this regard.

4 Now, the contra point to that is that if you see  
5 an effect despite all the noise, boy, you've really got  
6 something there. And I think that's really the basis of  
7 most clinical studies today, that if the signal emerges out  
8 of the noise, you have something. If you've got all this  
9 variability and it's clear you have less adhesions, you've  
10 got a clean product.

11 So, one, presence or absence of adhesions; two, an  
12 obviously strong clinical effect despite the variability;  
13 and, three, high quality primate studies, in my mind, and  
14 though people would argue that other models are just as  
15 valid, is what I would recommend.

16 DR. BLANCO: So what you're saying is that  
17 basically a good, solid primate animal model would be more  
18 the determining factor of efficacy than a human clinical?

19 DR. SCHWAITZBERG: I think you've got to show some  
20 efficacy in people. I think you've got to somewhere come to  
21 the table and show something. But I think behind that, if  
22 you've done really excellent studies, that that should be  
23 part of your supporting package. I think if you did really  
24 excellent studies, if you didn't have an effect, you  
25 wouldn't go to clinical trial; and that if you had a

1 successful clinical trial and you were able to show in your  
2 primate studies that your effect was generalizable  
3 throughout the abdomen, that should be sufficient.

4 DR. BLANCO: Yes?

5 DR. D'AGOSTINO: I'd like to follow that a little  
6 bit further, and I'd like to introduce myself as a  
7 statistician--

8 DR. SCHWAITZBERG: From Boston?

9 DR. D'AGOSTINO: --from Boston. We have the same  
10 Senator or Senators.W

11 DR. SCHWAITZBERG: We better take the train home.

12 DR. D'AGOSTINO: Exactly. What I'm trying to  
13 think of is the implication that the discussion or your  
14 presentation, which I thought was very informative, the  
15 implication that has on designing a clinical trial.

16 I agree, and some of the comments I was going to  
17 make as we move through the day is, the scoring systems are  
18 very rough, and once you get into them you get into ordinal  
19 scales and you have lots of problems. If you could cut  
20 points and say you have made a goal of therapy, you have  
21 total adhesions or maybe some percent or something like  
22 that, some measurement, that's a wonderful idea. But it  
23 then puts you at a disadvantage in terms of trying to show  
24 an effect, because now you're after a bigger goal.

25 And the other thing is that you've coupled now

1 with the surrogate as being the primary endpoint in some  
2 sense with the total absence, but the clinical efficacy is  
3 still there. How does one put together a trial in terms of  
4 what you're aiming for? Would you say that the trial should  
5 be that you're looking at the total absence of adhesions as  
6 your primary, and then the clinical of pregnancy or  
7 something, or whatever the appropriate clinical, as a  
8 secondary? Is that the way your presentation is to be  
9 interpreted?

10 DR. SCHWARTZBERG: I think that in one--I go back  
11 to my comments of why having, when you get the mounds of  
12 data, having experience in this field really is important in  
13 this arena. It is because when I helped design that trial,  
14 it was very risky because you were going to go put all the  
15 marbles on the table, and the presence or absence of  
16 adhesions was rather unique. The only secondary shot you  
17 got was the extent of adhesions along that, so really it was  
18 kind of risky. It was actually kind of avant guard for the  
19 time.

20 I think that as the sponsors put this together,  
21 they need a multitiered clinical evaluation. Number one,  
22 the presence or absence of adhesions is a good one. Then I  
23 think they should be allowed to apply a scoring system. And  
24 at the same time, you know, we get hung up on, "You said  
25 that adhesions would be reduced 42 percent and it's only

1 reduced 28 percent. Therefore, you didn't meet your goals.  
2 See you later."

3 I think that this is such a difficult problem,  
4 that people who design these trials would be smart, pre hoc,  
5 to say, "Primary goal, presence or absence of adhesions;  
6 secondary goal, if we fail the primary, because this is  
7 tough work, significant decrease in the adhesion score."  
8 And even if you didn't hit the first one, that if you hit it  
9 on the second one, that would be sufficient.

10 The clinical, the true really clinical bowel  
11 obstructions and things like that, those will never come up  
12 in any of these primary trials. And I think that we have  
13 to--the manufacturers are learning from each other's  
14 lessons. I mean, every time some trial goes down they say,  
15 "Oh, boy, I'm glad I didn't do that." But I think if people  
16 are smart in the way they design the trials ahead of time,  
17 giving themselves some opportunity to score in a couple  
18 different areas, looking for the effect that's in all this  
19 noise in clinical surgery, that they will be doing  
20 themselves the biggest favor possible.

21 DR. D'AGOSTINO: Yes, and just one question  
22 further. If the trial did show the clinical efficacy but  
23 the adhesions weren't statistically significant or  
24 dramatically significant in a clinical sense, would you say  
25 that the trial should be broad enough to accommodate that

1 type of an outcome also?

2 DR. SCHWAITZBERG: Well, that's the reverse  
3 scenario, where you made everybody better and the adhesions  
4 were still there. I think people are trying to put adhesion  
5 reductions on the table, and if you have helped them in some  
6 other way, they need to understand how their device helped  
7 them and get a different education. I don't think you can  
8 have your cake and eat it too. If you got everybody  
9 pregnant but it's a bellyful of adhesions, you don't have an  
10 adhesion device, you've got a pregnancy device.

11 DR. D'AGOSTINO: Well, you know, so the usual way  
12 you sort of think about it is that you show the clinical and  
13 then you want to make sure the mechanism is going, that you  
14 did in fact do it by the adhesions. And that would be sort  
15 of the traditional way of looking at it, and so you're  
16 saying that of course that also still makes sense.

17 DR. SCHWAITZBERG: That makes a lot of sense  
18 because, you know, as I--you know, you've got to be  
19 internally consistent. I've hammered out the adhesions are  
20 the target. If you get rid of the adhesions, regardless of  
21 what the clinical outcome is, that is a viable, realistic,  
22 and important goal, particularly in the realm, as patients  
23 get older and live longer, their odds of having subsequent  
24 procedures goes up and up and up and up. And regardless of  
25 the clinical endpoints, if you proved you reduced adhesions,

1 you've got a viable product. If you have hit your clinical  
2 endpoints but it's still a bellyful of adhesions, you've got  
3 to figure out why you have a clinically important product  
4 but it's not an adhesion reduction.

5 DR. D'AGOSTINO: Thank you.

6 DR. BLANCO: Are there any other questions? Yes,  
7 sir?

8 MR. : Thank you very much. That was an  
9 elegant presentation and I appreciate it very much.

10 My question to you is, based on your presentation  
11 of the individual who had an ovarian cystectomy and yet had  
12 an upper abdominal significant colonic adhesion, if I  
13 remember that--

14 DR. SCHWAITZBERG: Small bowel.

15 MR. : --small bowel adhesion, and the  
16 fact that in general surgery you don't customarily do second  
17 looks, and in gynecological investigations where second  
18 looks are done, typically no bowel investigations are  
19 performed, the question is, if agents are placed into the  
20 abdomen--I mean into the pelvis--and we don't know whether  
21 they gain access to the upper abdomen, how do we reconcile a  
22 reduction in potential adhesion score in the gynecologic  
23 structures with the suggestion that obviously upper  
24 abdominal adhesions would be prevented as well, if we don't  
25 look and don't see?

1 DR. SCHWAITZBERG: Well, I think that's because in  
2 the trial design, if you want to be able to have as broad a  
3 claim as possible, you've got to make sure your material  
4 gets to those potential targets.

5 The conduct in reality of a clinical study is  
6 often the limiting factor. It may not be practical, if  
7 you're doing fertility surgery, to open up the abdomen and  
8 get it up all over the abdomen. But the person that's doing  
9 a laparotomy, who has access to the whole abdomen, will be  
10 using it years later and making sure it's getting to those  
11 sites, will be able to accomplish their goals.

12 I think this particular adhesion was probably  
13 caused by a retractor plus a lap pad or something like that,  
14 but the study wasn't a study of upper abdominal adhesions,  
15 because of the nature of the ethics of doing a clinical  
16 operation on somebody. They went out to show that they're  
17 going to reduce adhesions down here. They didn't put it up  
18 here.

19 And so unless we want to force people to put it  
20 all over the abdomen and then score the whole abdomen, we  
21 don't have a way of accomplishing your goal. We can only  
22 say this was the study, this was the target, we reduced  
23 adhesions, we didn't put it up here, but these are  
24 peritonealized surfaces. We don't have a reason to not  
25 suspect the same effect.

1                   It's a tough problem. It's a terrible problem.  
2                   MR.                   : But, see, the very nature of doing  
3 the surgery, as you just suggested, maybe it was the  
4 retractor, maybe it was a lap pad. Yes, maybe it was  
5 drying, whatever it was. Sort of if the overall goal is  
6 reduce adhesions, then one, it seems to me, would be obliged  
7 to make sure that whatever agent you use has an effect  
8 there, and you investigate to determine that you've reduced  
9 the likelihood of de novo adhesions there.

10                   DR. SCHWARTZBERG: Oh, I would agree with that.  
11 The problem, the problems that you face are, you know, you  
12 look at the ethics of doing an operation and then doing  
13 other aspects just for research and not for particular  
14 benefit. When you're doing an operation, patients are  
15 expecting some benefit from participating in an adhesion  
16 trial. If you want to go start mucking around in the upper  
17 abdomen where people not necessarily would be, you are now  
18 doing surgical procedures for research, and then you start  
19 opening up, you know, cans of worm ethically that may be  
20 difficult.

21                   Maybe the sponsor should be obliged to make sure  
22 that it goes everywhere and scores everywhere, but I'm not  
23 necessarily--I'm not necessarily concerned about that. I  
24 think that you can make these trials--I mean, imagine the  
25 statistical analysis of trying to analyze different sites.

1 My own approach was a different approach. I'm  
2 going to get it down to one site and prove that there is an  
3 effect, and then march on, march on from there. Trying to  
4 show an effect anywhere is hard enough. Trying to show what  
5 you want to show is going to be a statistical nightmare that  
6 could increase the kinds of problems that we've seen in  
7 other trials. You know, you get bombs at the last second.  
8 You get differences in how to analyze mounds and mounds of  
9 data.

10 I think if we can show a clinical effect, that  
11 yes, what we saw in the abdomen worked in the person, to  
12 answer your question, we should use non-human data and do it  
13 the way ideally a true scientist would want to do it.  
14 Because we're not true scientists, we're doctors first, and  
15 you have--there are serious ethical problems of doing parts  
16 of the abdomen where you wouldn't normally concern yourself.  
17 I mean these are problems. I sit in IRBs and I listen to  
18 stuff every day, and I'm sure you do as well.

19 DR. BLANCO: Any other questions?

20 [No response.]

21 DR. BLANCO: I have one specific question. You  
22 had access to the draft of the guidance document. Would you  
23 care to make any comments on any suggested changes? You'll  
24 have the opportunity to participate in discussion so you can  
25 make comments later as we go through questions. I just

1 wonder if there are any key points that you wanted to bring  
2 up at this point about the guidance document.

3 DR. SCHWAITZBERG: Yes, I had marked a couple  
4 places. I think starting on page 12 of the guidance  
5 document--

6 DR. HARVEY: For panel members, if you don't have  
7 a copy handy, we have them at the back of the room. If you  
8 need one, raise your hand.

9 DR. SCHWAITZBERG: We're talking about the  
10 labeling should accurately reflect the data which has been  
11 collected on the device. I think that this data should be  
12 allowed to include non-human data, and that you can't make  
13 it to approval without showing some human efficacy  
14 somewhere, but I think that the labeling, which is obviously  
15 a partnership in discussion between the FDA and the  
16 sponsors, should be able to reflect well done, agreed upon,  
17 rigorous non-human data as well as data collected in the  
18 clinical trial. Because if you really want to answer the  
19 tough questions, things like interloop abscesses or not,  
20 interloop adhesions or not, the trouble with constructing a  
21 human clinical study to look at an interloop adhesion is  
22 mind-boggling, and that's the problem.

23 DR. BLANCO: Well, how much evidence would you  
24 require, then, to ensure that the animal model is truly  
25 reflective of what happens in the human? You yourself have

1 said that that's not always the case. As a matter of fact,  
2 I think you said that it's often not the case. So, you  
3 know, wouldn't you be concerned, as it were, in putting some  
4 new product into an abdomen for the first time, that now  
5 we're going to use an animal model that may not really  
6 reflect what happens in humans, and yet we're going to  
7 accept it?

8 DR. SCHWAITZBERG: That's obviously--that's a  
9 burning question. First of all I think you need to show in  
10 the animal model what you showed in the human model. If you  
11 wanted to show reduction of adhesions to the midline, you  
12 should be able to show that, that your model can at least  
13 replicate what you were able to accomplish clinically, and  
14 then say, "Well, we showed this, and it was about the same  
15 effect, but what we're able to do in a non-human model, we  
16 cannot do in people. We were then able to look at other  
17 potential effects that you can't study clinically."

18 The problem is that the clinical trial doesn't  
19 reflect necessarily what happens in the clinical person  
20 because of the ethical nature of doing the surgery. So the  
21 step one answer is, you better be able to show that your  
22 animal model at least was as good as what your human data  
23 showed, and then say, "In addition to that, this is in  
24 addition to the other findings that we were able to show  
25 with a high quality, rigorous model, that you can't study

1 ethically in people in any rational way."

2 DR. CARSON: I guess I'm a little confused about  
3 why you're objecting to it ethically. Maybe it's because  
4 it's not such a big problem to begin with, and you think  
5 you'd have to do a large number in order to show any? Or  
6 there's data certainly from Jensen in his third-look  
7 laparoscopies, that if you perform second-look laparoscopy  
8 and wipe down the adhesions between four and six weeks after  
9 surgery, that there is a decrease in their reformation. So  
10 that would give a benefit to that second look, but I guess  
11 that's because it's not--

12 DR. SCHWARTZBERG: Yes, but one of the problems is  
13 that, you know, looking at the adhesions to the abdominal  
14 wall is different than doing a thorough laparotomy where you  
15 run the bowel from the ligament of Treitz to the ligament of  
16 Treves, a process in itself which can cause adhesions.

17 DR. CARSON: Right.

18 DR. SCHWARTZBERG: And so the standard of care in  
19 general surgery is, if you do a lysis of adhesions on  
20 somebody and it isn't broke, and they are okay clinically,  
21 then to go back and do more--first of all, you'll never get  
22 it covered by an insurance company, number one, so  
23 clinically most people don't do that. If you have pockets  
24 of people doing it, they're not going to get approved in the  
25 majority of managed care.

1           That's one of the reasons why it's not a standard.  
2   What you do for research obviously could be different, but  
3   since you don't have a standard, you're going to have to  
4   look at patients and say, "You're going to have a  
5   laparotomy, general anesthesia, potential bowel injury, for  
6   research," because it is simply not the standard in general  
7   surgery.

8           DR. CARSON: I'm not--I just want to understand  
9   this. That's why I ask this. Now, you're saying that then  
10  --what I'm asking is, why can't you then do a laparoscopy  
11  and take down the adhesions from the bowel to the wall?  
12  Would that be of no benefit? I can understand not being  
13  able to run the bowel, although some oncologic surgeons  
14  certainly think they can do that through the laparoscope,  
15  but--

16           DR. SCHWARTZBERG: And I do.

17           DR. CARSON: And so what's wrong, then, with doing  
18  the second look and doing some potentially beneficial  
19  adhesiolysis?

20           DR. SCHWARTZBERG: Somebody would have to find a  
21  standard of care that exists in some local pocket where  
22  somebody is doing that. But nationwide, across the nation,  
23  general surgeons do not do second-look laparoscopies,  
24  period.

25           DR. CARSON: And you think it would be unethical

1 to set up a research setting where that is your standard to  
2 look at?

3 DR. SCHWAITZBERG: Well, one of the problems, you  
4 know, when you look, is when you sit on the IRBs, you can't  
5 change your standard to accommodate the fact that you want  
6 to do a research study. It's either your standard or it  
7 isn't your standard. And so if you can go to a patient and  
8 say, "I would do, as a general surgeon, second-look  
9 laparoscopies, but in this particular time I'm now going to  
10 study this product," that's fine, as opposed to going to a  
11 patient and saying, "I don't normally do second-look  
12 laparoscopies, but in this study I want to do so." That is  
13 considered a laparoscopy, an invasive procedure for  
14 research, which most and many IRBs will not approve.

15 DR. CARSON: That may be potentially beneficial.

16 DR. SCHWAITZBERG: If it's not the clinical  
17 standard now, then trying to make it into the clinical  
18 standard by putting it in a research question doesn't fly  
19 through most Investigational Review Committees. It's an  
20 operation.

21 It's just like, you know, on a lesser scale if you  
22 sat on the committee and said x-ray for research. Does the  
23 amount of radiation in that x-ray, since it's just for  
24 research purposes--although you may find something, you may  
25 find something, you may find a pneumothorax or a pneumonia

1 that day. Any study that you do may be beneficial, but it's  
2 got to be balanced against any study you may do may be  
3 harmful, particularly when it comes to an invasive surgical  
4 procedure.

5           It would be great, we would have solved all our  
6 problems if there were models of second-look laparoscopy in  
7 general surgery, you know. But the quality of advanced  
8 laparoscopic skills are just now getting to the point where  
9 you can find a large cadre of surgeons that could run the  
10 bowel from one place to the other. But it just doesn't  
11 exist as the standard of care, with the exception of a few  
12 people who have written some papers about the second look  
13 and the third look and, you know, across the country people  
14 go, "Sounds profitable" and leave it at that. It's a  
15 problem.

16           DR. BLANCO: Any other questions?

17           DR. SCHWAITZBERG: I just wanted to make one point  
18 about the video, if you were asking about the guidance  
19 document.

20           DR. BLANCO: Go ahead and proceed to your next  
21 point on the guidance document. Is that what you were  
22 doing?

23           DR. SCHWAITZBERG: Okay. Right. The use of video  
24 which is outlined on page 16--yes, 16--item 2, this is a  
25 double-edged sword, and it has proved to be a double-edged

1 sword for people that have tried to use it. I was a big  
2 advocate of this at the time, but I think that may have  
3 reflected my--a little bit of naivete of how hard this  
4 proved to be.

5 I think if people want to use video, you've got to  
6 video the whole case, and you have to video the whole case  
7 with sufficient quality recording equipment that a blinded  
8 observer would come up with the same score. And so I think  
9 that in order to do video recording, manufacturers should at  
10 least in some pilot phase prove that they can come up with  
11 the same score on the video part of the trial, because it  
12 gets to be a mess of you get a different video score than--  
13 when you're trying to score adhesions than the observer.

14 On the other hand, when you're looking for the  
15 presence or absence of adhesions, then the video is pretty  
16 good. They are there, and you've looked at the site, or  
17 they're not there. Scoring on video is very hard because  
18 the person in the operating room can feel it, he gets a  
19 better sense of the--you know, the vascularity, the  
20 tenacity, and so I think that there should be proof that you  
21 can come up with the same score prior to embarking on a  
22 full--if you plan on using this as one of your endpoints.

23 DR. BLANCO: Isn't part of the video, problem with  
24 the video, that you don't have a standardized protocol for  
25 what you're video taping? In other words, you say, well,

1 you should video the whole thing, but I would kind of--I was  
2 saying that the problem is, as Dr. DeCherney pointed out,  
3 you're just getting an idea of what it looks like and then  
4 you move on, because the person doing the video may get a  
5 better feel because they're there in view when it's actually  
6 happening.

7 I mean, I would think that if you're going to have  
8 a video, what needs to be done is that you have a  
9 standardized--you look, say if you're doing a pelvis, being  
10 an OB/GYN person, you look in the cul-de-sac and you want a  
11 view of the cul-de-sac for X amount of time that you can see  
12 the entire cul-de-sac, anterior, and then have a very  
13 specific protocol that you follow so that every single  
14 video, at least for a piece of it you're going to have this  
15 criteria met and have the same opportunity for someone else  
16 to view the exact same thing from one patient to another.

17 DR. SCHWAITZBERG: I think that exactly hits the  
18 nail on the head, and I think that's one of the great  
19 lessons learned from the prior video experience, that part  
20 of the protocol should be the entire exploration done  
21 hopefully essentially the same way every time, so that you  
22 can achieve your goal of doing that.

23 It's just that having reviewed a lot of tapes and  
24 a lot of--even my own cases, things that would seem like  
25 crystal clear to me at the time, go back and look at the

1 tapes and go, "Wow." And so was it the recording devices,  
2 is it the inability to get some sort of, you know, 2-D, 3-D  
3 parallax going? I don't know what it is, but I think that  
4 people ought to really be able to prove their point in some  
5 pilot way with the video prior to doing that.

6 And then the other problem is, you know, video  
7 like pictures is an alterable medium, and so using that as a  
8 primary endpoint is probably hazardous. I think at best it  
9 should be one of those secondary kinds of supporting  
10 evidences that people do, and that it's additional  
11 information.

12 But we got hung up on the difference between the  
13 video and the clinical results, and it was just--it was a  
14 nightmare. It was uninterpretable data, using the video. I  
15 think people should score it live with an independent  
16 observer.

17 So that goes to, as you look at the assessment  
18 tools, who should be doing the assessment? There are  
19 problems with the primary person putting the device in and,  
20 you know, is that a fair--and this is called masking on the  
21 subsequent page 17. I think the best way and the best way  
22 to get through this is, if somebody is going to score  
23 adhesions, then having a person at the table in real time  
24 scoring the adhesions as the primary endpoint should be  
25 recommended. Say having the guy there and saying, "I'll

1 hand the tape to you later," is fraught with all the hazards  
2 that we just discussed.

3           So I think you solve a lot of your dilemmas by  
4 having a second person do the scoring, because you're right,  
5 nobody wants to have a second surgeon. I mean, if you like  
6 your surgeon, you don't want a different surgeon. But I  
7 don't think that having a second surgeon in the room scoring  
8 would be a big problem.

9           So those are my comments on--

10           DR. BLANCO: Any question on that? Subir?

11           DR. ROY: I would just like your advice from a  
12 surgical or a general surgeon's point of view. What do you  
13 recommend in terms of scoring location, extent, severity,  
14 functionality, or impairment of functionality of adhesions?  
15 How do you approach that as a general surgeon?

16           DR. SCHULTZ: Let's go backwards. Assessing  
17 functionality is probably the hardest of all. You know, is  
18 an adhesion to a tube relevant? And I'm not a gynecologist.  
19 I'm married to one, but I'm not one. And I am amazed that  
20 some people get pregnant with a bellyful of adhesions and  
21 some people don't get pregnant with clean pelvises. And so  
22 I think that doing functionality is going to be the hardest  
23 of all.

24           I think extent is a good one. Severity is a very,  
25 very good one, but subject to some subjective problems with

1 the scoring system. But there clearly is a difference  
2 between concrete and filmy adhesions. You get into the  
3 middle, you know, some of these other scores, you have  
4 problems, but at least on the ends it is very clear what the  
5 differences are between a very solid adhesion and a wispy  
6 adhesion. So I think that you can score severity, but  
7 there's going to be some subjective bias reflected in that.

8           Vascularity is another thing that, either the  
9 adhesions appear vascular and when you cut them, they bleed  
10 or they don't, so those are some subjective things that you  
11 can lend to the scoring, but I think functionality is the  
12 worst of them all because the problems are too  
13 multifactorial for me.

14           DR. ROY: So in your investigations you use these  
15 criteria?

16           DR. SCHWAITZBERG: Yes, we use the scoring  
17 criteria, because we don't have a whole lot else to offer.  
18 I really am grateful when there's no adhesion. That's the  
19 best one. And then, short of that, I look for the big,  
20 broad stroke differences. Is this a tough adhesion or is  
21 this a wimpy adhesion? And I think you can make those types  
22 of subjective--if you get too many points on the scale, it  
23 gets too arbitrary. You know, the two- and three-point  
24 scales I think are the best we have to offer for just a  
25 terrible problem with that.

1 DR. ROY: So do you then just have a summary of  
2 locations and adhesions? Do you ever have an average  
3 adhesion score, where you take some sort of a scale that you  
4 apply to a given adhesion, the number of locations, and  
5 divide the number of locations into that composite score to  
6 come up with an average adhesion score?

7 DR. SCHWAITZBERG: I haven't tried tallying them  
8 into a meaningful number, so that this abdomen had an  
9 adhesion score of six based on three sites of double  
10 severity. I think that would make for some very interesting  
11 developmental research, but I think what you're left with is  
12 number of sites. I think you wind up analyzing all the  
13 separate.

14 But what you're suggesting certainly is food for  
15 thought for, you know, for the audience in trying to come up  
16 with a valid method of coming up with a number. You would  
17 like to, but then you've got to show that a 6 is different  
18 than a 10. I mean, sometimes you have to look at the data  
19 and say you reduced the extent of the adhesions or you  
20 reduced the severity of the adhesions or you reduced the  
21 number of adhesions, and then sit down and say, "Was that my  
22 endpoint?" Yes, sir?

23 DR. BLANCO: Let's move on, because this is really  
24 a discussion, and you're going to have the opportunity to  
25 participate in that. I think we need to--our whole agenda

1 is going to be a little changed, but I think this is  
2 valuable information that we're obtaining.

3           Could you hit a few more of the points that you  
4 think are the highlights of what you would like to see--

5           DR. SCHWAITZBERG: ...and that they shouldn't be  
6 surprised, that this is anticipated, this is part of their  
7 long-term commitment, because the FDA recognizes that we're  
8 not going to get a perfect, clean clinical trial out of any  
9 of this, because people want to know about clinically,  
10 people want to know about whether the adhesions, presence or  
11 absence is any good, things that manufacturers should be  
12 prepared to conduct long term Phase 4 postmarketing studies  
13 as part of what they get out of the deal for--for instance,  
14 in return for allowing non-human data.

15           Because, to answer your point completely, my  
16 concerns about animal trials are yours. What if the animal  
17 trial really didn't reflect it, and we just gave a labeling  
18 indication? So in order to help the manufacturers make it  
19 to market, their nut in all of this is, they could  
20 anticipate having to look at this clinically and provide  
21 registers of patients. That's the other end of the deal. I  
22 don't think you get one without the other, particularly in  
23 those cases where claims in labeling have been made  
24 partially on non-human data for efficacy. I think they  
25 should depend on that.

1 DR. BLANCO: All right. Any other points?

2 [No response.]

3 DR. BLANCO: All right. Well, why don't we--let's  
4 see how we're going to arrange the agenda. Why don't we  
5 take a break. We've been going for a while. Let's do about  
6 a 10-minute break. Then we'll come back and have the FDA  
7 presentations, and if we have time, we'll do the public. If  
8 not, we'll have to do the public after lunch.

9 [Recess.]

10 DR. BLANCO: All right. Let's go ahead and get  
11 started, and we've altered the agenda a little bit, but I  
12 think it's been very informative and important. I think  
13 what we're going to start out with now is Dr. Dan Schultz,  
14 our Acting Director, is going to make a presentation.

15 DR. SCHULTZ: A very brief presentation, no  
16 slides, no nothing. And first of all let me apologize for  
17 coming in late. I actually am amazed that all of you made  
18 it here this morning, and given the fact that my kids'  
19 schools were all cancelled, I thought everything was going  
20 to be cancelled. So I congratulate both the panel, all of  
21 the distinguished guests, and my own staff from FDA for  
22 being here.

23 I just wanted to make a couple of quick remarks.  
24 Again, I would like to--I made it through part of Dr.  
25 Schwaitsberg's comments, and as usual he was frank and

1 honest and to the point in terms of both the process and in  
2 terms of the problem at hand.

3 I would like to comment that one of the reasons  
4 for convening this meeting was to accomplish just what he  
5 suggested, which is to try to get the experts in this field  
6 into one room with our advisory panel and try to go through  
7 these issues one by one and allow people to voice their  
8 either positive, negative, constructive hopefully, comments  
9 regarding this guidance, so that we can move forward with it  
10 and hopefully move forward with this important group of  
11 medical devices.

12 We expect that the comments that are made, both by  
13 the panel and by the audience, will be extremely frank,  
14 honest, and as complete as possible. If we need to make  
15 changes, either minor changes or major changes, we are  
16 prepared to do that. The guidance is out in draft now for  
17 comment, but even, as the guidance--the guidance document  
18 process allows, even once the guidance is so-called final,  
19 we still can change it as necessary. And as we--as is  
20 discussed in the guidance document itself, it's meant to be  
21 a living document which changes over time, based on  
22 additional knowledge.

23 So, with that, with those comments in mind, again  
24 I look forward again to a very frank, honest, open  
25 discussion today, and learning a lot from all of you. I

1 think the first real speaker for the morning is Dr. Harvey--  
2 FDA speaker, I should say--and she will be talking about the  
3 preclinical aspects of the guidance, followed by Dr.  
4 Mitchell talking about the clinical aspects.

5           So again, thank you for being here, and I look  
6 forward to hearing what you have to say.

7           DR. BLANCO: Are your slides in Los Angeles?

8           DR. HARVEY: I am here in person, as well as my  
9 handout. I couldn't top Dr. DeCherney, that's for sure.

10           Well, I'll try to be as brief as I can because we  
11 really want to get to the task at hand, which is to hear  
12 from the panel on their recommendations. So, as you know,  
13 we're here to get your recommendations on our guidance.

14           This is where you can find the guidance on the web  
15 site, and we encourage everybody who hasn't already accessed  
16 it to do so. This guidance is the result of a lot of work  
17 by a lot of people in two divisions. I'm just going to  
18 present a brief overview of the other parts of the guidance  
19 besides the clinical portions. Dr. Mitchell will follow me  
20 with a more detailed presentation on the clinical aspects,  
21 which is what we're really asking you to focus on.

22           A little historical context. These kinds of  
23 products that have been used in the abdomen and pelvis have  
24 in the past and continue to be reviewed in two different  
25 divisions in our Center's Office of Device Evaluation. The

1 products with primarily GYN indication have been reviewed in  
2 the OB/GYN Devices Branch of the Division of Reproductive,  
3 Abdominal and Radiological Devices, while products having a  
4 general abdominal indication have been reviewed in the  
5 Plastic and Reconstructive Devices Branch of the Division of  
6 General Restorative Devices.

7           To date, we have two products approved for use,  
8 one by each division. Interceed is indicated as an adjuvant  
9 in gynecological and pelvic laparotomy surgery for reducing  
10 the incidence of postop pelvic adhesions after meticulous  
11 hemostasis achieved with microsurgical principles. And  
12 Seprafilm is indicated for use in patients undergoing  
13 abdominal or pelvic laparotomy as an adjuvant intended to  
14 reduce the incidence, extent and severity of postop  
15 adhesions between the abdominal wall and the underlying  
16 viscera such as omentum, small bowel, bladder and stomach,  
17 and between the uterus and surrounding structures such as  
18 tubes and ovaries, large bowel and bladder.

19           Of course we have several more adhesion barriers  
20 in various stages of clinical study, and these come with  
21 widely varying formulations, indications, and clinical study  
22 designs. Next.

23           As I mentioned, this was a joint effort. These  
24 are the two groups in our Office of Device Evaluation who  
25 have done this. We are very much collaborative.

1           The purpose of our guidance is to--first of all,  
2 there was increasing interest by industry in developing safe  
3 and effective adhesion barriers, and because of the  
4 increasingly overlapping nature of our two divisions'  
5 reviews, we wanted to make sure there was a source of good  
6 and consistent information regarding our recommendations for  
7 testing. We want to provide guidance which is consistent  
8 both across divisions and sponsors, and to provide guidance  
9 that reflects our current knowledge of the pathogenesis and  
10 clinical significance of adhesions.

11           The guidance contains several sections, including  
12 basic regulatory background and information, general IDE and  
13 PMA requirements, preclinical information, and the clinical  
14 investigational plan with references. Of course, as I said,  
15 we'll be asking the panel to concentrate on the clinical  
16 investigation plan. The remainder of my talk is going to  
17 focus on the preclinical information we currently have in  
18 the guidance, the draft guidance.

19           We ask for this preclinical information in order  
20 to get as clear an understanding of the device as possible,  
21 including its description, its chemistry, any in vivo or in  
22 vitro testing which has been done, as well as physical or  
23 mechanical bench testing and manufacturing and  
24 sterilization. I'll focus now a little bit on the in vivo  
25 and in vitro testing.

1           This covers a number of different kinds of testing  
2 which can help us characterize an adhesion barrier,  
3 including the standard biocompatibility and toxicology  
4 testing which is done for any patient-contacting medical  
5 device. There are standards in place which we rely on for  
6 those kinds of tests. We also like to see pharmacokinetic  
7 studies, so that we understand the fate of the product and  
8 its breakdown products; performance studies that help us  
9 understand the potential for the product to have efficacy in  
10 the human; and some additional special considerations that  
11 we think are important, particularly for adhesion barriers.

12           As I mentioned, these are all the standard tests  
13 which are well recognized by the industry for general  
14 testing of all medical devices--Colin, you can keep rolling  
15 through those--depending on the duration and type of contact  
16 with the patient, and this includes testing for  
17 cytotoxicity, sensitization, irritation, systemic toxicity,  
18 genotoxicity, and toxicity during subchronic implantation.  
19 We also believe that it's critical to understand the time  
20 frame and sites of absorption, distribution metabolism, and  
21 excretion for these products when they are placed in the  
22 abdomen, so we ask to have this information before the  
23 clinical study is commenced.

24           Understanding the performance of the adhesion  
25 barrier product in animal models is very useful for us and I

1 think for the sponsor as well. It provides preliminary  
2 information on how well an adhesion barrier might work. It  
3 can help refine aspects of the clinical study design,  
4 including dosing, application method, and methods for  
5 evaluating the adhesions, and there are several well  
6 established and commonly used models, although we're not  
7 currently aware of any models in place for laparoscopic  
8 surgery.

9           There is some additional testing--next slide,  
10 please, thank you--there is some additional testing which we  
11 ask of sponsors for adhesion barriers. First, and this is  
12 something we have already heard a little bit about this  
13 morning from Dr. Schwaitzberg, these products are used in  
14 the abdomen, where there is potential for undetected  
15 bacterial contamination at the time of surgery, so it's  
16 important to know whether an adhesion barrier has the  
17 potential for enhancing abdominal infection.

18           We also know that adhesion barrier products are  
19 commonly used in women who like to either preserve their  
20 fertility or treat their infertility, so effects on any  
21 aspect of reproduction or development would obviously be  
22 undesirable. To address this concern, we ask sponsors for  
23 information on the effects a barrier might have on  
24 conception as well as the embryo and growing fetus.

25           In addition, we ask for information on the

1 potential of the barrier to have any effect on healing,  
2 either at the site of application or at distant sites in the  
3 abdomen. And, finally, and this is something we also heard  
4 about, was if the product indication is going to be for use  
5 in patients with malignancy, additional testing is asked for  
6 in order to evaluate the barrier's potential for enhancing  
7 tumor growth or metastasis.

8           That was my really fast presentation. I just  
9 wanted to make sure you are aware of those other aspects of  
10 the guidance so you can bring any comments to our attention  
11 if you want to. I would like to introduce Dr. Mitchell, who  
12 will present her presentation on clinical study design  
13 aspects.

14           DR. BLANCO: While we're waiting, is there any  
15 questions about the presentation just finished?

16           DR. SILKAITIS: Yes. This is Ray Silkaitis. In  
17 terms of the guidance document and the reference to the ADME  
18 studies, in contrast to pharmacological products where there  
19 is a single entity identified as an active ingredient,  
20 medical devices are a little bit different, and devices tend  
21 to be polymers or composites of many different entities, so  
22 to conduct a typical ADME type study that is done on the  
23 pharmacological side may be impossible to do with medical  
24 devices.

25           And so what we ask is that some reasonableness be

1 looked at in terms of the extent of the metabolic studies  
2 that need to be done. Specifically, if there is already in  
3 the published literature some known fact about a particular  
4 polymer and its absorption, that should be adequate to  
5 address that. But to look at every single metabolic  
6 breakdown product would be impossible. And when drug  
7 studies are done for ADME studies. they don't look at the  
8 ingredients, either, in terms of their metabolic pathways and  
9 things like that.

10           So I just wanted to bring that particular point  
11 up. And I have two other things regarding the preclinical  
12 section, and one was the special considerations, the  
13 evidence of infection. I think it was mentioned before by  
14 our special guests about the difficulty of an animal model  
15 that correlates to the human situation, so I think the way  
16 the study is talked about in the guidance document assumes  
17 that this type of model is a well accepted model. So I  
18 would leave in the guidance document that this is an option  
19 and it is an attempt to see if there are potential issues,  
20 but not that it necessarily correlates with what we would  
21 expect in the clinical situation.

22           One item that was not talked about, and that was  
23 in the manufacturing section, to any changes to the product,  
24 that animal studies be done. Under the QSR regulations,  
25 certain changes can be made to the product that would be

1 appropriate.

2 I agree that substantial changes to a product  
3 would probably need some animal studies or even clinical  
4 studies to justify the change, but small manufacturing  
5 changes should not require that that product be tested in an  
6 animal model. I think there would be some animal welfare  
7 issues.

8 There was one thing that was also talked about  
9 earlier by our guest speaker, Dr. Schwaitzberg, and that was  
10 the suggestion to use primate animals for testing. And  
11 there are a couple of issues in that regard, and that is  
12 that--one is the availability of primate animals. They are  
13 not widely available. They are only located in certain  
14 centers. What you can do with primates is also restricted.  
15 Again, there are animal welfare issues with that, and I have  
16 heard of many professors and researchers in academia going  
17 to foreign countries to be able to do some specific research  
18 with primates.

19 And if I may, I would like to invite either Dr.  
20 Wiseman or Dr. Burns maybe to talk about the primates, if  
21 it's appropriate at this time.

22 DR. BLANCO: Let's leave that there. I think Dr.  
23 Burns is going to speak to us at the public session, maybe,  
24 and Dr. Wiseman, so maybe they could add it to their talks  
25 at that time.

1 DR. SILKAITIS: Okay. Thank you.

2 DR. BLANCO: Thank you.

3 DR. SILKAITIS: All right. Those were the three  
4 topics that I just wanted to--

5 DR. HARVEY: Dan, do you want me to respond, or  
6 shall we just take those for the record?

7 DR. SCHULTZ: Go ahead and let Diane give her  
8 presentation. I think we're starting to get into the meat  
9 of--

10 DR. BLANCO: We're starting to get into  
11 discussion, so we'll bring it up when we start discussing.

12 DR. SILKAITIS: Right.

13 DR. MITCHELL: Good morning, ladies and gentlemen.  
14 Thank you, Dr. Harvey, for that overview on the preclinical  
15 studies. As stated, I will review the clinical trial design  
16 section of the draft adhesion barrier guidance document that  
17 was made available on the worldwide web on December 10,  
18 1999. And if I don't say "draft" throughout my entire  
19 discussion, please excuse me. It is a draft, but I may  
20 forget to say "draft".

21 Before I begin to highlight the points discussed  
22 in the guidance, I would like to review the definitions of  
23 "safety" and "effectiveness" drawn from the regulations as  
24 they apply to premarket approval applications. I also plan  
25 to highlight some of the difficulties involved with