

1 developing guidances for the studies used to make these
2 determinations.

3 For safety, our mandate is--and I apologize for
4 the small print, it's a long mandate--there is reasonable
5 assurance that a device is safe when it can be determined,
6 based upon valid scientific evidence, that the probable
7 benefits to health from use of the device for its intended
8 uses and conditions of use, when accompanied by adequate
9 directions and warning against unsafe use, outweigh any
10 probable risks. The valid scientific evidence that may be
11 required, when appropriate, to determine that there is
12 reasonable assurance that a device is safe, are
13 investigations using laboratory animals, investigations
14 involving human subjects, and nonclinical investigations,
15 including in vitro studies. Next slide, please.

16 For effectiveness, our mandate is that there be a
17 reasonable assurance that the device is effective when it
18 can be determined, based upon valid scientific evidence,
19 that in a significant portion of the target population, the
20 use of the device for its intended uses and conditions of
21 use, when accompanied by adequate directions for use and
22 warning against unsafe use, will provide clinically
23 significant results.

24 Adhesions in the abdomen can be from infection,
25 endometriosis, foreign bodies, past surgery, and so forth.

1 They can be reformed, formed at surgical sites, or formed in
2 areas where there is no evidence of surgery. The exact
3 pathogenesis of adhesions is still under investigation.
4 Small bowel obstruction, chronic pelvic pain and infertility
5 have been attributed to the presence of adhesions. How to
6 predict when adhesions will cause these problems, or if some
7 types of adhesions are worse than others, is not known.

8 All of these issues must be taken into
9 consideration when developing a guidance for adhesion
10 barriers. Drugs, immune agents, and meticulous surgical
11 technique have all been considered as possible adhesion-
12 reducing agents. Adhesion barriers, a subset of adhesion-
13 reducing agents, include solutions, sheets and gels. Each
14 of these methods has different consequences for its
15 mechanism and location of action.

16 With so many possibilities for cause of and effect
17 from adhesions, so little understood about the best way to
18 evaluate the success of adhesion reduction, and so many
19 different ways to apply adhesion barriers with all of their
20 different properties, developing models by which to study
21 adhesion barriers can be very difficult. What may be the
22 best option for one barrier might not be the best for
23 another.

24 For example, solutions have the potential to act
25 all over the peritoneal cavity, whereas sheets can only act

1 where they are placed. As you can see, this has major
2 consequences in terms of study application and ultimate use
3 of the product.

4 Because of these issues, the guidance we have
5 developed is not a simple recipe to follow for developing a
6 study of adhesion barriers. Rather, it discusses the
7 various ways these issues can be approached, as well as the
8 advantages and disadvantages to each approach.

9 The topics in the guidance that I want to
10 highlight are listed here and on the next slide: A clinical
11 plan designed to develop the data needed to support the
12 intended use; the pivotal study hypothesis and endpoints;
13 the pivotal study design; the statistical evaluation of the
14 pivotal study; and safety. Next slide.

15 Before moving on to the pivotal study, I should
16 mention the discussion in the guidance regarding feasibility
17 studies. When developing an adhesion barrier, there are
18 many types of questions that need to be answered with human
19 use. Feasibility studies are investigations designed in
20 phases, can be ways of determining its use, such as this:
21 the method of delivery and placement; handling
22 characteristics of the device; anatomic site-to-site
23 variability; effectiveness for various types of adhesions;
24 dose response; resorption and elimination in humans; signs
25 of increased risk of infection and altered wound healing; as

1 well as early indications of safety.

2 There are also things that feasibility studies
3 cannot do. For example, an increased susceptibility to
4 infection from an adhesion barrier might be very difficult
5 to detect, particularly if the barrier enhances the severity
6 of the infections only when they are caused by undetected
7 bowel injury. This is an important concern, but not one
8 that can be addressed reasonably with human use. Therefore,
9 this is an example of an area that is better addressed with
10 animal study. The issue of infectivity will be the subject
11 of a discussion point during panel deliberations.

12 To begin a discussion of the pivotal study, let's
13 discuss the three interrelated topics of intended use,
14 purpose of the study, and study hypothesis.

15 The intended use of the device should state very
16 specifically where the barrier is to be used and what it is
17 supposed to do. The purpose of the study will then be to
18 show that the barrier can be used in the fashion defined by
19 the intended use, and the hypothesis should clearly state
20 what the study intends to show, in very specific terms.

21 The following three slides are an example of how
22 these topics are interrelated. So the intended use could be
23 that this adhesion barrier is designed to prevent
24 reformation of adhesions in women with moderate to severe
25 pelvic adhesive disease, as defined by the standard AFS

1 criteria, undergoing laparoscopic lysis of adhesions due to
2 chronic pelvic pain. De novo versus reformed adhesions in
3 clinical presentations, for example, should be taken under
4 consideration when considering the intended use of a device.

5 The purpose of the study should then be to prove
6 that the intended use is a reasonable one: For example, to
7 evaluate the safety and effectiveness of the barrier at
8 reducing the reformation of adhesions in patients with
9 moderate to severe pelvic adhesive disease, as defined by
10 the standard AFS criteria, undergoing laparoscopic lysis of
11 adhesions. Next slide.

12 Okay, and the study hypothesis: In patients with
13 moderate to severe pelvic adhesive disease, as defined by
14 the standard AFS criteria and chronic pelvic pain,
15 undergoing laparoscopic lysis of adhesions, this barrier
16 will reduce the reformation adhesion incidence by some
17 prespecified percent when compared to the control group.

18 This is the point, I think, that both Dr.--I think
19 a little bit this alludes to what Dr. DeCherney and Dr.
20 Schwaitzberg were talking about, in the sense that in the
21 introduction to the study there should really be a clear
22 explanation of why the study hypothesis will support the
23 intended use identified. So the point of this guidance is
24 that we are open to discussion, and as long as things are
25 understood in advance and agreed upon, you know, then we can

1 really work with companies to design the kind of study that
2 is intended to meet the intended use that they have
3 identified.

4 For example, if the device is to be applied only
5 to a specific area of the abdomen, but the claim is that the
6 device will reduce adhesions throughout the abdomen, there
7 should be a clear understanding of why this is so in the
8 protocol. Additionally, if the claim is for general surgery
9 but the patients in the study are gynecologic, the
10 relationship between the two should be understood and agreed
11 upon before the study begins. Finally, if the claim covers
12 only reformed adhesions but the study also looks at de novo
13 adhesion formation, or vice versa, then the importance of
14 this finding as it relates to the indication should be
15 clearly understood in advance.

16 There are several more examples in the guidance
17 itself. These three issues, indications for use, study
18 objective, and hypothesis, will all be the focus of
19 discussion questions.

20 The next topic that is covered in the guidance and
21 addressed in the panel discussion questions is the issue of
22 clinical versus surrogate endpoints. Here we come to a very
23 difficult road in looking at clinical trial design for
24 adhesion barriers.

25 Clinical endpoints that are applicable to

1 gynecologic surgery include increased fertility and
2 decreased pelvic pain. In general surgery the most
3 significant complication is small bowel obstruction.

4 The advantage to clinical endpoints is that when
5 using the device, the clinician will be informed that the
6 use of the barrier will help the patient with his or her
7 presenting complaint or future complications. The
8 disadvantage, as well laid out, is that there are often many
9 factors contributing to their cause and not just the one
10 identified in the study. In addition, we recognize that to
11 obtain clinical endpoints may require long studies.

12 The other option is to use surrogate endpoints,
13 defined as laboratory measurement or a physical sign which
14 is substituted for a clinical endpoint. Next slide.

15 For abdominal adhesions, at this point in time we
16 are pretty much limited to counting the adhesions in some
17 fashion at some point after the initial surgery was done.
18 Currently it is important to understand that none of the
19 adhesion measuring tools available have been well validated
20 clinically.

21 Many different investigators have looked at the
22 presence, quality--which includes severity and extent--of
23 adhesions as a way of grading adhesions. The thought has
24 been that by grading adhesions, we may be able to better
25 understand how the incidence, extent and severity of

1 adhesions impacts upon the clinical effects.

2 Adhesion scoring systems such as the more
3 comprehensive AFS and the standard AFS, for example,
4 therefore have the potential to be reasonable surrogate
5 markers. Other surrogates could be any one of those
6 parameters--incidence, severity or extent--measured
7 independently or counting the number of patients who are
8 adhesion-free after surgery.

9 The advantages of measuring the adhesions is that
10 the follow-up time can be relatively brief before the
11 outcome is known. The disadvantages are that many of the
12 parameters, for example, EXTAT, can be objective, leading to
13 variability in how to score, and there is not a well-defined
14 correlation between scores and clinical outcome. Again,
15 this point will be part of panel deliberations. We suggest
16 in the guidance that surrogate endpoints can be used for
17 device approval, but they should be accompanied by
18 postmarket studies looking at clinical endpoints.

19 Now, let's step back a minute and discuss studies
20 design. We believe that with careful consideration,
21 clinical investigation of adhesion barriers using adhesion
22 scoring as an endpoint can be randomized controlled clinical
23 trials. This means that some thought must be given to the
24 control and the type of randomization, as well as how to
25 blind the investigators. With regards to the control,

1 because there is currently no one widely used procedure or
2 agent to reduce adhesions, the choice of the control group
3 is up to the discretion of the sponsor in conjunction with
4 the FDA.

5 The second issue is randomization. There are many
6 different times in the patient's treatment course when
7 randomization is possible. Ideally, it is done at a time
8 when it can have the least impact on the patient's treatment
9 and introduce the least amount of bias into the treatments
10 the patient receives. An ideal time is after the first
11 surgery has been completed and before the patient has been
12 closed. The time of randomization relative to surgery and
13 device application should be prospectively planned and
14 clearly documented on the case report form.

15 The final issue is masking. If the second-look
16 surgery is done too soon after the first, there is the
17 possibility that the barrier is still present and easily
18 identifiable, which would eliminate masking for anyone. Be
19 that as it may, we are aware of three ways to mask.

20 The first is that the surgeon step out of the room
21 when the treatment or control is being applied. This way,
22 she or he could also perform the second-look without biasing
23 the study. The second way is for the second-look to be
24 performed by a different surgeon unaware of the treatment
25 the patient received in the first surgery. The third way is

1 for both surgeries to be videotaped and the videotapes be
2 reviewed, either in real time or later on, ideally by a
3 panel of independent observers who record the scores. And
4 the fourth method, that was discussed by Dr. Schwaitzberg,
5 would be to have a second surgeon in the room at the time of
6 the original surgery and perform the scoring at that time.

7 We believe that all of these methods have
8 advantages and disadvantages. The important point is that
9 in the protocol, the choice be clearly laid out and its
10 advantages and disadvantages be discussed and compensated
11 for, if possible.

12 The statistical component of any study is critical
13 to its success. In the guidance we strongly encourage
14 sponsors to meet with us in advance to review all components
15 of any study concerning adhesion barriers. Above are listed
16 the many different and critical statistical issues that
17 should be identified and well thought out in advance:
18 success/failure criteria; confounding variables; sample
19 size; number of study sites; spreadsheets; protocol
20 deviations; data auditing; dropouts; and this, of course,
21 the statistical procedures and analysis.

22 Let me just cite two examples from the slide of
23 the importance of good planning on these issues. The
24 success/failure criteria for any study are chosen based on
25 valid scientific evidence that this magnitude of change will

1 be clinically beneficial to the patient. These criteria
2 should be clearly laid out and discussed in advance. In
3 addition, how these criteria will be evaluated--parametric
4 versus non-parametric statistical evaluation, for example--
5 should be clearly outlined.

6 Another issue of concern is confounding variables,
7 not only across sites that might perform procedures
8 differently but also across adhesion types, for example, de
9 novo and reformation, that might respond differently. All
10 potentially confounding variables need to be anticipated in
11 advance and incorporated into an evaluation of statistical
12 considerations in the protocol submitted.

13 The next issues covered in the guidance that I
14 will discuss are listed above. After careful review of the
15 literature, we have concluded that the type of surgery
16 performed, laparotomy or laparoscopy, can affect the
17 formation of adhesions. As a result, in the pivotal study
18 we have asked that if a sponsor wants to label a study for
19 laparoscopy, the firm must have a study done on laparoscopy
20 patients.

21 Finally, the presence of malignancy raises
22 different concerns. There is the possibility that the
23 barrier might increase the risk of recurrence or the
24 development of metastases. Therefore, any adhesion barrier
25 indicated for use in malignant abdomens must undergo

1 additional testing.

2 Now, before I leave this slide, one of the other
3 differences between laparotomy and laparoscopy can be the
4 way the barrier is applied, and so that's something that
5 also needs to be looked at when you're talking about
6 laparoscopy choices.

7 The final point in the guidance I would like to
8 bring out is the safety of the device. Many of the safety
9 issues are addressed in the animal studies. However, there
10 are certain aspects of safety that can only be answered with
11 human use.

12 In the pivotal study, all adverse events should be
13 recorded. Sometimes it is not clear that an incident is
14 related to a device, but it is still important that we know
15 about it because that can help in labeling the device and
16 monitoring for future events. In addition, any organ that
17 may be affected by the barrier should be monitored during
18 the study. Optimally, all of these results are carefully
19 recorded in the pivotal study.

20 Well, I have tried to cover, in one degree or
21 another, all of these topics as they are addressed in the
22 guidance document. As you have gathered, this document is
23 not a recipe for putting together a study for adhesion
24 barriers, but rather guidances to the issues we consider
25 when reviewing protocols. In the future, perhaps, when the

1 science of adhesions is better understood, we can give more
2 directed guidance. Thank you.

3 DR. BLANCO: Thank you, Dr. Mitchell.

4 Are there any questions of Dr. Mitchell from the
5 panel? Diony?

6 MS. YOUNG: This is probably simplistic but, I
7 mean, I don't know anything really about these adhesion
8 barriers, but one of them--one type you mentioned is a
9 solution, and so obviously a solution, as you mentioned, can
10 sort of spread through the cavity, abdominal cavity. And
11 for that reason it makes me think of the effects of--the
12 potential effects could possibly mimic those of a drug, and
13 in that case I just wonder if there are any guidance
14 documents or guidance for drug use that would be applicable
15 to the use of solutions as adhesion barriers.

16 MR. : Well, I think part of what Elisa
17 was saying and part of what was alluded to in a comment that
18 was made, as well, was that some of these products do have
19 aspects that are device aspects as well as drug aspects.
20 And we have tried to be careful in requiring the types of
21 studies that were necessary to evaluate the individual type
22 of product, given its nature.

23 And that's why, as Elisa said, it's important to
24 accurately describe the device in its totality and for us to
25 be able to understand what it's breakdown products are,

1 where it could be going, what kinds of problems could be
2 related to its use. Because you're exactly right. A
3 solution is different from a film, is different from a gel,
4 both in terms of its effect and in terms of its possible
5 safety consequences.

6 And therefore, again, what we recommend is that
7 sponsors look at their own individual products and come to
8 us with a plan that reflects the nature of that product.
9 And, you know, it could include some of the things that our
10 sister centers look for in their products, as well. You
11 know, in fact there could be biologic aspects of some of
12 these products, and probably will be in the future as these
13 products are developed.

14 So I think, yes, you're absolutely right, we need
15 to look at all those things.

16 DR. BLANCO: Sandra?

17 DR. CARSON: Wouldn't a good analogy be the
18 protocols you have for the radiologic contrast medias?

19 MR. : Yes, I think that would be a good
20 analogy, other than the fact that the latest decision on
21 those was that they are all going to be drugs.

22 DR. CARSON: Oh.

23 MR. : And in which case we wouldn't be
24 discussing that, those types of products, in a device panel
25 anymore. But yes, you're right, and I think increasingly,

1 not only in this particular subject area but in a lot of
2 different devices that we are currently seeing, the borders
3 between drugs, devices and biologics are becoming
4 increasingly blurred, and we need to--you know, we need to
5 understand that. It obviously makes our jobs a little bit
6 more difficult and more challenging, but clearly we need to
7 understand that, and as is stated in the guidance, there may
8 be times when we would require, request and require reviews
9 from our sister centers to evaluate those aspects of a
10 product that they are more familiar with than we are.

11 DR. BLANCO: Don?

12 DR. CHATMAN: Dr. Mitchell, I'm not clear about--
13 is this on?--I'm not clear about one issue having to do with
14 the design of these trials that has to do with laparoscopy
15 and laparotomy. I think our two experts differed in their
16 opinion as to whether or not there was a difference. I'm
17 sure we all have our opinions, but what is FDA's position?
18 Are we to do--are we to separate out these devices according
19 to whether or not they have been used laparoscopically or by
20 laparotomy? I wasn't clear. I didn't understand fully what
21 you said concerning that issue.

22 DR. MITCHELL: The recommendation in the guidance
23 at this point is that if you're going to indicate for
24 laparotomy, you should perform a laparotomy study, and if
25 you're going to indicate for laparoscopy, you should perform

1 a laparoscopy study. Now, it is the position of the FDA
2 that if we are presented with, you know, valid scientific
3 evidence and good clinical information that we can indeed
4 extend from one to the other, and it's supported by animal
5 studies or other information, then we certainly will
6 consider that, you know, using one for the other. But some
7 of it applies to how the device is applied; some of it is
8 related to the difference between the two different type of
9 surgeries. So there's lots of issues that we need to look
10 at and consider before we make a determination of
11 overlapping the two.

12 DR. BLANCO: Ralph?

13 DR. D'AGOSTINO: I would like to ask a question
14 about I think one of the comments you made, is that there
15 are situations where the agency is willing to take
16 surrogates in a clinical trial and then look at
17 postmarketing. I did hear that correctly? Thank you.

18 What are those type of situations? Are they
19 where--some scenarios would be that it's almost impossible
20 within the clinical trial to see the clinical endpoint, and
21 so you're willing to get a surrogate that's very good and
22 then later on get confirmation. Another would be that the
23 studies or the condition is of such a benign type of issue
24 that surrogate is fine and just later on confirmation.

25 So could you just say some words on what would be

1 the scenarios that would lead to that type of decision?

2 DR. MITCHELL: I think you've identified two very
3 reasonable scenarios. Another thing that enters into our
4 decision-making actually is the time frame, because to do
5 second-look surgery for a gynecologic indication, for
6 example, it's a six-week, eight-week study, whereas if
7 you're looking at a clinical endpoint of say pregnancy or
8 reduced pelvic pain, you know, a year may be a more
9 reasonable amount of time to get that kind of information.

10 DR. D'AGOSTINO: Okay. Given that type of
11 situation, what would it be--what would be the nature of the
12 surrogate that would convince you that the surrogate is
13 sufficient for approval? Again, with the postmarketing
14 follow-up.

15 DR. MITCHELL: Well, we're willing to entertain
16 any of the surrogates that I suggested, either, you know,
17 absolute number of adhesions or a scoring system. You know,
18 we're not--we don't have--we haven't discovered a method of
19 scoring or looking at or evaluating adhesions that is the
20 best way to do it.

21 DR. D'AGOSTINO: Is there some level of validation
22 from the literature that would be needed, or is it some
23 common sense--

24 DR. MITCHELL: At this point we don't think that
25 there's any adhesion--way of scoring adhesions that has been

1 so strongly clinically validated that it is preferable over
2 all the others.

3 DR. BLANCO: I think to some extent, though,
4 you're asking them for some of the questions they're asking
5 us. Okay? Don?

6 DR. CHATMAN: I had a question on your intended
7 use thing. Basically you said that the company could come
8 in as a site-specific thing or a general type of indication.
9 So one company comes in and says, "All right, we're going to
10 use it for a specific for the uterus or pelvis," and then
11 the next company says, "We're going to come in and use this
12 as a model, and use it for generalized throughout the
13 abdomen," and then the other company comes back and says,
14 "Hey, this guy just used it, the same model that I used, to
15 get general use and I have got specific use." How can we--
16 how are you going to get away from those kind of conflicts?
17 It sort of seems like that--you know, the question is, is
18 the peritoneum different in one area of the abdomen than it
19 is in the other area of the abdomen?

20 And Dr. Schwaitzberg--

21 DR. MITCHELL: You know, we run into that
22 situation not infrequently and, you know, we are willing to
23 entertain what the sponsor comes to us with in terms of
24 proposals. If it comes to our attention that there is a
25 different way to look at things and it's related to, you

1 know, an adhesion barrier product, for example, often what
2 we do is inform the other sponsors that this is an option
3 that if they're willing to explore, make an argument for and
4 present to us, they're certainly more than welcome to do
5 that. So, I mean, that certainly can happen. It depends on
6 what the sponsor wants, and it depends on what we tell the--
7 and it depends on, you know, how things unfold after that
8 with the--

9 DR. BLANCO: Let me limit that a little bit
10 because we're starting to get into discussion, and I want to
11 save it until after lunch. I do want to get the public
12 hearing before lunch if we can. So let's have Dr.
13 Schwaitzberg's question, and then let's get the public
14 hearing going.

15 DR. SCHWAITZBERG: I think if nothing else gets
16 decided today, the single most important issue is whether
17 the panel will accept that the adhesion itself is the
18 clinical endpoint and no longer consider it a surrogate
19 endpoint. If you look at a cancer drug, the clinical
20 endpoint is reducing the cancer. If you look at an
21 infection drug, the clinical endpoint is reducing the
22 bacteria. And if you look at an adhesion product, then the
23 clinical endpoint is reducing an adhesion.

24 If the guidance document or the panel can come to
25 some clarity on that issue, if nothing else today, that

1 would be a major accomplishment, you know, for the day.
2 Both Dr. DeCherney and I feel that the adhesion is the
3 clinical endpoint, and the panel can vote and decide
4 whatever it decides, but if it comes to that determination
5 and clarifies that single point, they've done a great
6 service to everybody, including themselves.

7 DR. BLANCO: Make sure to bring that up when we're
8 doing the discussion and we'll get that.

9 DR. MITCHELL: Dr. Schwaitzberg, just let me ask
10 one question. When you say "reducing an adhesion," what do
11 you mean?

12 DR. SCHWAITZBERG: Presence or extent or severity
13 or functionality. I think those are all clinical aspects of
14 what an adhesion is.

15 DR. MITCHELL: Any of those?

16 DR. SCHWAITZBERG: Any of those, and that you can
17 make your claims appropriately. So I just wanted to comment
18 on focus.

19 DR. BLANCO: Okay, let's go ahead and move on to
20 the public hearing. We have four individuals and two
21 letters who have asked to present. Let me remind
22 individuals--Dr. Jim Burns for Genzyme on behalf of a group
23 of adhesion barrier manufacturers will be the first speaker.
24 Let me remind everyone to identify themselves for the
25 record, also identify yourself whether you have any possible

1 conflict of interest, any support from industry, et cetera.

2 DR. BURNS: Thank you, Mr. Chairman, and good
3 afternoon. I would like to thank Dr. Harvey for allowing us
4 to make our presentation here today. As was mentioned, I
5 represent an ad hoc task force of industry members that have
6 a lot of interest in doing research and developing products
7 for adhesion prevention, and we therefore have a lot of
8 interest in this adhesion guidance document.

9 I would like to, since this is for the public
10 record and I don't want to be outdone by Dr. Schwaitzberg
11 and Dr. DeCherney, my birthday is this coming Monday. So as
12 soon as I get my Power Point presentation up here, then
13 we'll get going.

14 We have, in very short order, put together a
15 presentation today to go through the issues that are of
16 importance to us, and particularly for clinical endpoints as
17 well as labeling issues. We have had a number of
18 discussions--Bonnie, actually if you can go to the next
19 slide--amongst all the task force that are represented here,
20 which is actually a pretty impressive list of all the people
21 that are in industry that are experts in the study of
22 adhesions as well as adhesion prevention. And we will
23 reserve the right, through separate correspondence with the
24 FDA, to indicate some of our issues that we may have on the
25 preclinical and the manufacturing and the other issues, but

1 for today I'm just going to focus on the clinical issues and
2 some of the labeling issues.

3 We are not coming forward here with our ideas
4 produced in a vacuum or only from an industry perspective.
5 Next slide, Bonnie. But we have actually elicited the help
6 of a number of surgical experts in this field to help guide
7 us in how we think about some of these clinical issues and
8 labeling issues. Some of those are here today, and I would
9 like to point out the clinical members of our ad hoc task
10 force: Dr. Randy Dunn actually is not here today. He is
11 still down in Texas. Dr. Michael Diamond is here with us.
12 Dr. Gere DeZiarga, Dr. Victor Gomel, and Dr. Russell
13 Malinak. And on behalf of the other industry members of
14 this task force, I would like to thank them for their
15 participation and help. Next slide.

16 So the four issues that I'm going to briefly
17 address with you today are shown here, and some of these
18 have already been addressed by Dr. DeCherney as well as Dr.
19 Schwaitzberg. The first one will have to do with clinical
20 endpoints for adhesion barriers, and we would like to state
21 our very strong position on this, that adhesion reduction
22 itself is a valid clinical endpoint.

23 We will also discuss briefly scoring systems for
24 post-surgical adhesions and what is meant by the word
25 "validated" with respect to those scoring systems. I would

1 also like to briefly talk about extrapolation of clinical
2 trials to labeling indications, how broad might we go, based
3 on the sometimes naturally narrow scope of clinical trials
4 for evaluation of these products. And as an extension of
5 that discussion, we will also talk about laparoscopy and
6 laparotomy for clinical product testing. Next slide.

7 In the 13 years--I'm sorry you can't read that.
8 This is a Gary Larson comic. I love this comic. It says,
9 "Well, I guess that explains the abdominal pains," and the
10 surgeon is pulling out a porcupine. I've been working this
11 area for 13 years, and there has been quite a bit of
12 evolution, obviously, in how we view the problem of
13 adhesions, the etiology of adhesions as well as what we can
14 do to prevent adhesions. Next slide.

15 But for sure what is known is that there is no
16 doubt that post-surgical adhesions cause significant patient
17 morbidity and in part a significant cost burden to our
18 health care system. I don't think there is any doubt about
19 this any longer.

20 That's why we feel very strongly that in the
21 guidance document, although it is implied that adhesion
22 prevention is an important endpoint, it should be more
23 clearly stated so that it's not ambiguous to future
24 sponsors, as well as the current ones, as well as future FDA
25 reviewers and panel members, that adhesion reduction in and

1 of itself is an acceptable and sufficient endpoint for
2 adhesion reduction product approval. Next slide.

3 This is substantiated by a number of precedents.
4 There have been a number of panel meetings that have
5 addressed this issue, and specific questions put to expert
6 panels, and those are indicated here on this particular
7 point. In two meetings of the General Plastic Surgery
8 Panel, both times the panel was asked, "Is adhesion
9 prevention an important clinical endpoint?" And the answer
10 to that question was yes. There has also been a similar
11 response for an OB/GYN Panel in April of '89, and more
12 recently for an Orthopedic and Rehabilitation Devices Panel,
13 for an adhesion prevention product. Next slide.

14 Further, the FDA has approved adhesion barrier
15 devices based on adhesion reduction endpoints. Importantly,
16 it was the opinion of the May 5, 1997 General Plastic
17 Surgery Devices Panel that, although adhesion reduction is a
18 valid endpoint for evaluating these products, there is no
19 further implied claim about other clinical outcomes such as
20 small bowel obstruction, pain or infertility in a product
21 label for adhesion reduction. Therefore, without exception,
22 adhesion reduction has been the primary endpoint for pivotal
23 efficacy trials for adhesion product approval.

24 That's for the clinical studies for these
25 endpoints. That doesn't always translate to a label for

1 those endpoints. And I think in the document, the guidance
2 document, it should also explicitly state that a product
3 label, if it is studied for adhesion prevention, obviously
4 should be for adhesion reduction for use of that product,
5 and that there is no implication of other clinical outcomes,
6 again, small bowel obstruction, infertility, pain,
7 reoperation time.

8 It should be up to the manufacturer's discretion
9 that they may add a product indication for these other types
10 of outcomes by electing to do postmarket outcome studies.
11 It should not be a requisite for approval of a product to
12 conduct postmarket outcome efficacy studies if the label is
13 explicitly stating "adhesion reduction." Next slide.

14 And this is again supported by some precedent, and
15 we support that precedent, that label indications for
16 location of use can be broader than those studied in
17 clinical trials, when this is scientifically appropriate.
18 And we heard some of that discussion from Dr. Schwaitzberg
19 today, as well as Dr. DeCherney. And the label should
20 indicate where the product was effective.

21 So although a product may be studied in one type
22 of clinical indication, when it is scientifically
23 appropriate, a broader label may be appropriate. The label
24 should state, though, where the product is actually shown to
25 be effective. Additionally, specific safety questions,

1 depending on how the product is or where it might be used,
2 can be addressed in either pre- or postmarket studies or in
3 animal studies.

4 I would like to extend this label discussion into
5 laparotomy versus laparoscopy, and we've heard some
6 interesting discussion about that already. The draft
7 guidance document currently states that there are
8 significant differences between laparoscopy and laparotomy
9 that might affect the potential efficacy of adhesion
10 barriers. Although this is stated and implied, there is no
11 sound scientific data to actually justify this position, and
12 actually there is a recent meta analysis by Dr. David
13 Wiseman in which adhesion formation at sites of trauma, as
14 well as reformation--in both cases there is trauma--is
15 essentially equivalent whether that is in laparoscopy or
16 laparotomy. Next slide.

17 So we feel that this supports that a separate
18 efficacy study by laparoscopy and laparotomy should not be
19 automatically required for every product that comes before
20 the FDA, as there is no known scientific evidence of
21 significant differences for adhesion reformation and
22 formation at sites of trauma. Admittedly, this may be
23 different for what are known as de novo 1-A adhesions.
24 Those are adhesions at sites of incidental trauma.

25 Studies may be necessary to demonstrate the safety

1 and compatibility of using barrier products in laparotomy
2 and laparoscopy. So if the main efficacy study is performed
3 in laparotomy, you may have to show that you can actually
4 use the product in a safe way through a laparoscope for
5 laparoscopic applications. And labeling should therefore
6 indicate separate instructions for use, product use, in
7 laparotomy and laparoscopy.

8 Another point I wanted to just briefly mention is
9 the issue concerning validation. In this particular case
10 we're talking about validated scoring systems. We agree
11 with the FDA on the need for validating scoring systems.
12 We'd like to clarify what that means to us. That is that a
13 scoring system should be defined prospectively between the
14 FDA and the end sponsor in the study protocol, and that this
15 scoring system should be shown to provide a reproducible
16 measure of adhesions.

17 In summary, we feel that reducing post-surgical
18 adhesions is an established and acceptable endpoint for
19 evaluating adhesion barrier products, and that manufacturers
20 may add to a product's indication by electing to conduct
21 postmarket outcome for bowel obstruction or other outcomes
22 besides adhesion prevention. Adhesion scoring systems
23 should be defined prospectively with the FDA in the
24 protocol, and should be shown to provide a reproducible
25 measure of adhesions.

1 We believe that data do not support significant
2 differences between laparoscopy and laparotomy for adhesion
3 reformation and adhesion formation at surgical sites, and
4 therefore we believe that separate clinical efficacy trials
5 should not be always required for these types of products.
6 We also support the precedent that the label indications for
7 location of use can be broader than were studied for a
8 particular clinical trial, and that the label should
9 indicate where the product was shown to be effective.

10 In summary, we would like to say that we welcome
11 the opportunity to comment on this draft guidance document,
12 and we look forward to collaborating with the medical
13 community and the FDA, hopefully in an active relationship,
14 to develop the optimal guidance document for resorbable
15 adhesion barriers to ensure the availability of these types
16 of products for the benefit of surgeons and patients. Thank
17 you, and I would like to indicate that we will be here for
18 the rest of the day if there are any questions that you
19 would like us to answer.

20 DR. BLANCO: Thank you very much for your
21 presentation.

22 We will go ahead and move on to the next speaker
23 on the list, and this is Dr. David Wiseman, speaking for the
24 International Adhesions Society.

25 DR. WISEMAN: Yes. Thank you, Mr. Chairman.

1 Thank you for allowing me to make this presentation today.

2 I am wearing a couple of hats today. Next slide, please.

3 Firstly, the International Adhesions Society is an
4 internet-based support group for patients with postoperative
5 adhesions. In addition, I have my own consulting company
6 that's devoted to the development of adhesion prevention
7 products, and in that regard I have received compensation
8 and have worked with a number of companies that are
9 represented here today and/or have financial interest in
10 some of those companies. Next slide, please.

11 Briefly, the International Adhesions Society, the
12 mission is stated here. It's for more awareness, to provide
13 support to patients, and to promote and conduct research.
14 Next slide, please.

15 The membership consists of men and women who
16 suffer from adhesion-related disease. The youngest age is 6
17 and the oldest is 90 we have, covering a variety of medical
18 specialties, predominantly in North America but also
19 throughout the world.

20 The typical problems are shown here. I want to
21 highlight the second bullet there to emphasize Dr.
22 Schwaitzberg's presentation, that many of our members have
23 had multiple procedures, anywhere from 4 to 20. These
24 procedures are hazardous, time-consuming and very expensive,
25 and there are a number of problems in accessing health care

1 for people that have adhesions. Next slide, please.

2 This, briefly, this is not the worst patient, but
3 when I drafted my presentation I sent it out to everyone for
4 comment, and somewhere down there this lady says that she
5 has had an adhesion between the omentum and the vagina which
6 has been cut two or three times, and the problem that it
7 causes goes away, and then it comes back again once that
8 adhesion grows back again. Next slide.

9 I want to address just two points in this part of
10 the presentation, one regarding clinical endpoints. We have
11 discussed that already. There is plenty of circumstantial
12 evidence, as Dr. Burns has pointed out, that links adhesions
13 and the endpoints, and we all understand now, I think, that
14 it's scientifically difficult to study these endpoints in a
15 validated type of method.

16 If these endpoints were made a condition of
17 approval, it would delay the approval of agents that might
18 help our patients, and furthermore discourage manufacturers
19 to develop products that could be of benefit. And so we
20 request that the approval of anti-adhesion agents should not
21 be contingent upon studies with these endpoints. Next,
22 please.

23 Furthermore, to emphasize the previous speakers,
24 adhesions in and of themselves are an endpoint, and the
25 study of Ellis has been mentioned, that adhesions are a

1 direct cause of hospital readmissions in such a number which
2 rivals admissions for common procedures such as bypass,
3 coronary artery bypass, appendectomy and hip replacement, as
4 well as being--adhesions are a financial burden on the
5 system.

6 Most importantly, because adhesion corrective
7 surgery is often hazardous and always time-consuming, it is
8 sometimes not even attempted, and so the lack of
9 availability of products such as the ones we're talking
10 about means that patients who suffer from these problems
11 don't even have the ability to go in for second, third, or
12 21st looks to correct their problems. So therefore, again,
13 we believe that adhesion reduction itself is a valid
14 scientific and clinically meaningful endpoint. Next,
15 please.

16 This is just listing some comments that I have
17 received. You can see patients have had procedures anywhere
18 from 4 in number to 18 I think is the highest number on that
19 slide. Next, please.

20 The next comment we want to make is that we urge
21 the panel to consider carefully imposing any requirement on
22 companies or scientists that has no scientific basis. And
23 the issue, the main issue at hand here is the issue of
24 laparoscopy versus laparotomy, and we believe that the same
25 standards of valid scientific evidence that FDA requires--

1 the law requires from sponsors must also apply to FDA when
2 it imposes additional requirements on the sponsors, and we
3 believe that such a policy may be implemented without
4 compromising patient safety.

5 And if you go to the number two, Bonnie, Dr. Burns
6 has asked me to go into a little more detail on the
7 laparoscopy issue. It's about the 10th slide down, so keep
8 going. Okay.

9 In the guidance document, this is a quote from the
10 guidance document, it says, "Due to significant differences,
11 both quantitative and qualitative, in adhesion formation,
12 the FDA's guidance document suggests that there are
13 differences between laparotomy and laparoscopy," and it
14 quotes two papers, Lunderoff and the Operative Laparoscopy
15 Study Group. Next slide, please.

16 I reviewed both studies. In fact, we reviewed
17 them for our meta analysis, the one that we cited earlier
18 that I conducted together with Drs. Diamond and Trout. The
19 first study that is cited by the guidance document is
20 Lunderoff, and indeed they found that more adhesions were in
21 laparotomy than laparoscopy.

22 However, a large number of patients, almost 30
23 percent, which were randomized through treatment did not
24 undergo second-look laparoscopy. And since the group
25 assignment of these patients was unstated and no intensive

1 treatment analysis was performed, it's very difficult to
2 reach any kind of conclusion as to whether in fact there
3 were more adhesions in laparotomy than laparoscopy.

4 The second study that is cited is in fact a study
5 which is only on laparoscopy, and in the discussion it makes
6 some comparisons between laparoscopy and laparotomy. At
7 that time in 1991 the classification of de novo adhesions
8 was ambiguous, and Dr. Burns has mentioned that there are
9 two different types of de novo adhesions, 1-A and 1-B. We
10 don't have into what that means at this moment, but suffice
11 it to say that since this classification is ambiguous, it's
12 difficult to make any comment on that.

13 And, lastly, in later review of this study, it has
14 turned out that some of the patients in that study were
15 treated with Dextrand 70, and so it's difficult to make any
16 kind of conclusion from that study about whether laparoscopy
17 or laparotomy has more adhesions. Next slide, please.

18 Furthermore, the guidance document or I believe
19 the questions to the panel suggest that some studies have
20 shown that the same barrier might not work well in
21 laparoscopic surgical environments, and we are unaware of
22 any studies that are like that. The only possible thing
23 that we could think of is in regard to one particular
24 adhesion barrier where there are four--there are many
25 studies showing its efficacy in laparotomy, there are four

1 studies in laparoscopy that show its effectiveness, one
2 study that shows it is not effective, and yet one other
3 study where the product was inappropriately applied and it's
4 difficult to draw any kind of conclusions in that particular
5 study. So we are unaware, we would like to be made aware if
6 the data exists, as to the basis for this comment. Next,
7 please.

8 So to summarize, there are some, even with the
9 caveats that I have mentioned, there are some studies that
10 suggest adhesions form less frequently in laparoscopy, the
11 Lundorff study that I mentioned, and secondly there are some
12 studies that suggest that adhesions form more frequently in
13 laparoscopy, and our meta analysis suggested there was a
14 slight increase but it was not statistically significant,
15 essentially the same. We thought that that was due to the
16 reduced ability to handle tissues atraumatically. There may
17 be some issues of gases being used during laparoscopy, and
18 also possible effects of cautery combustion products. Next
19 slide, please.

20 But there is no--but, despite these things, there
21 really is no evidence that the rates of adhesion development
22 are any different, other than this one unique category of
23 adhesions. There is no difference that the pathobiology is
24 any different. There is no ability--there is no evidence
25 that adhesion barriers work any differently in laparotomy or

1 laparoscopy.

2 And, based on the product, the one product that's
3 on the market, been on the market for 10 years now, there's
4 no evidence of differences in product safety. In fact, Dr.
5 Malinak, who is in the audience today, will recall a study
6 that he presented a few years ago saying that this
7 particular product, 60 percent of its use is off-label in
8 laparoscopy. and clearly there have been no safety concerns
9 with that.

10 So we believe that there is no justification to
11 require separate efficacy evaluations in laparotomy and
12 laparoscopy. There are some safeguards, of course. Next
13 slide, please.

14 That there should be adequate studies to show the
15 safe and effective deployment of the device. Where concerns
16 that a product may be compromised in the presence of
17 bleeding, the labeling should indicate that the surgeon
18 checks hemostasis by partial desiccation prior to deployment
19 of the device. And safety concerns can also be addressed by
20 safety studies and/or postmarket surveillance.

21 And I think that's it.

22 DR. BLANCO: All right. Thank you very much.

23 DR. WISEMAN: Thank you.

24 DR. BLANCO: All right, let's go ahead with the
25 next public speaker, Dr. Victor Gomel. Please remember to

1 identify yourself, your affiliation, whether you have any
2 support.

3 DR. GOMEL: Yes. I am Victor Gomel. I am a
4 professor at the University of British Columbia. I have
5 worked with adhesions all my life, my professional life, and
6 obviously I have had support by--from many companies,
7 research support.

8 What I would like to present briefly today is,
9 indeed adhesions in themselves are important, but they
10 affect outcome. I would like to show you three studies that
11 the AFS call that we use is a prognostically valid score,
12 and that reduction of adhesions also lead to clinical
13 results, to clinical outcome.

14 In this particular study from Japan, the patients
15 are grouped with--according to their adhesions, and you can
16 see these are ovarian adhesions. They are a group of
17 minimal adhesions, a group of mild adhesions, moderate
18 adhesions, and severe adhesions.

19 And you can see on your left the pregnancy rates,
20 which are about 70 percent, 60-odd percent in the patients
21 with minimal and mild adhesions, whereas that rate is
22 significantly lower, actually fairly low in patients who
23 have moderate and severe adhesions. So that you can see
24 clearly that adhesions in themselves affect outcome, and in
25 this case the degree of ovarian adhesions seem to indeed

1 affect pregnancy outcome. The second slide, please.

2 This is a study from Vancouver. They are all
3 human studies. This study involves 90 patients with distal
4 tubal occlusion submitted to salpingostomy, and according to
5 the AFS classification devised in 1988, and I was in that
6 particular committee, 17 of the patients were in the
7 prognostically good group, mild group, and you can see that
8 nearly 70 percent of these patients achieved a pregnancy,
9 whereas the 73 patients who were in the severe group had a
10 pregnancy of about--pregnancy rate of about 20 percent.
11 Next slide, please.

12 And I am delighted to show a very recent, yet
13 unpublished study, sent for publication, of 61 patients from
14 Greece. And here you see the characteristics of these
15 patients. They have a duration of infertility varying
16 between 1 and 9 years, with a mean of 3.5, primary and
17 secondary infertility divided as 75/25 percent.

18 But what is very important in this study, if we go
19 to the next and last slide, you will see here these were
20 patients who had reasonably good tubes. In other words,
21 they were submitted to salpingostomy but, according to the
22 classification, their tubes were considered prognostically
23 good. But in the upper bar there were no or minimal
24 periadnexal adhesions.

25 In the lower graph with triangles there were

1 moderate to severe adhesions present. And you can see a
2 statistically significant difference between the pregnancy
3 rate achieved by these two groups of patients, again clearly
4 demonstrating the influence of periadnexal adhesions on the
5 outcome, on the pregnancy outcome. In the upper bar the
6 pregnancy rate was 46 percent, and in the lower it was about
7 28 or 29 percent.

8 So I rest my case. Thank you very much.

9 DR. BLANCO: Thank you. The next speaker that we
10 have registered is Dr. Russell Malinak.

11 DR. MALINAK: Thank you, Mr. Chairman. I am
12 Russell Malinak, professor of OB/GYN at Baylor College of
13 Medicine. I have been a reproductive surgeon since 1968 and
14 have spent a majority of my time in performing surgery,
15 teaching residents, fellows and students, and doing
16 research. I am not paid to be here, but I have had industry
17 support from numerous sources for both research and teaching
18 over many years.

19 I am here as a patient advocate. I am here in the
20 interest of the health care of women, regarding prevention
21 or reduction in postoperative pelvic adhesions. I have been
22 privileged during my career as a gynecologic surgeon to
23 observe, over decades now, improved outcomes from
24 technologic advances in anesthesia, blood transfusions,
25 surgical instrumentation, suture materials, and minimally

1 invasive surgery. Yet one outcome which has not been
2 substantially improved has been the complication of
3 postoperative adhesion formation.

4 I encourage the FDA to extend their partnership
5 with the academic institutions and industry in support of
6 clinical trials to ensure that the very best science and
7 surgical acumen can be applied to resolution of this
8 problem. These trials should be based on documentation that
9 the anti-adhesion method has in fact reduced adhesions
10 beyond that achieved by controls. Outcomes such as
11 pregnancy are too nefarious to document efficacy of an
12 adhesion reduction method.

13 I consider postoperative adhesions, with their
14 attendant morbidity and occasional mortality, to represent
15 the largest unmet need in the advancement of the art and
16 science of surgery. Thank you for the opportunity.

17 DR. BLANCO: Thank you, Dr. Malinak.

18 Is there anyone else in the audience who would
19 like an opportunity to make comments to the panel?

20 [No response.]

21 DR. BLANCO: Not having anyone volunteer, there
22 are two letters that FDA received, that their writers
23 requested that their letter be read into the record and also
24 read to the panel. The first letter is from Dr. Steven
25 Wexner, and I'll go ahead and read them.

1 "Dear Dr. Harvey: I am Chairman of the Department
2 of Colorectal Surgery at Cleveland Clinic Florida. I have
3 been involved in the evaluation and clinical study of
4 adhesion barrier products for the last many years. I am
5 carrying forward the tradition of my late partner, David G.
6 Jagelman, M.D. He studied with Professor Harold Ellis,
7 O.B.E., in London, England, pursuing adhesion research
8 several decades ago. I am writing to forward my clinical
9 opinion on the adhesion barrier guidance document, which is
10 the topic of the Advisory Panel meeting to be held on
11 January 25th, 2000. Unfortunately, due to a prior
12 commitment, I will be unable to attend much as I would like
13 to discuss these issues with you in person.

14 "The clinical section of the guidance document
15 make frequent reference to studying specific clinical
16 outcomes whenever possible. Unfortunately, it is
17 impractical, unfeasible, and in fact potentially deleterious
18 to patients to perform a well controlled randomized blinded
19 trial if the primary clinical outcome is small bowel
20 obstruction. The fact of the matter is that the vast
21 majority of patients want to know whether or not a device or
22 a substance has been placed in them as well as what
23 technique has been used. Since patients worry about
24 recurrence of cancer, diverticulitis, and inflammatory bowel
25 disease, three of the most common indications for colorectal

1 surgery in this country, it is easy to understand their
2 concern. Unfortunately for the patients, these diseases do
3 recur; however, serendipitously reexploration for problems
4 such as recurrent Crohn's disease and repair of ventral
5 incisional hernias does allow the unique opportunity to
6 assess adhesions. Such assessment is a valid endpoint that
7 is clinically of paramount importance. Adhesions cause not
8 only bowel obstruction, but increase the length of operative
9 time, thereby potentially increasing the risk of surgery,
10 and increase the possibility of enterotomy and myotomy,
11 therefore potentially increasing the risks of post-operative
12 sepsis and fistula formation--fistulization. One of the
13 potential advantages of studying adhesions over obstruction
14 is that adhesions form within a few days after surgery,
15 whereas obstruction may occur up to five to six decades
16 later. Therefore, were a study to rely strictly upon bowel
17 obstruction, an infinite endpoint would be necessary. The
18 attrition which would occur over such a long period of
19 follow-up would make the denominator for the study virtually
20 unachievable. However, since so many patients who undergo
21 colorectal surgery require reoperation for a variety of
22 reasons, the presence or absence of adhesions can be easily
23 studied.

24 "As an academic colorectal surgeon, I am engaged
25 in many fields of research. My interest in publications

1 includes the gamut of functional disorders such as
2 constipation, incontinence and rectal prolapse; to
3 malignancy, including colonic and rectal carcinoma; to
4 inflammatory bowel disease, including mucosal ulcerative
5 colitis and Crohn's disease; to techniques such as
6 laparoscopy; to improvement of outcomes. Clearly a
7 reduction in bowel obstruction represents a significant
8 improvement in outcome, as adhesions are formed after the
9 vast majority of transabdominal operations performed to the
10 colon and rectum. In the absence of being able to prove a
11 reduction in obstruction, it is at least gratifying to
12 hypothesize that these operations can be performed more
13 quickly and more safely due to a reduction in adhesions. I
14 strongly suggest that evaluation of adhesions be allowed as
15 a clinically important surrogate to bowel obstruction in
16 future adhesion reduction studies. I, for one, look very
17 much forward to offering some hope to the plethora of
18 patients whose lives are adversely affected by adhesions. I
19 eagerly await the day when we can improve outcome by safely
20 preventing adhesions. Verification of their presence and
21 quantification of their diminution after therapeutic
22 intervention is a logical and necessary first step.

23 "Should you require any additional information
24 from me, please let me know. Sincerely, Steven Wexler."

25 The next letter is from Dr. Harold Ellis, emeritus

1 professor of surgery, University of London, King's College,
2 London.

3 "Postoperative Intra Abdominal Adhesions.

4 "I am the chairman of a group of surgeons,
5 gynecologists and a health economist in the U.K. who are
6 interested in the problems of post-operative intra abdominal
7 adhesions. We have published a number of studies in this
8 field, including a major report in the Lancet on adhesion
9 related admissions to hospital after abdominal surgery. See
10 reference list.

11 "I have been carrying out clinical and laboratory
12 research in this field since 1958. A summary of our main
13 findings is as follow:

14 "(1) Intra abdominal adhesions are almost
15 invariably after abdominal or pelvic surgery. Certainly 95
16 percent of patients will demonstrate adhesions to the
17 laparotomy scar and/or the site of surgery on reexploration
18 of the abdomen. The exceptions are surgery for 'cold'
19 appendectomy in some cases and the lower segment Caesarian
20 section.

21 "(2) A proportion of patients will develop post
22 operative intestinal obstruction as a result of adhesions,
23 which account for 65 to 75 percent of all cases of small
24 bowel obstruction in the Western World.

25 "(3) The risk of this complication of abdominal

1 surgery is lifelong. About 1 to 2 percent of patients will
2 obstruct within the first year following surgery, but about
3 25 percent of cases will have had their initial abdominal
4 surgery 10 years or more before their first obstructive
5 episode.

6 " (4) Some operations are at particularly high
7 risk of developing subsequent obstruction. For example,
8 total colectomy and ileal pouch surgery has a 25 percent
9 risk of subsequent adhesive obstruction.

10 " (5) We surveyed the population of Scotland, 5
11 million people, in a retrospective cohort study. A 10 year
12 survey of a cohort of 54,380 patients undergoing abdominal
13 surgery in 1986 revealed a 5.7 percent readmission rate to
14 hospitals in Scotland classified as directly adhesion
15 related, with 3.8 percent requiring operative treatment.
16 Readmissions occurred steadily over the 10 year period of
17 follow-up.

18 " (6) In addition to the problems presented by
19 adhesive obstruction, adhesions increase the time taken to
20 enter the abdomen in a second laparotomy, in our study a
21 mean of 24 minutes; increase the danger of inadvertent bowel
22 perforation, 21 percent in a recent major study; are a
23 leading cause of female secondary infertility; and, in the
24 pelvis, may result in pelvic pain and dyspareunia.

25 "Conclusion: Post-operative intra abdominal

1 adhesions are the commonest cause of small bowel
2 obstruction, as well as being responsible for other serious
3 and common surgical and gynecological problems. Any means
4 that might reduce the incidence of adhesions would be a
5 valuable contribution to the surgical armamentarium.

6 "Harold Ellis, emeritus professor of surgery,
7 University of London."

8 And several selected references are hereby entered
9 into the record by reference to this letter.

10 That ends the open public hearing section of this
11 panel meeting. We will reconvene again at 1:30, at which
12 time we'll begin the discussion. Thank you very much.

13 [Whereupon, the panel adjourned, to reconvene at
14 1:30 p.m. the same day.]

1 AFTERNOON SESSION

2 DR. BLANCO: All right. We're going to go ahead
3 and reconvene the meeting. We have totally redone the
4 agenda, but now we're back hopefully on track, and we'll see
5 if we can go through this and finish up.

6 Now the rest of the time will be dedicated to
7 panel deliberations and the panel discussion of a set of
8 prepared questions that the FDA has for us. Just so that
9 the audience is aware, one of the speakers talked about
10 voting. There really is no voting in this type of format.
11 We're just discussing it and either coming to conclusions,
12 or hopefully in a friendly manner agree to disagree, and
13 express opinions for enlightenment of the Food and Drug
14 Administration personnel that are here.

15 For those of you on the panel, you should have in
16 your packet the discussion questions that we are asked to
17 discuss and give some guidance to the FDA on, and I'll begin
18 reading the general document and then we'll go question by
19 question and discuss the various issues.

20 Recently a draft guidance document, guidance for
21 resorbable adhesion barrier devices for use in abdominal
22 and/or pelvic surgery, was jointly issued by two divisions
23 in CDRH's Office of Device Evaluation. This panel is asked
24 to discuss how the following issues are addressed in the
25 guidance document and provide recommendations for additions,

1 deletions or modifications to the document. The purpose of
2 this discussion will be to provide FDA with insight to
3 further refine and improve the guidance.

4 The first question that we are asked to look at
5 has three parts. Number 1: Regarding study endpoints for
6 adhesion barriers used in the abdominal-pelvic cavity:

7 (a) Please discuss the importance and value of
8 studying clinical endpoints in adhesion barrier
9 investigation, i.e., reduction of small bowel obstruction,
10 improvement of fertility, reduction in chronic pelvic pain.
11 Please also comment on the best methods to evaluate them.

12 (b) Please discuss the strengths and weaknesses
13 of the following assessment tools used to measure pelvic and
14 abdominal adhesions in terms of accuracy, reproducibility
15 and the ability to accurately predict clinical outcome:
16 one, incidence of adhesions; two, extent of adhesions;
17 three, severity of adhesions; four, AFS scoring system;
18 five, modified AFS scoring system; six, number of adhesion-
19 free patients; seven, other methods for evaluating
20 adhesions.

21 (c) Please discuss the use, advantages and
22 disadvantages of surrogate endpoints listed above in 1(b)
23 versus clinical endpoints for the approval of an adhesion
24 barrier.

25 The floor is open for discussion. Any panel

1 member would like to make some comments at this point? And,
2 Dr. Schwaitzberg, please feel free to join in with us. And
3 if we need some questions from some of the audience, we have
4 several experts in the audience, and we will try to call on
5 them as we need. Anyone want to--have you got a comment,
6 Ralph? Why don't you start it off?

7 DR. HARVEY: And please use the mike if you can.

8 DR. D'AGOSTINO: I'm sorry. To get the discussion
9 going, in terms of the clinical endpoints, it's hard for me
10 to see on the surface why one wouldn't want the clinical
11 endpoint to be the major endpoint. And, again, this is not
12 necessarily where I'm heading for final, but just in terms
13 of the discussion.

14 And I don't necessarily hear anybody saying, even
15 though they're multifactorial and what have you, that they
16 aren't appropriate endpoints as long as there's a mechanism.
17 And I think one possible scenario for clinical trials is to
18 have these endpoints, the reduction of small bowel
19 obstruction, fertility, reduction in chronic pelvic pain, as
20 the main endpoint, followed by a close look at the adhesions
21 to make sure the mechanism is in place and that there's an
22 understandable mechanism.

23 And if that's one possibility for putting a
24 clinical trial together, I would think that that would be
25 sort of the preferred clinical trial. And I would really

1 like to hear what people have to think about that or say
2 about that.

3 DR. BLANCO: Well, I guess I'm going to disagree a
4 little bit with that because I think it's not only the issue
5 of multifactorial, I think it goes back again to what is
6 going to be the indication for use and how is the product
7 going to be marketed. And I think, you know, if you're
8 going to say that your product helps the pregnancy rate, say
9 from--that it helps the pregnancy rate, well, that's a claim
10 that you've got to prove.

11 But if your indication for use--and this was one
12 of the things that one of the speakers this morning said
13 they later wanted to broaden, I think you can't have your
14 cake and eat it too. I think you've got to say, "Okay, I
15 want to show that my product reduces adhesions" in whatever
16 way, shape or form it's decided that you're going to measure
17 that, and then that's what you've got to claim, that by use
18 of this product you have got a lower rate of adhesion
19 formation.

20 Now, obviously the implied hope there is that by
21 lowering the rate of adhesion formation, you eventually will
22 make an impact on all of these clinical diseases that create
23 problems for patients. But, I mean, I can see very
24 problematic issues with intestinal obstruction in terms of
25 the number of years that it would take to really know what

1 the rate is.

2 I think a perfect example on the pregnancy side is
3 a look at the recent 10 to 20-year data out of the CDC
4 looking at the failure rate of tubal ligations and showing
5 that you still have failure rates, you know, a significant
6 number of years past the procedure. And I think that to be
7 able to prove that claim would be impossible, and I think
8 it's just a matter of you can't make that claim. You have
9 to narrow the claim to what you think the product can do.

10 DR. D'AGOSTINO: So, I mean, can I just respond?

11 DR. BLANCO: Sure. Go ahead.

12 DR. D'AGOSTINO: So in place of these particular
13 clinical endpoints, then we'd have to switch to some sort of
14 measure of adhesion, such as in the 1-B. And if we were--
15 and again, I'm just trying to talk this out as opposed to
16 necessarily say my particular view--but if we were to say
17 that there was a particular operation being done for the
18 fertility problem or for the small bowel obstruction, would
19 we not need to--would we want to think of the way we look at
20 the adhesions as somehow relating to that particular
21 problem?

22 And if we had an endpoint in mind, a clinical
23 endpoint in mind, it would inform us I think in terms of how
24 to look at the adhesions. And I would think that just
25 looking at adhesions, period, might lead us to a global type

1 of study where we don't know what we have at the end, where
2 if we had a clinical endpoint in mind, then we might be
3 driven by some way of--particular way of looking at the
4 adhesions.

5 DR. BLANCO: I'm not sure that I follow that. I
6 mean, I would think just the opposite, that adhesions, it's
7 clear-cut. You go in, you traumatize a tissue, you know,
8 that's one of the risk factors for adhesion; other things
9 that can happen that maybe we don't understand, whether the
10 immune status of the individual, something else.

11 And that's one of the things that I would comment.
12 I think when studies are being done for these particular
13 types of products, things that would benefit industry and
14 would benefit clinicians is to not just look for the
15 particular effect but to try to understand a little bit
16 better why some patients have a very high rate of adhesion
17 formations and others you do multiple surgeries--I mean, I
18 don't know if that happens in general surgery, but in OB/GYN
19 you'll do four operations on a women and, you know, the
20 pelvis looks like it's nothing, you've never been in there.
21 And another one, you'll do one and it looks like a grenade
22 went off in there.

23 So I think there are other issues that need to be
24 looked at, but I think it would be very--I think there are
25 so many multifactorial issues going into a pregnancy or an

1 intestinal obstruction, that I think you would be more
2 muddled, you would have more muddled data with using that as
3 an endpoint.

4 Jerry?

5 DR. SHIRK: I think I agree with you, Jorge.
6 Basically, the problem is that, you know, if you say this
7 thing improves pregnancy, then is the surgeon going to go in
8 and say, "All right, if I put this in the patient it's going
9 to improve her pregnancy rate."

10 I mean, it's--I mean, I think that that--if we use
11 specific clinical endpoints, then it implies that the
12 product has some specific clinical outcome, which is not
13 necessarily true. It obviously depends on the surgeon, what
14 was there. Again, that's a multifactorial thing that's even
15 broader than just what's going on inside the patient. And
16 so I think that the only real scientific approach you can
17 have is, with a single parameter endpoint is basically
18 whether the adhesion is there or whether it's not, or if
19 it's there, how much reduced is it?

20 DR. BLANCO: Don?

21 DR. CHATMAN: I'll just chime in with similar
22 comments. I mean, the functional outcome is extremely
23 important, and of course that's where we all would like to
24 go, and that research can be done but, you know, it's time-
25 consuming, it's very, very difficult. And it may be

1 impossible to do, because one thing we haven't discussed is
2 the technique, the operator, the person who does the first
3 operation, for instance, and what input that has into the
4 development of adhesions. That's going to be almost
5 impossible to do, to factor that in.

6 So the reduction of research to the number of
7 adhesions or the location of the adhesions or the extent of
8 the adhesions or something like that is going to be hard
9 enough as it is, because you've got this AFS scoring system
10 here to use for that. And if this AFS scoring system--I'm
11 not sure if it's been analyzed the way the endometriosis AFS
12 scoring system has been analyzed, and it has been shown very
13 clearly that from person to person, inter-observer, the same
14 observer in a week or so, you get different scores, you get
15 different observations, you get different evaluations, in
16 endometriosis at least. I'm not sure, again, if this
17 adhesion scoring system has been analyzed in that way.

18 And so it's going to be hard enough just
19 quantitating adhesions, you know, in and of itself, and
20 having some kind of consistent results show up in order to
21 evaluate a device or a solution or whatever. It would be
22 ideal to have functional results but I don't think it's
23 really practical.

24 MR. : I think, you know, I think your
25 viewpoint is, you know, the measuring of what is an

1 adhesion, you know, sort of like what should be what you
2 measure. And I think what you're saying is, it may be
3 difficult to measure what is a significant adhesion, in
4 other words, what methodology is available. Is that what
5 you're saying?

6 DR. CHATMAN: I'm saying that if you look at an
7 adhesion and I look at the adhesion, we're probably going to
8 see two different things. If I look at the adhesion today
9 and I videotape it and I look at it a week from now, I'll
10 probably get a different score altogether. The
11 endometriosis research shows that very clearly.

12 I mean, you know, you can videotape something
13 today--you know, this has already been commented on,
14 obviously--but you can videotape something today and look at
15 it a week from now, get a different score altogether again.
16 If I look at it today and you look at it today, we may get
17 different opinions about the adhesions. It's going to be
18 difficult enough quantitating the adhesions, is basically
19 what I'm saying.

20 MR. : But if you had no chronic pelvic
21 pain, would you say the way you were measuring it and the
22 way I was measuring it and the way someone else was
23 measuring it was necessarily the crux of the matter?

24 DR. CHATMAN: Well, I think that when you're
25 talking about chronic pelvic pain, evaluating that is

1 another whole very, very difficult area, difficult subject.

2 MR. : Yes. Let me just--

3 DR. CHATMAN: Trying to evaluate the results of
4 adhesiolysis and the relief of chronic pelvic pain is--

5 MR. : Let me just say what I--

6 DR. CHATMAN: --a mine field.

7 MR. : If you don't mind, let me say where
8 I'm coming from in terms of trying to play the devil's
9 advocate. I've been doing things with the FDA for about 25
10 years on different panels, and one of the very first issues
11 we had was distress after a big meal, post--intestinal
12 distress, and there was a whole literature that we gathered
13 about how to measure it. You could stick tubes down
14 people's throats and take the gas. You could look at
15 distension and so forth. We had all these physical
16 measurements, and none of them correlated to what the
17 subject said in terms of relief.

18 And I think one of the things that we should be
19 aware of, I think, as we make--as we go down the line here,
20 is what is the endpoint? What is the person taking the
21 procedure for? If the person's taking a procedure for
22 fertility and you tell her the adhesions are gone and she
23 should be happy, there's something that may not match in
24 terms of the expectations of the population and the actual
25 way we're saying the product is to be evaluated.

1 MR. : In clinical practice, though, you
2 actually don't tell a patient that because you remove her
3 adhesions, she's automatically going to get pregnant. I
4 mean, you don't make that promise.

5 DR. BLANCO: All right. Let's have Dr.
6 Schwaitzberg join in.

7 DR. SCHWAITZBERG: I'd like to address Dr.
8 D'Agostino's concerns. I think that for the first part you
9 have to believe that the elimination of an adhesion, in and
10 of itself, regardless of whether the patient gets a bowel
11 obstruction or pregnancy or relief of their chronic pain, is
12 a benefit. Now there's no science to this because there's
13 all opinions.

14 And a couple of years ago Dr. Diamond and I
15 queried surgeons and got a large number of responses, and
16 we've finally gotten around to writing it up. And surgeons
17 believe that the elimination of an adhesion, in and of
18 itself, without any other symptomatology issues attached to
19 it, is a clinical benefit for the patient for a number of
20 reasons.

21 We've discussed reoperative surgery. Sometimes it
22 means the difference between whether a patient could be
23 laparoscoped for some down-the-line operation. But getting
24 back to the pregnancy issue, if you eliminate the adhesions
25 and the patient doesn't get pregnant, is that a failure?

1 Not necessarily.

2 In the practice of clinical medicine, sometimes
3 you have to take things off the plate. For instance, the
4 management of right lower quadrant pain, we will often do an
5 appendectomy as part of a combined general surgery and
6 gynecological laparoscopy because we want to take it off the
7 plate. If that patient--some patients will have
8 appendicitis and you've helped them. Some patients didn't
9 have appendicitis, but you've eliminated one more clue,
10 reason why they right lower quadrant pain.

11 In the case of the analogy that you gave in
12 pregnancy and adhesions, we know it's multifactorial, and
13 regardless of whether the patient can get pregnant or not,
14 if you're able to eliminate one more cause of infertility
15 off the plate, you may--or it may fail--get closer to the
16 real causes of the patient's infertility.

17 So I would submit that the adhesion, in and of
18 itself, the poor little adhesion is getting a bum rap here.
19 The adhesion itself is a clinical entity. And these aren't
20 bowel obstruction products, they're not pregnancy products.
21 They're adhesion products that will allow the surgeon, the
22 gynecologic surgeon, to eliminate one more thing off the
23 plate for why their patient may be having problems with
24 pain, infertility, et cetera.

25 DR. BLANCO: Sandy?

1 DR. CARSON: Well, I guess I was going to probably
2 say something along those lines, but I think some of the
3 problem that we're having here is lumping all these things
4 together. I don't think that if there was some sort of a
5 non--and let's assume that there was some non-invasive
6 technique that could find out that I had pelvic adhesions
7 and abdominal adhesions all over the place, but I'm totally
8 asymptomatic, I don't desire fertility, and so why should I
9 have surgery?

10 Well, no reason right now, but if on the way to
11 the airport, which I hope I get to today, I'm in a car
12 accident, I really would like the surgeon to be able to get
13 my spleen out and stop the hemorrhage before it stops me.
14 So I think that adhesion prevention after surgery is a good
15 idea.

16 Now, having said that, that doesn't mean taking an
17 adhesion score of 10 and reducing it down to 9, and that's a
18 bit of a problem. And I think that you have to either
19 commit to preventing adhesions or not, and not waffle
20 between, "Well, maybe a little adhesion or a light adhesion
21 or a this adhesion." I think you have to really show that
22 it does prevent adhesions, period, yes or no.

23 Now--and I think that's one issue. I think then
24 the second issue is fertility, and it doesn't matter whether
25 there's adhesions there or not. You can design a study and

1 look at fertility before and after an event, and you can
2 look at patients who have no other infertility factors
3 except adhesions, lyse the adhesions, and then look at the
4 infertility factors. That's hard to do, sure, but it's been
5 done. We have just recently published an article in the New
6 England Journal for another reason. It is possible. It's
7 hard but it's possible. And that's a separate study,
8 though, and a separate indication.

9 Bowel obstructions, as we've heard, probably, I
10 don't know enough about that but it probably is not possible
11 even to do in any reasonable time frame. Pelvic pain,
12 again, it's hard, but there are validated instruments in the
13 psychiatric literature and in the anesthesia literature that
14 can show before and after an intervention relief.

15 And so I think that labeling can take care of each
16 of those indications, and I think that they should be
17 separated but definitely shown, and each is possible.

18 DR. BLANCO: Diony?

19 MS. YOUNG: Well, I was just going to say that I
20 agree with Dr. Schwartzberg on the issue of the clinical
21 endpoint, you know, being the adhesion. And I think that
22 you are looking from the standpoint of the woman who is
23 desperately trying to get pregnant. I think it would be a
24 real mistake to get her hopes up with the implied promise
25 that, you know, the endpoint of her having the surgery or

1 whatever, the removal of the adhesion, that that is--the
2 promise, the implied promise is there that she's going to
3 get pregnant, and I think that that would be a mistake
4 because I think that too many women will sort of see it as a
5 sort of magical type of thing.

6 And so I would think, not having been in this
7 position myself, but I would think that it would be--I would
8 prefer to have--to not be given promises that might not
9 happen. I would prefer to know that the adhesion--this is
10 something that could be helpful to my general health or
11 whatever, but not that down the road this is going to enable
12 you to get pregnant.

13 DR. BLANCO: Nancy?

14 DR. SHARTS-HOPKO: I agree. I would look at--not
15 being a surgeon, I look at adhesions as kind of globally
16 like other benign growths. Whether they are a problem or
17 not depends on what they are near and what they impinge upon
18 and what they put pressure on, and maybe they don't do any
19 of those things; or what they're in the way of, if you're
20 trying to save Dr. Carson's spleen.

21 DR. CARSON: Take it out.

22 DR. SHARTS-HOPKO: So I think the elimination of
23 that growth is a good thing in and of itself. As for
24 scoring pain, the folks in the International Pain Society
25 have some very fine instruments that are patient ratings,

1 patient self-ratings, but very well validated.

2 DR. BLANCO: Let me address a couple of issues.
3 Sorry, the audience, we don't even call on you. You don't
4 get a chance. You had your chance.

5 Let me try to clarify one issue, because I think
6 we're all talking about a whole slew of different issues
7 because there are several clinical settings, and I think
8 part of it has to be very strict indications for use.

9 You have spoken of one clinical setting, which is,
10 you have never--and I will take it a little--say you've
11 never had any surgery and you're going in to have some
12 surgery and your surgeon says, "Well, in your type of
13 procedure," and we've had some mention in here, "the rate of
14 adhesion is very high, and if we ever have to go back and
15 reoperate on you or do something else, these adhesions are
16 going to create a problem, so I would like to use this
17 particular product to lower your adhesion rate so if we have
18 to go back to surgery, there is less of a problem when we
19 get in." That's one indication, that's one use, that's one
20 way of using the product, and I think we need to look at
21 that. If that's the intended use for the product, then
22 adhesion formation is really the endpoint.

23 Now, another possible use, and it's sort of
24 implied in what we said, is that we go in, a woman has
25 infertility, comes to the infertility specialist, is

1 evaluated and nothing is found other than she has adhesions
2 at the time of laparoscopy, and now we think the adhesions
3 are causing her infertility. And so we're going to go in
4 and lyse the adhesions, and we want something to prevent the
5 adhesions from growing back. Okay?

6 And here's where it gets a little tricky. We want
7 to keep them from coming back, but are we also going to say
8 that their not coming back will affect her rate of
9 fertility? And, again, it's what is the intention for use
10 and what is the indication. Okay? If you're going to make
11 that claim, if you're going to put that as a way to use your
12 product, then I think the clinical endpoint of pregnancy has
13 to be included. But that may not be necessarily the claim
14 you want. Same thing if you're going to make the claim for
15 intestinal obstruction.

16 So I think part of our confusion and part of, I
17 think, the issue of the discussion, is that it depends on
18 how you're going to use the product and what the intention
19 is as to how far the claim has to be.

20 MR. : I think this gives--we have to give
21 a little credit to the gynecologists and the surgeons who
22 can identify individual patients in whom they feel,
23 regardless of the clinical outcome, that eliminating
24 adhesions in any one particular patient is important. And I
25 think that in Sandra's case I can tell you very clearly.

1 I did a staging laparotomy in a woman with a
2 splenectomy and she developed gallstones about a year later.
3 Now, in this particular patient I had not used an anti-
4 adhesion strategy, and I had just a terrible time getting
5 in. An effective anti-adhesion strategy just to the midline
6 incision would have made all the difference in the world to
7 her.

8 Now, how do you study that? You don't study that,
9 but as a surgeon, I could have said, "You know, preventing
10 adhesions down the line in this patient is a primary goal
11 because she might need surgery later." She was a young
12 woman. It would have been a satisfactory goal.

13 I think you're absolutely right, we need to
14 separate the clinical claims. Pain can't be part of a claim
15 unless you prove what the pain is for. Pregnancy can't be
16 part of a claim unless you prove it with a pregnancy thing.
17 But surgeons across America, gynecologists across America,
18 consider from just a purely clinical standpoint reducing the
19 existence and extent of adhesions as a primary goal, a valid
20 goal.

21 But you've opened up a can of worms. There's
22 adhesion reduction and adhesion prevention. Now, this is a
23 can of worms that I don't think anybody really wants to get
24 into, but it allows you to take whatever data that you have
25 --let's say you have a clinical trial where you have reduced

1 the severity of adhesions pretty convincingly, but the
2 number of patients who had adhesions was the same. Well,
3 now you've reduced adhesions but you haven't prevented
4 adhesions, and that's been substantiated it, you've shown
5 it, and it's safe, if it were.

6 Then it's up to the clinical surgeons. Is
7 reducing adhesions important in any one patient? If yes,
8 you now have a tool that you can apply. The claims are
9 limited to what you are able to show, and the clinicians
10 will embrace this because our surveys indicate that simple
11 reduction of adhesions with nothing else guaranteed is
12 desperately needed and sorely looked after, looked for.

13 DR. BLANCO: All right. We're going into 1-B
14 here. Let me--I want to make some comments on that, kind of
15 getting away from 1(a) and going to 1(b), but that may be
16 okay.

17 MR. : Could I say something about 1(a)
18 first, before we--

19 DR. BLANCO: Well, let me--I've got to respond to
20 Dr. Schwaitzberg. I'm sorry. I'm going to take the
21 prerogative of the Chair.

22 I think the issue is, if you get scoring systems,
23 you get things that are statistically significant, that have
24 no clinical meaning. So I agree with Sandy in that the
25 issue is, did you prevent the adhesions or did you not, or

1 at least you have to be able to show that there is a major
2 enough difference, not just statistically significant
3 between, hey, this group had an average score of five and
4 that group has an average score of seven, and it's
5 statistically significant so I reduced adhesions.

6 I mean, I think as surgeons, a filmy adhesion is
7 different than the very thick, concrete, you know, adhesion,
8 and that makes sense, and I think you could sell that to
9 most anybody. But just, well, you scored five or seven, and
10 gee, let's use this on everybody to prevent, you know,
11 adhesions because it goes from seven to five, that's not
12 enough.

13 All right. Having said that, go ahead.

14 MR. : Okay. What I was--I'm going to
15 agree with all of the things you just said on 1(b), but what
16 I was going to say about 1(a) pertains to an issue that was
17 raised a few weeks ago. And that is that if you do have
18 information in the postoperative time period pertaining to
19 pain and/or fertility, we need to account for how that will
20 be allocated or processed. Not so much that it's a
21 requirement, but it shouldn't be a deficit.

22 For example, intent to treat, it was suggested
23 that one reason why some individuals didn't fit into the
24 category of having the second-look procedure was that they
25 either had no more pain or they were pregnant. Well, let's

1 tabulate that information. Let's not penalize the study for
2 positive beneficial effects, recognizing that it may or may
3 not have had anything to do with whether they reformed
4 adhesions. But at least let's accumulate that and judge it
5 or handle it in an appropriate manner. And I'm not about to
6 tell you what the appropriate manner would be. I just say
7 that we should account for that.

8 MR. : Just in terms of 1(a), finishing
9 it, my sense is that we do have--we do see value in looking
10 at fertility, reduction of chronic pain, small bowel
11 obstructions, in barrier investigations. However, those
12 lead to much more serious or much more elaborate clinical
13 trials, and the inclusion/exclusion criteria may be quite
14 hard to fulfill and so forth, but we do see value in it.

15 And the point I'm--I want to make sure I
16 understand is that the proof of the pudding in fertility
17 would be fertility, but we are still thinking that one
18 should look at the adhesion, even in that context, one
19 should look at what has happened to the adhesions. Now we
20 go to B and we say we think adhesions in and of themselves
21 are great to look at, but within A it's the endpoint of
22 fertility but still the mechanism of adhesions. Is that
23 what we're saying?

24 DR. BLANCO: Well, I think that's the consensus.
25 I think that there is--people are saying--it's again what is

1 intent of treatment, of use of the product, and what is the
2 indication that's going to be claimed, and you look for
3 that. There is value to adhesion prevention and possibly--
4 and value to adhesion reduction. How you measure that, the
5 reduction, is probably going to be much more problematic. I
6 think that that can be looked at for those specific claims.
7 If other claims are desired with clinical outcomes, then
8 you've got to make those claims.

9 Now, I'm fully aware that there will be all sorts
10 of--you know, off indicated use and so forth. We deal with
11 that all the time, but we can't--you know, that's not a way
12 we can control. That's clinicians. But I think that that's
13 what we're saying in 1. Is that the committee's
14 summarization of that? Jerry?

15 DR. SHIRK: Well, I guess what we're really doing
16 is looking at this like we did with endometrial ablation,
17 where reduction of bleeding was our endpoint, where our
18 surrogate reduction of adhesions is our endpoint, but that--
19 and looking at the clinical issues as the life quality
20 issues that we included in the endometrial ablation thing.
21 So I think that, you know, the clinical issues should be
22 included sort of as life quality issues, you know, and be
23 encouraged to be in these studies but not necessarily the
24 primary endpoint.

25 DR. CARSON: I would say that I agree with what

1 you said, except that prevention of adhesion should be one
2 category, each of those clinical outcomes another category,
3 and adhesion reduction I think, however, is something else.
4 Because adhesion reduction per se needs to be tied to--I
5 mean, adhesion reduction in my splenectomy that I told you
6 about isn't necessarily going to get to my spleen easier if
7 I go from a nine to a seven. I might still die there.

8 However, maybe it does have an effect on
9 fertility. Dr. Gomel presented some studies, the last of
10 which I'm not familiar with because it wasn't published, but
11 the others were not intervention trials. They were looking
12 at staging of adhesions and clinical outcome. They didn't
13 use an adhesion barrier, which might end up killing sperm or
14 affecting the eggs, or we don't know, so it's--we think that
15 just initial staging of adhesions, yes, prevents pregnancy
16 outcome as he showed, but that doesn't mean that reduction
17 of those adhesions necessarily leads to that same outcome.

18 So I think reduction of adhesions is different,
19 and if you're going to look at reduction of adhesions, you
20 have to tie it to a clinical outcome.

21 DR. CARSON: That means free? Okay.

22 MR. : Well, I mean, whatever. If you
23 want--

24 DR. BLANCO: Just to remind, I'm sorry, I have to
25 remind the panel that part of our deliberations do not

1 include costs.

2 MR. : No, I understand that, but the
3 clinician would use it. You have labeled it as minimally
4 effective and it was accessible to the clinician.

5 The other point is, if you reduced adhesions with
6 one mode and eliminated adhesions with another mode, you now
7 have opportunities for multimodal therapy you would have
8 been denied.

9 MR. : But is total elimination of
10 adhesions always a good thing. Obviously you pointed out
11 that there are good adhesions. I mean, that if somebody
12 with a bowel anastomosis, you know, has a small leak, I
13 mean, what's the fatality rate or reoperation rate because
14 you have created a complication? So I guess my question to
15 Sandy would be, if the endpoint is total elimination of all
16 adhesions, is that always a good thing?

17 MR. : Well, I think that's part of your
18 preclinical package.

19 DR. BLANCO: Okay. Any other comments on 1(a)?

20 [No response.]

21 DR. BLANCO: I think probably we've discussed that
22 one enough. Let's move on to 1(b). Now, we've discussed
23 the importance of adhesions. Let's talk a little bit more--
24 we've actually discussed this one in part, but does anybody
25 want to add some more to 1(b).

1 I'm still going to disagree with you, Dr.
2 Schwaitzberg. I think even if--you know, if you're going to
3 do a reduction, if that's going to be your indication, then
4 you've got to prove that reduction means something. Because
5 I don't know what reduction means without, you know, without
6 some corollary to it. I mean, if you've got adhesions,
7 you've got adhesions. And yes, I will grant you a concrete
8 versus a filmy is--intuitively, you would think, makes a big
9 difference, but where in that spread is the difference?

10 DR. SCHWAITZBERG: I think in the middle it would
11 get muddy, but if somebody produced data for you that said
12 the score is 15 and the score is 3, but the absolute number
13 of adhesions is the same in those, the data will guide your
14 hand, but in those instances you would say it seems
15 important.

16 DR. BLANCO: Yes, you're probably right, if say
17 you have a score of 1 to 10 and it goes from--you reduce it
18 from 9 to 2. But the point is, you can get a statistically
19 significant study, you know, that will show you a difference
20 from 6 to 5 that may, you know, without some clinical
21 application, may be statistically significant but not
22 clinically of any import, and that's where you get into
23 trouble.

24 DR. SCHWAITZBERG: But if it's safe, and you only
25 go from 6 to 5, nobody will use it anyway and so it's not a

1 problem.

2 DR. BLANCO: Well, but in fairness to the FDA,
3 part of their regulatory mandate is that it not only has to
4 be safe, it has to be clinically effective. Okay?

5 MR. : What's the clinical endpoint, if
6 we don't have any clinical--

7 MR. : The adhesion is the endpoint.

8 MS. : The adhesion.

9 MR. : So you're tying it to some
10 absolute measure of amount of adhesions with these scales?

11 DR. BLANCO: What I'm trying to point out is that
12 there are different scenarios that we're lumping together,
13 and the scenario, one, is one of prevention where there is--
14 you know, you would handle it one way. This is one where
15 you're dealing with reduction. And what I am saying, I
16 guess, is that to some extent in reduction you've got to
17 show some benefit to that reduction.

18 MR. : Beyond the adhesions themselves?

19 DR. BLANCO: Beyond just that it's, yes, from five
20 to four or six to five or whatever.

21 DR. ROY: Could I ask--oh, I'm sorry.

22 DR. BLANCO: Go ahead, Subir.

23 DR. ROY: No, no. No, no.

24 DR. CARSON: I was going to say, I mean, in
25 response to you, the problem with the previously identified

1 clinical endpoints is, not everybody troubled with adhesions
2 is seeking pregnancy. It might take 60 years to know how
3 their bowel is going to do. You can know about everybody's
4 pain reduction, but that's the only one that you can assess
5 in every candidate.

6 MR. : I think, you know, just--I think,
7 you know, Jerry's comment about quality of life is actually
8 a very good setting, that you can tie it, I think, to
9 quality of life scales like pain, other types of quality of
10 life, yes.

11 DR. BLANCO: All right. Let's go 1(b), 1(b), 1, 2,
12 3, 4, 5, 6, 7. What are you--I'm sorry, Subir. You had
13 something else.

14 DR. ROY: I think it is, because we're looking at
15 a period, I mean, look at the individual, I mean,
16 therapeutic intervention and then a follow-up. To me, the
17 location, the degree, the extent, the character of adhesions
18 first encountered and subsequently either reformed or
19 developed in a lesser degree, that sort of paired,
20 stratified accumulation of data, and then subsequent
21 analysis, is what's important.

22 If you have thick adhesions that you divide,
23 vascularized adhesions, and then you follow up and they are
24 filmy, that at least suggests that the method accomplished
25 something. Whereas if at the same time you had dense

1 adhesions someplace else, then it gets much more
2 problematic.

3 I think the reason we've gone to these various
4 schematics of AFS or modified AFS scoring systems is that
5 it's very frustrating to try to make sense of the data, but
6 the fundamental concept of whether intervention is
7 accomplishing a goal is what we really want to know. And if
8 it's complicated, it's complicated. We're not going to
9 simplify it by trying to pretend we can massage the way in
10 which we manipulate the data.

11 So we have to look at it, I believe, in a
12 stratified way and let it play out. If it turns out that
13 the adhesion product is so good that you end up with
14 virtually no adhesions, well, that's great. Then it doesn't
15 matter what scoring system you use. The problem is that it
16 doesn't work that well.

17 DR. BLANCO: I think someone made the remark about
18 signal-to-noise ratio, and I think that's a problem.
19 There's not a very high signal-to-noise ratio. Yes, sir?

20 MR. : Well, I think some of the issue
21 about quantity of adhesion formation or reduction can be
22 basically established in the animal models, I would think.
23 Then you could stop this thing way back in the animal model
24 phase, in the preclinical trial phase. I mean, you should
25 have that data before you allow it to go to a clinical

1 phase, and so that you're going to--I would think the place
2 to handle that issue would be in the preclinical phase,
3 where they have to show a certain percentage of reduction or
4 it doesn't go to clinical trials.

5 DR. BLANCO: Would you care to make a comment, Dr.
6 Schwaitzberg?

7 DR. SCHWAI T ZBERG: I don't know if there's any
8 study where the clinical trial efficacy was better than the
9 animal trial efficacy, and so I think your animal trials
10 probably give you the top limit of efficacy. And I think if
11 somebody knew of a trial where it worked better in humans
12 than it did in animals, they ought to have an opportunity to
13 speak up and enlighten us.

14 So I would agree, to a certain degree, with that.
15 And the--and, again, we have talked about all the problems
16 of animal trials, but they are your first pass at answering
17 some of these questions, and I think that I just wanted to
18 clarify a point that I made earlier about these animal
19 models. I think the use of animal models are good to
20 elaborate on points that you can't prove clinically.

21 I mean, I don't think you should have to do a--if
22 you're going to do a gynecology study and prove a very
23 specific point, that it reduces adhesions to the tubes, that
24 you have to have that exact animal model. I think the
25 purpose of the animal models are to elucidate, once they get

1 through screening, specific things that you can't do
2 clinically. So I wanted to make that clear.

3 And the same thing is true for Phase IV studies.
4 If you proved that you, you know, eliminated pelvic
5 adhesions, well, then, you proved it. But if you want to
6 expand your claims, then those are the opportunities for
7 some of these follow-on and add-on trials. So I think we're
8 looking for a good degree of clinical efficacy in the
9 preclinical models as our method for proceeding forward.

10 DR. BLANCO: Now, let's bring it back. Let's
11 bring it back because we got into animal models, but we're
12 really trying to discuss how are you going to measure that
13 improvement and what are you going to look for, and I think
14 that is what Dr. Roy was bringing up.

15 I mean, how do we do that? Because, you know, one
16 adhesion in the small bowel, is that the same thing as, you
17 know, 20 adhesion sites in the small bowel? I mean, how--
18 what--how do you measure? You know, we talked about
19 adhesions. We think adhesions are important. Now, how do
20 we go--if we know, as you said, as you yourself said, we
21 know no adhesions and adhesions. That one we can tell, but
22 it's the how do we measure adhesions in some reasonable
23 manner.

24 DR. SCHWAITZBERG: Sticking with de novo
25 adhesions, because the model you cited is actually an

1 adhesion reformation model and we have to sort of, you know,
2 keep focused very clear at what we're talking about, pairing
3 the sites of operative injury to the subsequent adhesion,
4 which is the same line of thinking, those pairs of operative
5 injury/adhesion, yes or no, yes, you can kind of mix up the
6 data, come up with some scores and get some funny numbers.
7 But I would agree that providing detailed information for
8 adhesion prevention, pairing the site of operation to the
9 subsequent adhesion, yes or no, is critical.

10 That's what made doing some of these studies hard,
11 because some of these patients had adhesions already, and
12 then excluding the already present adhesions is what makes
13 statistical analysis enough to give you just a gigantic
14 headache, because in some patients that site is available
15 for analysis, in the next patient it's tied up because it
16 already had an adhesion.

17 But, sticking to that, we lysed something here if
18 you're doing reformation, or we operated here and we're
19 looking for, you know, an operative site adhesion. That's
20 got to be the only methodology.

21 Now, when you have the remote adhesions, then you
22 get a little bit more free rein because now you're looking
23 for, you know, if you've got adhesions at the non-operated
24 sites and they have been reduced, then you still have a
25 valid endpoint, remembering that the benefit may be not

1 realized until you do get in the car accident. Maybe you
2 had an open laparotomy or a laparotomy for something, and
3 you didn't realize the benefit until you got in the car
4 accident and needed that, because your remote site adhesions
5 were decreased or prevented.

6 DR. BLANCO: So one item that should be looked at
7 as part of an endpoint is adhesion formation at site of
8 surgery, yes or no. I would think you would include also
9 adhesion formation to wound, to abdominal, anterior
10 abdominal wall, as another one that's pretty easy, yes or
11 no.

12 DR. SCHWAITZBERG: Well, that's the site of
13 surgery.

14 DR. BLANCO: Well, okay. I was thinking vaginal
15 cuff for hysterectomy, small bowel if you do a small bowel
16 resection, so forth. So those would be clear endpoints.
17 Okay? Now are you going to--is the panel agreed with that?
18 Is that reasonable? What about quantitation? I mean, is
19 there any value to quantitating that, and how would you go
20 about doing that?

21 MR. : Have we discussed the entire (b)?

22 DR. BLANCO: Oh, we're just sort of free-for-all
23 doing it. We're not--

24 MR. : Because it says in the beginning,
25 I think (b) (1) is incidence of adhesions. We haven't talked

1 about that at all. Is it different for a myomectomy as
2 opposed to--

3 DR. BLANCO: Well, incidence would be whether it
4 happens or doesn't happen. I mean, you know--

5 MR. : I see. We're going to talk about
6 just, you know, you enter the abdomen by laparoscopy or
7 laparotomy, you do a hysterectomy or a myomectomy, and
8 you're going to lump all that together and say--

9 DR. BLANCO: Well, you're going to lump site of
10 surgery, is what I thought we were discussing. So you go in
11 and you do a myomectomy, you would look whether you had
12 incidence of adhesions to the myomectomy scar, yes or not,
13 and to the abdominal wound, to the abdominal peritoneum.

14 That's what I thought we were talking about. Hysterectomy,
15 vaginal cuff, the pelvic sidewall if you took out the
16 adnexum. Small bowel surgery would be the anastomosis site.

17 So that would be the incidence. Okay. Now, going
18 from there to the next one, which is extent--

19 MR. : Were we told that we were supposed
20 to separate laparotomy from laparoscopy? Is that--

21 DR. BLANCO: Well, we can discuss--that's not one
22 of the questions, but we're going to. It's later. It's
23 later.

24 MR. : I see. Okay.

25 DR. BLANCO: It's later.

1 MR. : That's not a problem.

2 MR. : We don't get off easy.

3 DR. BLANCO: Yes, it's later. Don't worry.

4 Okay, what's your point, Don?

5 DR. CHATMAN: Incidence of adhesions.

6 DR. BLANCO: Right.

7 DR. CHATMAN: It is different for laparoscopy as
8 opposed to laparotomy, and should it be talked about here or
9 not?

10 DR. BLANCO: I think I'd rather talk about it,
11 because that's going to be a big issue, and it's going to
12 derail us from these issues at this point, so let's--

13 DR. CHATMAN: When we talk about, when we say
14 incidence of adhesions, under what circumstances are we
15 discussing--

16 DR. BLANCO: Whatever the surgery is that they're
17 doing. I mean--

18 MS. : Whatever the study.

19 DR. BLANCO: --whatever the study is, yes. And
20 then the issue is, is laparoscopy equivalent, equal to
21 laparotomy in creating them, and that's later on.

22 MR. : So we're talking about our scoring
23 system right now?

24 DR. BLANCO: Yes. We're talking about (1)--I
25 think, I hope we're talking about 1(b), and I thought we

1 were talking about (1) and moving on to, okay--

2 MR. : That's all part of the scoring
3 system, right?

4 DR. BLANCO: Well, whether--no, I'm not saying the
5 scoring system. I'm saying what should be the system. I
6 don't know that I have the answer. I mean, what is the tool
7 that you want to use? I mean, should it be thick and thin?
8 You know, you want to put a number? Vascular, someone said
9 where there's vascularity to it. I mean, that's what we're
10 here to discuss.

11 Yes, Dr. Schultz?

12 DR. SCHULTZ: Maybe just in terms of focusing the
13 discussion a little bit, this might or might not help, but
14 there is a part of the guidance, it's on page 16, it's
15 called assessment tools, and there are a number of criteria
16 that are listed.

17 And a lot of what I have heard discussed thus far
18 is right there, and I think what might help us a little bit
19 is for you to look at those sections and say to us, be able
20 to tell us, do you agree with what we have listed there as
21 being the important criteria? Are there criteria that are
22 not listed there, that should be listed there? Are there
23 criteria listed there that shouldn't be listed there? Or
24 are there ways in which those criteria should be changed?

25 I think that there is a clear recognition that you

1 can do this a number of different ways and, you know,
2 depending on the particular study, that some of those ways
3 might be more appropriate than others. But I think what we
4 would like to see in terms of the discussion, again for the
5 purposes of maximizing the utility of this guidance
6 document, is are we talking about the right things in the
7 right sections of the guidance document?

8 If I could, while I have the floor, I would just
9 like to make one comment about the clinical surrogate issue,
10 because I think that that's clearly a very important issue.
11 It has been stressed in a number of presentations that we
12 have heard so far.

13 One thing I would like to point out, and I think
14 it's interesting, when you listen to any of these
15 presentations about the importance of adhesions--and believe
16 me, as a general surgeon I certainly concur with my surgical
17 colleagues that this is an important problem and one that we
18 need to deal with. But when we look at the pictures, when
19 we talk about the billions of dollars and all the things
20 that people present to show how important a problem this is,
21 what we are talking about is the clinical results of
22 adhesions, and I think we need to be very, very clear about
23 that.

24 When you put up slides--and they are good slides,
25 the numbers are correct--but you put up slides showing \$1.7

1 billion, \$1.4, people with tubes coming out of their noses,
2 people having 17-hour operations, they are not just having
3 those operations, those dollars are not just being spent
4 because there are adhesions present in the belly. They are
5 being spent because people are developing bowel
6 obstructions, because they are infertile, because they are
7 having pain, and because of all the other things that Dr.
8 D'Agostino pointed out and the other things that we're
9 talking about in terms of clinical endpoints.

10 So I would just like to point that out, that, you
11 know, while it's fine to say that adhesions in and of
12 themselves are a problem, and I think we have concurred with
13 the fact that if a sponsor can show either elimination--and
14 obviously elimination is wonderful because it's a black and
15 white and it's easy for all of us, and I think again Dr.
16 Schwaitzberg pointed that out, and that's what made the
17 Seprafilm study so nice because, you know, it was 90 percent
18 versus 10 percent or whatever it was. It was real easy for
19 all of us.

20 But when you start getting into those gray zones,
21 that's when it becomes difficult, and that's what--you know,
22 that's what we tried to focus on in the guidance, was
23 saying, look, if you can show us the clinical endpoints,
24 great. If you can't show us the clinical endpoints, the
25 next best thing is probably to show us absence of adhesions.

1 The next best thing from there is to show us some reduction.
2 But if you're going to show reduction, you have to pay
3 attention to all of these details and, again, in some cases
4 at least you need to be able to tie it to something in order
5 for a panel of experts or the FDA to be able to make some
6 kind of rational decision regarding efficacy.

7 DR. BLANCO: Well, but I think all you're saying
8 is it depends on the intended use or the indication for us.
9 And, you know, I would make the analogy that we use--you
10 know, I'm not sure which one would be better, would fit
11 better, but in obstetrics we know that women with group B
12 strep that are pregnant have a risk of passing that on to
13 their baby and having their baby die. We're giving
14 antibiotics to practically every woman in labor to try to
15 eradicate that, to make that small prevention, and a lot of
16 the proof is that we eradicate group B strep.

17 You could look at prophylactic antibiotics and
18 surgical procedures with a high risk rate of infection. I
19 mean, it doesn't directly--it's not a direct analogy but
20 it's essentially sort of the same issue. You know, you
21 don't know who's going to develop an intestinal obstruction.
22 You don't know when Sandy's going to need her spleen
23 removed. God, I hope nothing happens really, Sandy.

24 DR. CARSON: I'm getting scared now.

25 [Laughter.]

1 DR. BLANCO: You know, you don't know that, so if
2 your indication is prevention, then you need to do
3 adhesions. It's not the clinical issue.

4 So I think your point is well taken, but there are
5 other issues besides just having to show pregnancy and
6 pelvic pain and intestinal obstruction. I also--you know,
7 it would be fine for us to look at the assessment tools,
8 but--he's being talked to, so--I mean, we were supposed to
9 go through the questions, which is what you wanted us to do,
10 so I need a little guidance as to which one you want me to
11 do. You want me to go through the questions or you want me
12 to go through the document?

13 DR. HARVEY: Well, the questions are there to
14 guide you through the deliberations today, but insofar as
15 the questions fairly directly relate to the content of the
16 guidance, if you want to look at the guidance while you're
17 going through the question, it may be helpful.

18 DR. BLANCO: All right. Well, I'll just take
19 chairman's prerogative on that one.

20 Yes, sir? Go ahead.

21 MR. : Dr. Blanco, I think in order to
22 answer Dan's point, what's missing from the \$1.7 billion is
23 all of the prolonged hospital stay, enterotomies. That \$1.7
24 is the number of admissions for adhesions. The prevention
25 of adhesions itself doesn't show up in those dollars because

1 it doesn't include the guy that got an enterotomy on the
2 second laparotomy, it doesn't include the five extra days in
3 the hospital because de novo adhesions formed, so there are
4 some missing dollars. To get to your point directly--

5 DR. BLANCO: Let's get back onto the questions and
6 answers. Let's get back, either a comment on the assessment
7 tools, or let's get back to question 1(b).

8 MR. : I think the guidance document is
9 very correct the way it is. If we try to lock all
10 investigators into the AFS score or the modified AFS score,
11 then we're doing a disservice to very intelligent people.

12 I think the key point of this is that whatever
13 method they pick, they ought to be able to defend why they
14 picked it, why it's valid for their product--gel, film,
15 solution--why remote sites are not important if you're
16 putting a gel in an isolated place. They've got a number of
17 things to choose from. What's incumbent on the sponsor is,
18 is defend his choice before the study starts, with the
19 agreement of the FDA, of why he made the choices, why he or
20 she picked this scale out of 1 to 7, and then what the
21 labeling indications are at the end of it all, if you prove
22 it, if you don't prove all of your points but some of your
23 points.

24 And I think that if you can show--you know, you
25 may say, "Well, we're going to show reduction of incidence,

1 severity and extent," but you only caught two out of the
2 three. Well, that will have different labeling indications.
3 But all of those things, the key point is, in the guidance
4 document it says, "Figure it out in advance. Defend it.
5 Understand what the implication is of failing to show a
6 reduction of incidence."

7 If you just did an extent study and you didn't pay
8 attention to all the pregnancy things or pain things that
9 are clinically available to you, then you've hamstrung
10 yourself. And I think the guidance document gives the
11 investigators and the sponsors leeway to choose, based on
12 their material, what they see fit, and be prepared to live
13 and die with the consequences of making good and bad
14 choices.

15 DR. BLANCO: All right. Go ahead, Don.

16 DR. CHATMAN: I don't want to beat a dead horse,
17 but we cannot discuss this without 1(b). There's no way for
18 us to talk about reduction or prevention without knowing
19 what the incidence is. There's no way to design a study
20 without knowing what the incidence is, and there's no way to
21 find out. You know, we need to have that baseline
22 information before we do anything else, I would think.

23 DR. BLANCO: All right. Any other comments from
24 the panel?

25 MS. : Well, I just have a question. I'd

1 like someone to define for me what a severe adhesion is.
2 What are the--what is actually--what's the difference
3 between the severity--I mean, does that include the extent
4 or is it the size or what it's attached to, or what is a
5 severe?

6 DR. BLANCO: Well, I think partly, as Nancy said,
7 that's one of the things we're looking at, what should it
8 be. I think the issue, as Dr. Schwaartzberg pointed out, you
9 need to go into the study, it needs to be very standardized
10 and it needs to be very tight, that you can show, if you're
11 going to do a multi-site study, that you're calling things
12 the same thing from one site to another and one place to
13 another, and you need to have some sort of education.

14 Now, what an absolute definition is, again, I'm
15 not sure that I would want every investigator tied into one
16 single definition. I think that there is--you know, you
17 have to define it in your situation, what you're going to
18 particularly look at it for, what your intended use is, and
19 then make sure that within your study from beginning to end
20 it's standardized and reproducible.

21 Yes, sir?

22 MR. : Yes. Dr. Blanco, could I request
23 Dr. Diamond to talk a little bit about the various scoring
24 systems and the incidence of adhesions, to help clarify for
25 us the differences between them?

1 DR. BLANCO: Is that agreeable to the committee?

2 SEVERAL VOICES: Yes.

3 DR. BLANCO: Please, Dr. Diamond.

4 By the way, Dr. Diamond is a member of this
5 committee. He recused himself. So he is well known to all
6 of us. Is that good or bad, Mike?

7 DR. DIAMOND: You can probably answer that in
8 about two minutes.

9 My name is Michael Diamond. I am professor of
10 obstetrics and gynecology at Wayne State University. I am a
11 consultant to many of the companies in the audience, and I
12 have also received research funding from several of these
13 companies for work related to adhesion-related products.

14 With regard to what Don Chatman has been saying, I
15 think incidence--if you're going to talk about how to grade
16 adhesions, I think incidence is the key thing, because it's
17 either there or it's not there, and that by far is the
18 preferable endpoint to utilize. But unfortunately that's
19 not always possible and, as others have been saying, as Dr.
20 Schwaitzberg was reporting out, a filmy adhesion is much
21 easier to separate at the time of subsequent surgical
22 procedure than is something that is called a cohesive
23 adhesion, where you have one side right up against the other
24 without any intervening adhesive band. With the latter
25 type, a cohesive adhesion, you are more likely to injure

1 those structures, you are more likely to have a greater
2 amount of time, and so the potential patient morbidity is
3 significantly greater.

4 Severity of adhesions has been looked at various
5 ways by different people. One way that some people have
6 looked at it is by whether the adhesions have vascularity or
7 do not, with less vascularity being less severe. Others
8 have graded it by whether it's filmy or dense and/or
9 vascular, or a third category might be just cohesives. And
10 again, those relate to potentially the relative ease of
11 separation at a time of subsequent surgical procedure.

12 The third characteristic on the top list here is
13 extent, and that could be expressed in a number of different
14 ways. It could be the percent of an organ that's involved
15 with adhesions, whether that be an ovary or a fallopian
16 tube, and that could be expressed either as picking a 5
17 percent or 37 percent or 93 percent, to on quartiles or by
18 thirds. Or another way yet is to look at raw surface areas
19 at the completion of the procedure, because a uterus, for
20 example, can be ten week size or it could be an alipara
21 size. And the amount of raw surface area, the amount of
22 surface area available and at increased risk for adhesion
23 development may vary greatly depending on that, and so 30
24 percent of the surface which is raw and potentially more
25 likely to form adhesions may be very different in those

1 different scenarios.

2 There are a number of systems that have tried to
3 combine a number of these different characteristics, and
4 that's where the AFS system and the modified AFS systems
5 have come in, often combining a lot of these different
6 characteristics into one different place, and often trying
7 to look across different sites, as well. If you have a
8 material barrier that you're going to place on one site,
9 most of those are not designed to work at distant sites.

10 But what would be desirable, clearly, would be
11 something that you could apply that would cover multiple
12 sites all at one time, not only the surgical site, whether
13 that be the site of a myomectomy or cystectomy or
14 adhesiolysis, but other sites that might become adherent to
15 it, we also ideally would want to have treated. And with a
16 gel or with a liquid, that potential exists, and so there is
17 a value to be gained from looking at these other sites
18 throughout the abdominal cavity, as well.

19 But as was brought out by several people, then
20 trying to combine information from all those sites together
21 adds a great deal of complexity. It further can have
22 complexity if some of those types are absent from prior
23 surgeries or if adhesiolysis is not complete.

24 And therefore the comment that was being made just
25 now, I think it was by Dr. Schwaitzberg, that these things

1 being presented as entities then probably should be left to
2 the sponsor, in my mind, based on what specifically is their
3 product, how they hope to deliver it into the abdominal
4 cavity, other particular characteristics of their product.
5 Does it adhere, does it not adhere? Does it require
6 suturing, doesn't it require suturing? Is it something they
7 expect is going to be able to cover large surface areas, or
8 is it just going to be able to be applied to a small area?

9 Based on specific product properties, there may be
10 a variety of different characteristics that the sponsor
11 might want to look at, and which would be relevant for one
12 but not for others. And so I think to come up with one
13 specific, precise scoring system is not something that's
14 going to be adequately applicable to all the different
15 situations that might come before you in the next several
16 years.

17 DR. BLANCO: Thank you, Dr. Diamond.

18 Any more comments on 1(a), (b) or (c)? I mean, I
19 think we've pretty much discussed all the various aspects of
20 that question. Are we ready to move on? Let's move on.

21 Number 2: Please discuss the merits and
22 limitations of using surrogate endpoints in the premarket
23 phase of device evaluation and clinical endpoints in the
24 postmarket phase. And we have kind of touched on this
25 already, but let's go ahead and devote a little bit more

1 time to it. Who wants to start? Everybody got quiet? Go
2 ahead, Jerry.

3 DR. SHIRK: Well, again, I think it comes back to
4 what I said before, that basically you use the surrogate as
5 your primary endpoint, and that's obviously what you judge
6 your clinical or preclinical phase on it, but I think
7 certainly postmarket phase, you know, somewhere in these
8 studies we should have some of the life quality issues type
9 of thing, and that's what I see most of the clinical issues
10 as, life quality kind of issues. Does the patient get
11 pregnant? Does the patient have relief from pain? Does the
12 patient, you know, have other things that, you know, that
13 are basically affecting their life quality? So I think life
14 quality issues are certainly extremely important in the
15 postmarket phase.

16 DR. BLANCO: Yes?

17 MR. : There's a couple of possibilities
18 here. If a sponsor came in saying that they do affect
19 fertility and go through all of the ritual that we had
20 described before, and do that in the premarket phase and get
21 approval, then they leave that activity with the claim
22 presumably for the adhesions, because they have shown that,
23 plus their claim for the fertility.

24 If you do the other, the latter, of getting the
25 surrogate done in the premarket and then the clinical

1 endpoint is investigated in the postmarket, one could be for
2 ultimately changing a claim or adding a claim, which I think
3 is a reasonable thing to do. And I think that the concern
4 that I would have is the rigor in which that data is
5 collected, but if it were done in a rigorous fashion that
6 lived up to our standards of not clinical trials but sort of
7 outcomes research, this type of research, I think that would
8 also be a reasonable way to do it, especially given some of
9 the context of the discussion I heard today, where it takes
10 a while for some of these things to be measured. So I think
11 both of them work.

12 DR. BLANCO: Any comment? I think the only thing
13 that--oh, sorry.

14 MR. : I had a question.

15 DR. BLANCO: Sure.

16 MR. : I think there has been some talk
17 about using ultrasound to measure the presence or absence of
18 adhesions to the abdominal wall, and if we did a study where
19 we used ultrasound to see if there was an adhesion, that's
20 truly a surrogate evaluation of the adhesion. I think that
21 the question that I would essentially beg the chairman to
22 poll the panel, is an adhesion itself a clinical endpoint?
23 Can we move it out of this sort of dungeon that it's in,
24 that the adhesion is a surrogate of goodness, not goodness
25 of itself?

1 Because you may need your spleen out some day, and
2 if you had just the adhesion prevented--you have no pain,
3 you have 10 kids, you never had a bowel obstruction--but
4 preventing that adhesion made it so that when Pat Reardon
5 had to take your spleen out, he got in there safely, is
6 there an opportunity to poll the members to say, "Does the
7 adhesion, in and of itself, deserve elevation to be a
8 clinical entity?" Remember, this is the adhesion
9 prevention.

10 DR. BLANCO: Yes, let me address the issue. I
11 think, I don't know, maybe I'm trying to look at it too
12 simplistically in terms of semantics. That's how the FDA
13 has put the words. I think the panel feeling, without
14 having to poll them, just from what the discussion has been,
15 number 1 is that adhesions in and of themselves are a
16 significant problem and a significant issue.

17 Now, whether you want to call them a surrogate or
18 whatever, I don't know. I think the fact is they are real
19 and it's a real indication and it's a real endpoint to look
20 at. I don't know quite what more than that it is that you
21 want.

22 MR. : But the guidance that the panel
23 provides is that, in other panels at other times they have
24 gotten sort of on this trail, "Well, it's just a surrogate.
25 I want something clinical." My point is that if the panel

1 gives the guidance to the FDA that the adhesion isn't a
2 surrogate, that the adhesion is a clinical thing, we're
3 going to have a new terminology moving forward.

4 DR. BLANCO: Go ahead.

5 DR. HARVEY: I think again the problem that we
6 might be having is, I don't think anybody would disagree
7 with it being there or not being there as an endpoint.
8 That's easy. But what about if it's just there a little
9 bit, just like a little string? Is that clinically
10 meaningful?

11 So when we have these adhesions scored, again, I
12 think we have a problem. I don't think we have a problem
13 with going from a 10 to a zero. I think we have maybe,
14 well, okay, what about a 9 to a 1? Well, what about an 8 to
15 a 2? Well, what about a 7 to a 6? Et cetera. And that's
16 the problem that we get into, and when we go to these
17 intervening numbers, that's when we need to tie it to a
18 clinical outcome.

19 DR. HARVEY: But, you see, you may have answered
20 your own question, though, that the presence or absence of
21 adhesions is now a clinical endpoint, and maybe reduction
22 now is what is left as a potential surrogate endpoint.

23 MS. : No, I think what we're saying is
24 that we don't really--when we say adhesions as an outcome,
25 we mean presence or absence. That's easy. What we don't

1 know is adhesion reduction. We don't know what that means
2 clinically, and so that's a separate--then we're talking
3 about, one, adhesion prevention, zero, plus or minus, versus
4 clinical outcomes; adhesion reduction, not--

5 MR. : See, I agree with you completely,
6 but in the past adhesion prevention has been considered a
7 surrogate endpoint, and maybe we can move forward and say
8 that maybe just adhesion reduction is the surrogate endpoint
9 and adhesion prevention is a valid clinical endpoint.

10 DR. BLANCO: Well, let me--we're going to go ahead
11 and move on. I don't see a strong feeling from the panel to
12 tackle whether we call adhesions surrogates or not, so I
13 don't think you're going to win on that one. I know this
14 panel.

15 [Laughter.]

16 DR. BLANCO: So let's go back to number 2. I
17 mean, it's in the record, as Dr. Harvey points out, what our
18 feelings are in terms of that it's a real clinical entity
19 and should be an endpoint. It's an issue of the company has
20 to come forth and prove its point about how it's going to
21 measure that clinical entity. Okay? Would everybody agree
22 with what I just said?

23 All right, so number 2, the only comment that I
24 would add--I mean, I think we have already gone over this--
25 is that I think we shouldn't be so rigid as to only gather

1 the clinical outcome data in a postmarket analysis. I mean,
2 it would be a shame to do a real rigorous premarket analysis
3 study that has an endpoint of just adhesion reduction and
4 not know about all these other factors, because what we
5 often find when we get presented data on the panel and we're
6 trying to make these very important decisions, is that all
7 of a sudden something like that pops up but nobody--they
8 didn't really look at it in any kind of rigorous way.

9 So I guess my take on number 2 is that I think the
10 endpoints can be adhesion and how eventually the company
11 wants to measure adhesion or no adhesion, and they ought to
12 look at the clinical endpoints, and it's to their benefit.
13 It's not--this is not a place where that's an extra added
14 burden, because if they gather enough pre- and postmarket,
15 they may be able to have a much more radical, a much more
16 important indication and intention for use. So I think that
17 it ought to be done--

18 MR. : I didn't at all mean to exclude
19 that. Matter of fact, I think that would be part of what
20 you're doing. I mean, if you're dealing with a population,
21 even in the premarketing phase, that is women who have
22 pregnancy problems and so forth, and fertility problems,
23 that you may accumulate enough data for the endpoint of
24 adhesions and indications of something with the fertility,
25 and you need the postmarketing to clarify that and bring it

1 to a head.

2 DR. BLANCO: Right. Dr. Schultz wanted to say
3 something?

4 DR. SCHULTZ: You know I'm not going to let you
5 off the hook here. I'm going to try to pin you guys down a
6 little bit more, because I think that there were a couple of
7 comments made in the presentations that were given, if I
8 recall some of Dr. Schwaitzberg's comments regarding the
9 need for postmarket studies to be a part of, an integral
10 part of the developmental plan for these products. And I
11 sort of, I guess I hear what I want to hear, and I enjoyed
12 hearing that comment.

13 The thing that concerns me, and this sort of gets
14 back to this other issue of surrogate clinical in some
15 sense, and in some sense that's a semantic issue but in some
16 sense it can become a real issue if you say that once you
17 have shown some type of reduction or elimination of
18 adhesions, you're done. And that's really what I'm
19 concerned about when you talk about making this a clinical
20 endpoint in and of itself, that at that point you say,
21 "We're done. We've done everything we have to do, and
22 there's nothing else that needs to be known about this
23 product." I am concerned about that.

24 I think the point was very well taken that if you
25 provide the adhesion information and a clinical reference

1 point in the premarket, sure, we don't need a postmarket
2 study. I mean, it's all there. The question that comes up
3 is, especially in those cases where the adhesion reduction
4 information is equivocal, then should it be tied to a
5 clinical endpoint, not as just--and it can be simply a
6 matter of extending the labeling, which is--which would be
7 at the company's discretion. And again, that's in here, the
8 reasons, the different reasons for doing postmarket, but are
9 there also situations where a postmarket study should be
10 tied as a condition to the approval?

11 And I would like to see the panel address each one
12 of those scenarios. If the data is all there, adhesion
13 reduction, elimination and a clinical endpoint, you're done.
14 Data that's equivocal may not totally have a clear
15 understanding of what the clinical import of a particular
16 reduction is, then postmarket to help define that. And the
17 other scenario where the sponsor has done something but
18 wants additional labeling.

19 DR. BLANCO: Well, I'm going to get off the hook
20 this way. I'll tell you what I'm going to do. I think that
21 you can't do that ahead of time. I think that you have to
22 wait and see. I mean, you know, let's just recall a few of
23 the PMAs that we've looked at just recently. Most of them
24 have been accepted with conditions, many of them which have
25 been postmarket studies.

1 And I think what we need to tell or what I would
2 tell the industry, or what I think is being conveyed to
3 them, and I think the panel would agree with this, is that
4 you're in an area where you've got a very low signal-to-
5 noise ratio and, you know, you're going to get a clinical
6 endpoint that you can look at, but there are lots of other
7 important clinical endpoints that you need to look at and
8 that you need to study, and that is going to be part of your
9 development of these particular products if you want to do
10 that.

11 And so--but I think it depends on what data gets
12 brought forth. I mean, I think it doesn't take a rocket
13 scientist to figure out what you said, which is if they
14 bring in all the data, that they don't need to do anything.
15 You know, they've done it. If they don't bring, you know,
16 all the data, and they want indications, then they need to
17 do more things. So I--

18 MR. : Can I--

19 DR. BLANCO: Yes, go ahead.

20 MR. : We had a long discussion with 1(b)
21 where I thought most of us or a number of us were saying
22 that sort of the complete elimination of the adhesion was--
23 if you have just adhesion standing alone, its complete
24 elimination. So wouldn't that follow, in responding to 2,
25 that if there was no clinical information available or if