

1 over here and actually I have one question afterwards.

2 Go ahead.

3 DR. DUBEY: Yes, this goes for Dr. Cooper or
4 Dr. Wright. Can you answer the question about if the
5 device is extending into uterine cavity, and from the
6 slide, I see about three to eight expanded coils will be
7 hanging in the uterine cavity on either side, what will be
8 the tissue development there, and how much uterine cavity
9 will be compromised? This is mainly for the patient who
10 may need IVF for the implantation process. Do you have any
11 idea about that?

12 DR. COOPER: We have no experience with
13 patients in the clinical trials who have chosen IVF.
14 Undoubtedly this will happen as the years go by. My own
15 personal opinion is that the device will not offer a
16 problem for IVF, and my reason for thinking this is that
17 approximately three or four millimeters of this device
18 extend into the uterine cavity and can really only be seen
19 with rather significant distention of the uterine cavity.

20 As we know, under normal circumstances, the
21 walls of the uterus are all but touching each other, and I
22 think it's unlikely that this small nidus that may in fact
23 be covered over with fibrosis anyway is likely to interfere
24 with a pregnancy. That's just one man's opinion, but we
25 have no clinical evidence to support or refute that view.

1 DR. SEIFER: In the material, there was a
2 recommendation for -- there's 18 coils that are visualized
3 in the uterine cavity, and you're supposed to leave the
4 device in place, is that correct?

5 DR. COOPER: Do you want to speak to this?

6 MS. DOMECUS: Go ahead.

7 DR. COOPER: We believe that the ideal-
8 positioned device has three to eight coils extending from
9 the uterine cavity.

10 DR. SEIFER: Right.

11 DR. COOPER: We believe that a device that has
12 as many as 15 or 18 coils will probably be effective in
13 achieving long-term contraception. There's a difference
14 between an effective device and what we would view as ideal
15 placement.

16 DR. SEIFER: Right.

17 DR. COOPER: What you have to appreciate is
18 that the black positioning bump has allowed us in our
19 clinical trial to develop a far greater assuredness that
20 our device is placed at the ideal position, but the device
21 is four centimeters in length for just that reason, to be
22 certain that even if it were extending slightly more into
23 the uterine cavity that it would achieve long-term
24 contraception.

25 DR. SEIFER: Do you have any idea of what the

1 frequency is of having the device hang out that amount? In
2 other words, of the 20 investigators, what sort of
3 incidence occurred that you would have improper placement
4 of the device but you would leave it in place?

5 MS. DOMECUS: We can look up the rates of those
6 long trailing lengths in the trial, but I wanted to clarify
7 the reason that labeling suggests that you should try to
8 remove a device with a trailing length of 18 or more coils
9 is because we found in the clinical trials that such
10 devices are likely to expel and that the labeling instructs
11 that the removal should occur immediately during the
12 placement and not allow the tissue ingrowth process to
13 occur.

14 DR. SEIFER: But do you think the labeling
15 might reflect something regarding potential adverse effects
16 if it stays in place and it's not properly in place?

17 MS. DOMECUS: I'm sorry. The question is?

18 DR. SEIFER: In other words, if 18 coils are
19 hanging out or less but it's not properly placed, would the
20 response with regard to Dr. Dubey's question -- I think Dr.
21 Brown's question -- would it change?

22 MS. DOMECUS: If 18 or more coils are trailing
23 into the uterine cavity, by definition, it's not well
24 placed, and we'd recommend that such devices be removed so
25 that the patient doesn't undergo a subsequent expulsion of

1 it.

2 DR. SEIFER: I don't mean to quibble here, but
3 if it's not 18, it's 16, whatever?

4 MS. DOMECUS: Right. Then it should be left in
5 place.

6 DR. SEIFER: And would your concern about
7 difficulty implantation or scarring of the uterus or any of
8 the sorts of concerns that have been brought up, would that
9 change your attitude about that?

10 MS. DOMECUS: I think --

11 DR. BLANCO: I'm going to go ahead and cut that
12 short. If you want to think about what you want to answer
13 that, we'll give you some time later on, but we're running
14 out of time.

15 I'd like to ask one question. In the issue of
16 hysterosalpingogram versus the pelvic x-ray, have you
17 looked at this device with ultrasound as a method to
18 confirm placement at the end since you can see the uterus a
19 little bit better with ultrasound than you can with just a
20 plain x-ray of the pelvis?

21 DR. CARIGNAN: In our Phase II study, a number
22 of the investigators did use ultrasound to visualize the
23 device location at three months. We did not control it to
24 evaluate it against the location as seen on x-ray.
25 However, with our own internal retrospective review of the

1 x-rays and the hysterosalpingograms, including the scout
2 film of those hysterosalpingograms, in the Phase II study,
3 it would show a strong correlation with what was seen on
4 ultrasound versus the x-ray, but as I said, we've not
5 controlled for that. All of the investigators, though,
6 anecdotally reported they can see it well and commercially,
7 there are people who are obviously very interested in
8 looking at using ultrasound to identify device location.

9 DR. BLANCO: Thank you.

10 We are now running 15 minutes late, for which I
11 apologize to the panel. We'll go ahead and take our break.
12 It's now 11:15. We'll start promptly at 11:30 with the
13 rest of the presentation.

14 Thank you.

15 (Recess.)

16 DR. BLANCO: All right. Let's go ahead and get
17 started with the presentation by the FDA, and we'd like to
18 go ahead and begin with Lisa Lawrence, the lead reviewer
19 for this particular PMA.

20 MS. LAWRENCE: Thank you.

21 Good morning, ladies and gentlemen,
22 distinguished panel members, and guests. I am Lisa
23 Lawrence, lead reviewer for FDA on this PMA, and I'm here
24 to give you a brief overview of the review process that we
25 have gone through on the Conceptus Essure Micro-Insert.

1 My presentation will cover a brief overview of
2 the following: device description, I will highlight the
3 PMA review areas and the review team, overview of the IDE
4 and PMA review history, and preclinical reviews. After me,
5 Julia Corrado, our clinical reviewer, will discuss the
6 clinical studies, and Gene Pennello, our biostatistician,
7 will discuss the biostatistical aspects of these studies.

8 The intended use of the Essure Micro-Insert
9 System is for permanent birth control by occlusion of the
10 fallopian tubes. On the top is the picture of the Micro-
11 Insert System. On the left is a close-up look at the
12 distal portion of the delivery catheter which has the
13 Micro-Insert. On the right is the Micro-Insert as it
14 appears when it is expanded.

15 Next, I would like to acknowledge the review
16 team. The next two slides list our review team. As you
17 can see, a number of people have been involved in the
18 review of the PMA application. Dr. Harvey, Dr. Julia
19 Corrado, Dr. Pennello, and Dr. Marinac-Dabic are looking at
20 the key clinical and proof-of-concept studies. Dr.
21 Virmani, Dr. Kammula, and Dr. Zaremba are looking at the
22 material safety. Continuing with this slide, Ms. Price,
23 Dr. Whang, and Mr. Kuchinski are looking at the preclinical
24 concerns. Inspections are being done by Ms. Crowl and Mr.
25 Murrain-Ellerbe, and Ms. Mendelson is reviewing the

1 professional and patient labeling.

2 Next, now I'd like to briefly review some of
3 the history leading up to the Conceptus PMA submission.
4 There are four clinical studies that appear that support
5 this PMA. In 1996, we approved two clinical feasibility
6 studies, the perihysterectomy study where patients were
7 scheduled for hysterectomy immediately following the device
8 placement and a prehysterectomy study where patients were
9 scheduled for a hysterectomy six to 12 weeks following
10 placement. In 1998, we approved a multicentered clinical
11 study to test the device in a woman who went off
12 alternative contraception, the so-called Phase II study.
13 This is still ongoing and we have a limited amount of two-
14 year data available, and finally, in 2000, we approved the
15 pivotal study. We will spend a lot of time today talking
16 about this study which is still also ongoing.

17 In June of 2000, we had a meeting with
18 Conceptus. Pardon me. I'd like to talk a little about the
19 determination/agreement meeting we had with Conceptus in
20 June of last year. Obviously the pivotal study was already
21 underway but Conceptus was seeking additional commitment on
22 the part of FDA for the clinical development plan. During
23 this meeting, FDA and Conceptus agreed that FDA will file
24 the PMA if the pivotal study had a minimum of 400 patients
25 with one-year follow-up and these subjects met formal

1 inclusion/exclusion criteria, adhered to predetermined
2 follow-up schedule, had met specific age requirements.

3 It was also agreed that the Phase II study
4 would have 100 subjects with two years of data and that
5 Bayesian statistics would be used to analyze the one-year
6 and two-year failure rates. Finally, the mechanism of
7 action of the device would be supported by data from the
8 pre hysterectomy study.

9 When Conceptus submitted its PMA, the company
10 requested an expedited review. In particular, Conceptus
11 noted that in contrast to other devices for tubal
12 sterilization, typically the laparoscopic length of the
13 Essure device could be placed without an abdominal incision
14 and without general anesthesia. We granted the request for
15 the expedited review, citing one of the four criteria to be
16 used; namely, that this device offer significant advantages
17 over existing approved alternatives. Expedited review
18 means that the application takes a higher priority than the
19 due process. It does not mean the length of review
20 standards.

21 We are only 90 days into the PMA review process
22 and many of the reviews are still ongoing. We do not think
23 that this should keep this important PMA from coming before
24 the panel, but I would like to briefly advise you of the
25 status of some of the reviews. On the left, I have listed

1 reviews we've already completed. The animal studies went
2 on to support initial proof of concept and provide some
3 basis for moving into the clinical phase. Obviously we're
4 well past that phase. Our review gave us some confidence
5 of proof of concept and potential for effectiveness. Our
6 review of the MRI compatibility showed that women with
7 implanted Essure devices can undergo MRI procedures without
8 fear of adverse effects.

9 On the right are the ongoing reviews. The
10 engineering review covered the mechanical properties of the
11 device. No issues have surfaced so far. For chemistry and
12 shelf life, we looked at corrosion of the metals and
13 continuing functionality following aging. We are also
14 looking at mutagenicity and device sterilization of the
15 material that could contact the patient body. For material
16 safety, we found that the appropriate testing was conducted
17 for this implant device. The sponsor has chosen a material
18 that has a long history as an implant material.

19 Our PMA review also includes inspections. We
20 inspect some of the sites in the clinical trials as well as
21 the data collection analysts sent us. This bioresearch
22 monitoring review looks at study execution, recordkeeping
23 and informed consent. We also expect the manufacturing
24 facilities to ensure compliance with design controls.
25 These inspections are still ongoing.

1 I have reviewed a brief device description.
2 The review areas highlighted the PMA review process, giving
3 you an overview of the IDE and PMA review history and this
4 concludes my presentation.

5 Thank you, and next, Julia Corrado will be
6 speaking on the clinical issues.

7 DR. BLANCO: Thank you.

8 DR. CORRADO: Thank you, Lisa.

9 Good morning, everybody. My name's Julia
10 Corrado, and I'm the medical officer in the Obstetrics and
11 Gynecology Devices Branch who reviewed this PMA.

12 The outline for my talk will be as follows:
13 I'm going to give an introduction to the device and a
14 little bit of background in the area of transcervical
15 sterilization. I will then focus on the safety and
16 effectiveness of the Essure System, based on the clinical
17 studies, and I will throughout my talk draw your attention
18 to the discussion questions that we have provided for the
19 panel.

20 To remind everyone, the indication for use of
21 the Essure System is permanent birth control. That is,
22 female sterilization by occlusion of the fallopian tubes.
23 The principle of operation is that polyethylene fibers that
24 are wound throughout the inner coil of a double-coil system
25 elicit a tissue response that results in ingrowth of

1 fiberglass smooth muscle and inflammatory cells. This
2 process eventually causes complete occlusion of that
3 portion of the fallopian tube where the Micro-Insert
4 resides.

5 As Dr. Cooper alluded earlier in his
6 presentation, the Essure System is not the first
7 transcervical sterilization device that has seen clinical
8 use in the United States. There were two investigational
9 stage devices that saw clinical use in the 1980s and
10 possibly into the 1990s. I want to make the point that
11 these devices are completely unrelated to the Essure device
12 and also that they never saw commercial use in this
13 country, only investigational use. One was a tubal plug
14 and one was a chemical sclerosing agent.

15 I'm not going to say any more about this,
16 except to make the point that there were sterilization
17 failures following use of these devices. Some of those
18 failures were related to misreading or misinterpretation of
19 pelvic x-ray and/or hysterosalpingogram and that this point
20 will come up later in my presentation when I'm discussing
21 the Essure device.

22 As you've heard, there was a perihysterectomy
23 study done at the time of hysterectomy. There has been a
24 prehysterectomy study where the placement as well as
25 tolerance to the device and histology was evaluated. The

1 Phase II and the pivotal studies provided contraceptive
2 efficacy data as well as long-term safety data and they are
3 still ongoing. I also want to say that I am not going to
4 discuss the perihysterectomy study at all. I'm going to
5 begin with the prehysterectomy study, the objectives of
6 which were to evaluate device placement, tolerance to the
7 procedure, relative long-term wear -- that is, wear out to
8 approximately 14 to 20 weeks -- and the stability of the
9 device in the fallopian tube once it's placed and
10 occlusion, and the objectives of the study identified that
11 occlusion might be evaluated as early as 24 hours up to
12 approximately 12 weeks.

13 I highlighted tissue response here because
14 that's really all I'm going to say about it, and in that
15 light, I will just briefly reiterate what we've already
16 heard from Dr. Wright. The results of this study were as
17 follows: 53 women actually wore devices. The wear time is
18 as indicated on this slide, from predominantly between four
19 and 14 weeks.

20 One of our panel discussion questions had to do
21 with the tissue response. You have had an opportunity to
22 discuss that at length already, and I don't see any need to
23 spend a long time on this slide, except to just reiterate
24 that PMNs were common in shorter wear times and in dense
25 fibrosis set in after approximately four weeks of

1 placement. Also, I'd like to emphasize a couple of points
2 that were said earlier, and that is that there was no
3 evidence of any serosal reaction following placement and
4 normal fallopian tube architecture was observed
5 approximately five millimeters distal to the tip of the
6 Micro-Insert.

7 Now, I'd like to turn my attention to the Phase
8 II study, the objectives of which are noted here and
9 virtually identical to the pivotal study. The company
10 wanted to evaluate long-term safety, stability, and
11 contraceptive effectiveness. This study and the pivotal
12 study were prospective multicentered non-randomized studies
13 with planned five-year follow-up with subjects.

14 The demographics of the Phase II study is
15 listed here. I'd like to just point out that the
16 demographics of this study are different from the
17 demographics of the pivotal study. Gene Pennello, our
18 biostatistician who will speak after me, will discuss the
19 differences in the demographics of these two studies.
20 Suffice it to say that a large proportion of the Phase II
21 patients were 34 to 45 years old. In the pivotal study,
22 the age distribution was much younger.

23 In the Phase II study, 18 women were treated
24 with the beta version of the device that was eventually
25 discontinued. 227 women were treated with the gamma

1 version of the device in a total of 233 procedures. The
2 results for the gamma device are as follows. We've been
3 very interested in bilateral placement rates at first
4 attempt. That is, on the first trip to the operating room,
5 what percent of the patients came out of the operating room
6 with devices successfully placed in both tubes. In the
7 Phase II study at first attempt, that percentage was 86
8 percent. Of those women, at three-month post-device
9 placement, hysterosalpingogram, 97 percent had bilateral
10 occlusion and so the point I'd like to make with this slide
11 is that successful bilateral placement does not necessarily
12 equal successful bilateral occlusion, although the
13 bilateral occlusion rates weren't very high.

14 Briefly, I wanted to mention an aspect of the
15 Phase II study experience with that earlier, now
16 discontinued, beta device. The bilateral placement rates
17 for one thing were lower than for the gamma device and the
18 company may be in a better position than I am to talk about
19 this contributing to their development of the gamma device,
20 but I would like to say that there was one pregnancy with
21 the beta device in a woman who was relying on that device
22 for contraception. Regarding that pregnancy, the following
23 things can be said. The optimal nature of device placement
24 was questionable from what I've been able to glean from
25 that case. That is, there were somewhat conflicting

1 results on x-ray and, I believe, pelvic ultrasound,
2 although the company may want to address this.
3 Nevertheless, there was not a clearcut satisfactory device
4 placement in that case.

5 However, the woman, the patient, in that case
6 did rely on the device for contraception and at
7 approximately 23 months post-reliance, she was diagnosed
8 with an intrauterine pregnancy. She carried that pregnancy
9 to term. It was uncomplicated, except that at full term,
10 she developed preeclampsia and she underwent delivery by
11 repeat Caesarean section at approximately 38 weeks.

12 Around nine months after she delivered, she
13 began to experience groin and thigh pain and this got to
14 the point where she believed that it might be due to the
15 device and she requested removal. Therefore, she had
16 surgical removal of this device, following which all of her
17 symptoms had resolved. As the sponsor mentioned this
18 patient in their presentation, one of the devices was in
19 the pouch of Douglas. The other device was in the desired
20 position in the utero-tubal junction on the left, in the
21 left fallopian tube.

22 Regarding effectiveness for the Phase II study,
23 as of the database freeze in late May of this year, 194
24 subjects had relied on the device for 12 months, and there
25 are no pregnancies in that group. Neither are there any

1 pregnancies in the women in the Phase II study have now
2 gone out to 24 months.

3 Regarding the gamma device in the Phase II
4 study, I'd just like to summarize some adverse events.
5 There was six perforations in a total of 233 procedures.
6 Two women had vaso-vagal reactions, either in the OR or in
7 the recovery room. Ninety-three percent had the procedure
8 performed under local anesthesia or IV sedation. Only 4
9 percent had general anesthesia. One-hundred fifty-three
10 out of 233 in responding to a question regarding
11 intraoperative pain reported that they did experience
12 intraoperative pain. However, 63 percent of that 153
13 stated that the pain was less than or equal to what they
14 expected during the procedure and 26 percent responded that
15 it was greater than what they expected during the
16 procedure.

17 Within one week of the procedure, 81 percent of
18 these subjects reported some bleeding which might have
19 constituted spotting, 1.7 percent reported fever. However,
20 in all cases, the fever had responded within 12 hours, had
21 resolved within 12 hours. There was one expulsion
22 diagnosed at three months post-procedure. Acceptability
23 was good to excellent as reported at one week. That was
24 for a rate of 90 percent, and at 3 to 24 months post-
25 procedure, 88 to 94 percent of the subjects reported

1 excellent tolerance.

2 I'd like to now turn to the discussion of the
3 pivotal study and as you can see, the objectives and the
4 design were virtually the same as the Phase II study.
5 Question 2 had to do with demographics of the pivotal study
6 population. As I pointed out earlier, the demographics of
7 the Phase II study were somewhat different from the pivotal
8 trial. In the Phase II study, the women were older,
9 basically 70 percent of them were older than 34, and in
10 this study, the distribution was approximately 60 percent
11 were younger than 33, and I also would like to say in
12 fairness to the sponsor that their study design did not
13 break out the demographics into three groups. FDA wanted
14 to look at it as we understood that the demographics in the
15 CREST Study had been considered.

16 Question 5 had to do with bilateral placements.
17 446 out of 507 patients in the pivotal study who underwent
18 an attempt using the device had successful bilateral
19 placement on that first trip to the operating room. Of the
20 women who did not have successful bilateral placement in
21 the first attempt, some of them after HSGs demonstrating
22 tubal patency, went back for a second attempt and that
23 brought the total number, the total percentage of women who
24 ultimately had bilateral placement up to 92 percent.

25 Of women who got bilateral placement, the 464

1 that is who got bilateral placement, 452 are relying on the
2 device for contraception. Twelve women were lost from the
3 relying group because at three months, there were
4 perforations diagnosed. There were unsatisfactory device
5 locations and expulsions.

6 Question 1 had to do with the effectiveness,
7 and I'd like to say here that as of our database freeze in
8 late May, there were data in on 408 of the 452 in the
9 population of women relying on the device. As of that
10 date, we were expecting data for 27 women and there were
11 patients who were lost to follow-up. These numbers have
12 changed somewhat, based on data received on patients who
13 have had their follow-up since May 24th. There continue to
14 be no pregnancies, and I should also mention that we expect
15 all of the 12-month data from the pivotal study to be
16 received prior to the end of the 180-day review period for
17 the PMA.

18 Regarding pivotal study, I'd like to just
19 highlight that within 24 hours of the procedure, the
20 following adverse events were observed: one perforation
21 was diagnosed within 24 hours, there were two cases of
22 hypervolemia, and three women experienced vago-vasal
23 responses. At three months post-procedure, there were some
24 additional perforations that were diagnosed on
25 hysterosalpingogram. Also, there were some device

1 expulsions diagnosed on HSG.

2 The next group of adverse events described at
3 three months were intramenstrual bleeding, irregular
4 menses, heavier menses, and lighter menses, and what I'd
5 like to say about this table is although these data are in
6 the PMA, they might in some cases represent one episode or
7 a single incident of one of these events. So they don't
8 imply a recurrent or persistent adverse event. In that
9 light, I'd just like to look at the following table. I'd
10 like to spend a minute or so going through this table. On
11 the top row, we've identified the number of patients who
12 filled out questionnaires at baseline, at three months, at
13 12 months, and then that last column represents a category
14 that consists of women who reported this particular adverse
15 event at all four of the follow-up visits that occurred
16 after device placement. So persistent means she complained
17 of this problem at all of the visits. So if we look at
18 irregular bleeding and look at the baseline percentages and
19 then at three and 12 months and persistent, you get a
20 perspective on how often these happen from the persistent
21 column. Similarly, with intramenstrual bleeding, that
22 three-month number is 24 percent. That seems very high
23 compared to baseline, but as it turns out, perhaps only one
24 of these cases was actually a patient who persistently
25 reported this problem, and with that, I'd just like to in

1 all fairness note that there were women who noted lighter
2 bleeding, who reported lighter bleeding after the device
3 placement procedure than before.

4 Pelvic pain. I'd like to just go through a
5 similar analysis. You can see the baseline rate of this
6 complaint, and we've broken down pelvic pain into
7 dysmenorrhea, dyspareunia, ovulatory pain, or other, and
8 other means none of the above three. If you look at this
9 table, it would suggest that, gee, dysmenorrhea which
10 occurred in 35 percent of the women was occurring at
11 baseline really improved after the device placement and
12 that is not necessarily the case, but nevertheless these
13 are women who reported significant complaints following
14 device placement. Nevertheless, the numbers who are
15 considered under the persisting category are either zero or
16 very, very small.

17 The last row that is entitled "Other" I'd like
18 to draw your attention to because this is going to be a
19 question that we ask ourselves when we're looking at the
20 labeling for the device, and that is whether or not there
21 is some pelvic pain that women experience after placement
22 of the device that is not dysmenorrhea, it's not
23 dyspareunia, it's not ovulatory pain, and the question
24 being is there any kind of discomfort, residual discomfort
25 following placement of the device? Again, the three-month

1 and 12-month data would make us wonder, yet when we ask who
2 experienced this complaint persistently at all four visits,
3 it's very low.

4 As the sponsor mentioned, there were four
5 pregnancies during the pivotal study. However, these
6 pregnancies were not among women who were relying on the
7 device for contraception. As a matter of fact, early first
8 trimester sonogram confirmed that conception occurred prior
9 to Micro-Insert placement, although these pregnancies had
10 not been picked up on the pregnancy test that was required
11 within 24 hours of the procedure. Three of these women
12 chose not to continue the pregnancy and one had spontaneous
13 AB and all four of these women are in the population of
14 women relying on the device, and they did not have any
15 further Essure procedure following the initial placement.

16 Earlier this morning, the panel discussed the
17 issue of device removal. I think that that is very
18 important. In the event that a woman would like to have
19 the device removed, the procedure, as a generalization,
20 cannot be performed hysteroscopically. There have been no
21 requests for device removal among women and in the pivotal
22 study, it was left as an option to remove the device at
23 pelviscopy in women who were undergoing a pelviscopic
24 approach to sterilization.

25 I should mention that in the Phase II study,

1 one woman underwent surgery to have the device removed
2 because of a complaint of pain. In the pivotal study,
3 there were four attempts to remove devices that had
4 perforated. All of these attempts took place during
5 pelviscopy, the purpose of which was to undergo an
6 alternative form of sterilization. Two devices were
7 successfully retrieved at pelviscopy and two were not. The
8 women who continued to have those devices in their
9 peritoneal cavities are apparently without complaint.

10 Patient comfort has been very good, as you see
11 from this table. PDP in that middle column stands for
12 post-device placement. So those statistics were gleaned
13 from questionnaires filled out at three months after the
14 device was placed. In the next column, PAC stands for
15 post-alternative contraception, and although post-
16 alternative contraception was 15 months post-device
17 placement for many patients, nevertheless because some
18 women required repeat HSGs, that one-year post-alternative
19 contraception is not necessarily 15 months following device
20 placement, and if you calculate the percentages that fall
21 into the very good and excellent category, we're in the
22 mid-90th percentile for both groups at three months post-
23 device placement and at a year post-alternative
24 contraception and the percentages of women reporting poor
25 comfort are extremely low, as you see.

1 Patient satisfaction. I'm not going to go
2 through that same analysis. The story is basically the
3 same. Very high rates of somewhat to very satisfied and
4 very low rates of very dissatisfied.

5 Question 7 has to do with the training program.
6 Basically, the training program the sponsor's proposing for
7 commercial use involves didactic materials, experience and
8 practice with the hysteroscopic simulator, and preceptoring
9 of initial cases. I'd like to point out that when we
10 consider the question of are we going to get the same types
11 of bilateral placement rates, for example, in commercial
12 use as we had in the pivotal trial, that a lot of the
13 investigators in the pivotal trial had prior experience
14 with the device. So our question was is it going to be
15 enough to get didactics, to get simulator training, and
16 preceptoring? It might be a small point, but nevertheless
17 those perihysterectomy cases did provide some of the
18 investigators with actual OR experience placing the device
19 prior to going into the Phase II and the pivotal studies.

20 The three-month work-up is another issue, and
21 here, I'd just like to recall for you all that when I was
22 talking about those earlier transcervical sterilization
23 investigational trials, that there were pregnancies among
24 women who were told on the basis of pelvic x-ray or on HSG
25 that they could rely on the device for contraception who

1 subsequently became pregnant, and also in the Phase II and
2 the pivotal study for this device, the women did get HSG at
3 three-month post-placement. So we think that it's
4 important to get the panel's input on whether or not a
5 pelvic x-ray is going to be satisfactory in lieu of HSG.

6 Now, I'd like to also point out that this would
7 only be the case if pelvic x-ray indicated that device
8 location was satisfactory. If there was questionable or
9 suspicious or unsatisfactory device location on pelvic x-
10 ray, that patient would not be told that she could rely on
11 the device and she would go on to further evaluation.

12 One of our issues also has to do with
13 postmarket surveillance, and we were very fortunate this
14 morning to have a presentation by Dr. Costello about the
15 findings of the CREST Study, and I'd just like to highlight
16 a couple of the lessons that were learned and that was the
17 cumulative rate of sterilization failure continues to
18 increase beyond two years, that there were ectopic
19 pregnancies as we all know in women who have sterilization
20 failure, that the device and patient age seemed to have a
21 bearing on sterilization failures, and very importantly,
22 that the duration of follow-up is one of the things that
23 makes that CREST Study such a landmark study, that, you
24 know, they followed up approximately 10,000 women well past
25 two years, many of whom were followed out to 10 years, and

1 in that light, we want to more or less capitalize on
2 lessons learned in that study and ask the question: how
3 far out should you follow a patient population following a
4 sterilization procedure to learn about things like
5 sterilization failure and the rate of ectopic, and how many
6 women do you need to follow out, and also what are the
7 lessons learned from CREST in terms of minimizing loss to
8 follow-up?

9 In summary, I have hoped to present for you a
10 summary of FDA's review of the effectiveness and the safety
11 of the Essure Micro-Insert System and also provide for the
12 panel a feel for patient acceptability, and I've tried to
13 tie some aspects of our review into specific discussion
14 topics that we've identified for the panel.

15 At this time, I would welcome any questions the
16 panel might have, and if there are none, I would like to
17 turn the podium over to Gene Pennello, our biostatistician.

18 Are there any questions?

19 DR. BLANCO: Dr. O'Sullivan?

20 DR. O'SULLIVAN: You said there were several
21 cases of what is listed in the data that we have of luteal
22 phase pregnancies that occurred prior to insertion of the
23 device.

24 DR. CORRADO: Right. That's correct.

25 DR. O'SULLIVAN: The device was supposedly

1 inserted between the seventh and the 14th day.

2 DR. CORRADO: These were luteal phase
3 insertions. Actually, they might have even been late
4 luteal phase insertions.

5 DR. BLANCO: Thank you.

6 DR. CORRADO: At this time, Dr. Pennello will
7 present the biostatistical review.

8 DR. PENNELLO: Thank you, Julia.

9 Good morning, panel members. My name is Gene
10 Pennello, and I work at the Division of Biostatistics at
11 CDRH, and I provided a statistical review for this
12 Conceptus Essure System, and I'd like to summarize that
13 review for you today.

14 Just to give you an outline, I'd like to talk a
15 little bit about this study design in the pivotal and Phase
16 II studies, give you some facts about the patient
17 population, review the patient tree that is available in
18 your handout or in your panel packet, and then I'll give
19 you an accounting of the patients and then go to talking
20 about the effectiveness analysis and mention some adverse
21 event results that I think are notable and summarize.

22 First, the study design. I'm only going to
23 consider in this presentation the pivotal and Phase II
24 studies. In the pivotal study, there were 20 investigators
25 at 13 sites and to date, there's data available out to one-

1 year follow-up post alternative contraception. In the
2 Phase II study, there were five investigators at five
3 sites, and there's data available at two years, and I want
4 to mention up front now that in the effectiveness analysis
5 was a Bayesian analysis which I'm going to explain a little
6 bit about later. Bayesian analysis is useful for combining
7 prior information with clinical data and the Bayesian
8 analysis was used to combine the Phase II data with the
9 pivotal study data using the Phase II data as prior
10 information into the pivotal study.

11 The two studies were conducted worldwide and
12 here's a breakdown of investigators and sites. I'd like to
13 mention that in the Phase II study investigators, all five
14 of them participated in the pivotal study, so they had the
15 benefit of the experience in the Phase II study going into
16 the pivotal study. There was also one investigator not in
17 the Phase II study that participated in the
18 perihysterectomy studies and so that investigator had the
19 benefit of that experience, and I bring that up as
20 information related to Question 7 on training.

21 Now, here's some variables that give you an
22 idea of the patient population and also some protocol
23 requirements. First, the protocol requirements require
24 that the women had to have had at least one live birth and
25 once they're enrolled in this study and got the Micro-

1 Inserts, that they needed to have four to eight coital acts
2 per cycle during the study. The median age was 32 with a
3 range of 21 to 40 years of age in the pivotal study, and
4 the median gravidity was three and the median parity was
5 two with the ranges given here.

6 I'd like to make a comparison with the CREST
7 Study of the pivotal and Phase II studies in terms of the
8 age distribution. As has already been mentioned in the
9 protocol, it was required that the pivotal study be age-
10 matched to the CREST Study in terms of women aged over 33
11 years of age and that was met. As you can see, the
12 percentage was 36 percent in the pivotal study and it was
13 32 percent when you consider all methods studied in the
14 CREST Study. So it was more or less matched to the CREST
15 Study for that age group.

16 Nevertheless, I wanted to break it out a little
17 further into three different groups that were looked at in
18 the CREST Study, and if you do that, you can see that for
19 women younger than 28 years of age, the percentage in the
20 pivotal study is only 17 percent which is about half of
21 that in the CREST Study for all methods used. So there are
22 fewer younger women, and also that the Phase II study was
23 not matched at all to the CREST Study in terms of these
24 distributions of age in that there were 70 percent that
25 were over age 33.

1 Now to give you a brief patient tree, and this
2 is for the pivotal study, there were 650 enrolled initially
3 and then due to voluntary withdrawals and subsequent
4 findings of inclusion/exclusion criteria violations, the
5 intent-to-treat population was only 518 and at the
6 operating table, there were 11 in which it was decided not
7 to attempt placement and so the evaluable group is only
8 507. The loss to follow-up was 17, three during the three-
9 month post-device placement time period and 14 following
10 that up to one-year post alternative contraception.

11 The bilateral placement was achieved in 464
12 women, 446 on the first attempt. There was a total of 24
13 additional second attempts at achieving bilateral placement
14 and 18 were successful. Among the women that got bilateral
15 placement, the 464, 456 underwent the hysterosalpingogram
16 at three months post-device placement, so nearly all of
17 them got an HSG. To give you some of the HSG results,
18 there was satisfactory device location and tubal occlusion
19 that was confirmed among 421 of the women out of the 456
20 that had the HSG, 19 had unsatisfactory device location and
21 most of those were expulsions.

22 I should mention here that among the 13
23 expulsions, nine agreed to undergo a second attempt at
24 placement and all nine achieved satisfactory device
25 location after their second attempt. There was

1 satisfactory device location among 16 women who were
2 observed to have patency in the tubes and so for these
3 women, they had to undergo second or third HSGs to see if
4 there was really tubal occlusion further on and for all 16,
5 there was at the second or third HSG.

6 There were 449 total women that were able to
7 rely on the Micro-Inserts for bilateral contraception,
8 excluding the three that were lost to follow-up, during the
9 three months post-device placement, and 420 of those were
10 able to rely after the first attempt at placement and the
11 first HSG. There were nine others that were able to rely
12 after the second attempt at placement. There were 16
13 others that needed additional HSGs to confirm occlusion and
14 three are relying on the device without HSG confirmation of
15 occlusion and satisfactory device location.

16 The bilateral placement rate at first attempt
17 is then 88 percent, if you consider the device evaluation
18 group as a denominator, and the bilateral placement rate
19 when you consider all attempts is 92 percent. The
20 bilateral reliance rate when you're using the number of
21 women that went to HSG, it's 92 percent initially and 98
22 percent ultimately when you consider second attempts and
23 additional HSGs. I'd like to mention that the denominators
24 here are still being evaluated as far as what is the proper
25 denominator to use to report these rates in the labeling.

1 I'd like to go to the effectiveness analysis
2 which was a Bayesian analysis, based on the 449 women that
3 were relying on the device for bilateral contraception.
4 Bayesian statistics, to give you an idea, is a
5 scientifically valid way of combining previous information
6 with current data and it's been used at CDRH for other
7 kinds of devices. There's been other devices that have
8 been approved in which the primary analysis was Bayesian.
9 So this is not the first time, and the way it works is you
10 think about the possible values for the parameter of
11 interest and here, we're thinking about the one-year
12 cumulative probability of pregnancy as a primary endpoint
13 or cumulative rate of pregnancy and we're thinking about
14 the possible values for that and you assign prior
15 probabilities to those possible values. So you would
16 assign a probability for a 1 percent or a 2 percent rate,
17 and these are assigned according to some prior information,
18 such as the Phase II data, and then you update these prior
19 probabilities to posterior probabilities after observing
20 clinical data, like you would in the pivotal study, and you
21 make your emphasis based on the posterior distribution.

22 Here are the results from the Bayesian analyses
23 by the sponsor. As was mentioned, there's 408 patients at
24 one year of follow-up in the pivotal study, although the
25 analysis considered all women-months and considered other

1 women that had women-months accumulated but at less than
2 one year of follow-up. There were no pregnancies and so
3 the estimate is zero, and the 95 percent interval, which is
4 called an HPD interval, is between 0 and .69 percent. If
5 you consider the Phase II data only, again there were no
6 pregnancies and the results are as follows: 0 percent is
7 the estimate and there's the interval estimate there.

8 If you combine the Phase II and pivotal
9 studies, where you think of the pivotal study as prior
10 information going in the pivotal, Phase II data as prior
11 information going into the pivotal study, you get these
12 results, and the interval estimate is the upper bound is
13 lower. It's only .48 percent here compared to .69 when you
14 consider the pivotal study data only. You can also look at
15 the second year of follow-up and look at the cumulative
16 probability of obtaining pregnancy in the second year using
17 the Phase II data where you had two-year follow-up and you
18 get these results here.

19 If you'll bear with me, I'd like to show you
20 the posterior distribution just to give you an idea of this
21 Bayesian analysis. The posterior distribution gives you
22 the range of all the probabilities that are assigned to
23 each of the possible values for the one-year rate and so
24 the X axis gives you possible values for the one-year rate
25 and the Y axis is the posterior probabilities assigned to

1 those rates, and you can see that at zero, you've got the
2 most likely value that has the highest posterior
3 probability and so that's why that's the estimate, although
4 you could also consider the averaging over all the possible
5 values according to their posterior probabilities to come
6 up with a mean rate as an estimate and when you do that,
7 that's this line here and that's actually above zero.
8 That's .23 percent. This is based on only the pivotal data
9 and now if you combine that with the Phase II data, you can
10 see that the posterior distribution is being pulled more
11 towards zero and so that's why your upper bound on your
12 interval estimate is lower.

13 Here are some notes on this. The analysis is
14 based on women-months, not just the 408 that made it out to
15 one year follow-up, and the results are comparable to those
16 like what you would normally see in the life table method
17 approach, a product of Kaplan-Meier survival analysis
18 approach. The problem with the life table methods is that
19 with zero pregnancies, there's no standard error on the
20 estimate and so there's no way to compute a confidence
21 interval. The Bayesian estimate will give you an interval,
22 a confidence interval-like estimate without having to have
23 any pregnancies.

24 There was an assumption that the monthly rate
25 of pregnancy was assumed constant over each of the 12

1 months of follow-up in that one-year rate and that the
2 monthly rate was used to compute the yearly rate of
3 pregnancy. The Bayesian estimate of zero is the most
4 likely value according to the posterior distribution, I
5 already mentioned that, and this interval estimate that I
6 gave you in the table is called the highest posterior
7 density interval and it's generally regarded as the most
8 valid Bayesian interval and it's analogous to a 95 percent
9 confidence interval in a non-Bayesian analysis.

10 There was additional effectiveness analysis in
11 which some of the women-months were censored due to not
12 enough coital acts per cycle and/or also due to reduced
13 fertility of the partner due to alternative contraception
14 or surgical techniques, but when you remove these women-
15 months, it really didn't make any difference to the
16 results.

17 What I think might be more important in terms
18 of labeling is that the analysis that I've just presented
19 that were given by the sponsor didn't have any kind of age
20 adjustment. You need an age adjustment in that the Phase
21 II study data were not age-matched to the CREST Study in
22 terms of this greater than 33 years of age category, and so
23 if you were going to combine the Phase II data with the
24 pivotal study data, you really ought to have some kind of
25 age adjustment so that you could account for these much

1 older women in the Phase II study.

2 Even though the protocol only considered age
3 matching to the over 33 years of age category, I'm going to
4 look at all three of these groups and age adjust with my
5 own analysis and I'm considering two age adjustments where
6 I consider the age distribution in the pivotal study and
7 age adjusted at distribution or I consider the age
8 distribution in the CREST Study and adjust to that
9 distribution, and I used the method of direct
10 standardization which is a common method in epidemiology to
11 make these age adjustments, and I use that to compare
12 multiple populations that might have different age
13 distributions.

14 So the first line in this table is no age
15 adjustment which I've already given you and the upper bound
16 on the interval estimate is .48 percent, but when you
17 adjust to the age distribution in the pivotal study, you
18 get a slightly larger upper bound of .51 percent and if you
19 age adjust to the CREST Study, you get an even larger but
20 still very small upper bound of .67 percent which I think
21 is reassuring.

22 We asked the company, since there was 27 women
23 that hadn't been followed out to one year yet, we asked the
24 company what is the chance of these women getting pregnant
25 in the remaining women-months, and you can use in Bayesian

1 statistics, you can use what's called a predictive
2 analysis, predictive probabilities to make this calculation
3 for you, and if you use all the women-months that have been
4 observed so far, the probability of no pregnancies among
5 these 27 women is about 99 percent, the probability of one
6 is about 1 percent, and there's virtually no probability of
7 two or more pregnancies.

8 We also asked them to only consider the women-
9 months experience in terms of months 11 and 12 of follow-up
10 because among the 27 women, the women-months that were
11 missing were mostly months 11 and 12. So if you only
12 consider those, the probability is 95 percent of no
13 pregnancy and about 4 percent for one pregnancy, and this
14 is not considering the Phase II data. So if you add that
15 into this analysis, the probability of no pregnancies will
16 most likely be even higher.

17 You could also do a hypothetical analysis.
18 Suppose there was one pregnancy among the 27 women, then
19 what happens to the results? Here, the current analysis is
20 given in the first line and I've given you the mean one-
21 year cumulative pregnancy rate and instead of the 0
22 percent, the median rate is .23 percent as I showed you
23 earlier and it about doubles to .44 percent if you consider
24 one pregnancy in the remaining women-months for the 27
25 women not followed out to one year, but both the estimate

1 and the interval estimates are still pretty low.

2 There was a learning curve analysis that was
3 done by the sponsor as they mentioned. Here are some
4 results. They considered the number of procedures that
5 each of the investigators had done and to see whether that
6 had an effect on hysteroscope time and placement rate. The
7 hysteroscope time decreased with increasing procedure
8 number from about 18.4 minutes in procedures 1 through 5 to
9 10.3 minutes after you've had more than 20 procedures.
10 However, there didn't seem to be any effect on placement
11 rate in terms of how many procedures you had done.

12 I also would mention that among the 14
13 expulsions, four occurred in the first few procedures by
14 investigators, and I'm just mentioning that as part of
15 disclosure. I don't know how to interpret that. It may
16 not be statistically significant but it did occur.

17 Here are some adverse event results that I
18 think are notable for your consideration. The rate of
19 adverse events initially preventing reliance was
20 significantly higher at one site than at other sites and
21 that rate was 17 percent, and in the P value, non-Bayesian
22 analysis, is less than .05. So that's why it's
23 statistically significant. The expulsion rate varied
24 significantly by site. The reasons for this are still
25 being investigated. There were some women that experienced

1 sharp pain or sudden or severe cramping that was thought to
2 be related to the device and it was borderline association
3 between unsuccessful bilateral placement and pain on
4 average since the procedure with a P value of about .08.
5 The rate of return to regular menses was 5.9 percent.
6 That's about three and a half times that at baseline, and
7 by recurrence, I mean that a woman who's reported irregular
8 menses at at least two of the for follow-up times, and the
9 rate of recurrent intramenstrual bleeding was 8.7 percent.
10 That was about 3.8 times that at baseline.

11 To summarize, the bilateral reliance rate was
12 92 percent initially and what I mean by that if you
13 consider only the women that got bilateral placement and
14 that went to get a hysterosalpingogram that you saw, that
15 they had satisfactory device location and occlusion. Now,
16 the rate would be lower if you included all the women in
17 the device evaluation group or in the intent-to-treat
18 group. The cumulative one-year pregnancy rate was 0
19 percent. The 95 percent interval varies by whether you
20 add in the Phase II data or make an age adjustment, but the
21 upper limit on the interval estimate is still pretty low in
22 any of the analyses that I presented here, and as was
23 mentioned previously, the patient satisfaction was high.
24 Some issues that relate to training is that sites varied in
25 adverse events preventing reliance and there was a learning

1 curve effect in hysteroscope time.

2 So that concludes my presentation. Thank you
3 very much.

4 DR. BLANCO: Thank you.

5 Any questions of fact from the panel?

6 DR. SEIFER: Yes.

7 DR. BLANCO: Go ahead.

8 DR. SEIFER: Could you elaborate a little bit
9 on this sites varied and adverse effects preventing
10 reliance?

11 DR. PENNELLO: Well, I'm not a clinician. I
12 look at variation by site because, of course, that could
13 relate to a training issue. The significant variation was
14 due to adverse events that initially prevented reliance,
15 not ultimately preventing reliance. So in some cases, I
16 believe some of the women were able to get by --

17 DR. SEIFER: So by reliance, you mean bilateral
18 placement?

19 DR. PENNELLO: Yes.

20 DR. SEIFER: Is that what you mean?

21 DR. PENNELLO: I mean bilateral placement.

22 DR. SEIFER: Is the one site, is that in the
23 U.S. or outside the U.S.?

24 DR. PENNELLO: It was outside the U.S. It was
25 in Europe.

1 DR. BLANCO: Any other questions?

2 (No response.)

3 DR. BLANCO: All right. If we don't have any
4 questions, let's go ahead and take a recess for lunch.
5 It's now 12:35. Let's begin promptly at 1:20.

6 (Whereupon, at 12:35 p.m., the meeting was
7 recessed for lunch, to reconvene at 1:20 p.m.)

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AFTERNOON SESSION

(1:31 p.m.)

1
2 DR. BLANCO: All right. If we could settle
3 down, please, so we could go ahead and get started.

4 I think that if we look at our agenda, we're
5 going to begin the panel discussion, but before we do that,
6 we had some questions for the company, and I believe
7 they're ready with some of the answers to some of the
8 questions that we had. So let's begin with that and we'll
9 read the definitions and all that as soon as they finish
10 with the questions.

11 Ms. Domecus?

12 MS. DOMECUS: Dr. Carignan can address all the
13 questions raised earlier by the panel.

14 DR. BLANCO: Well, bring him on.

15 (Laughter.)

16 DR. CARIGNAN: Is it okay if I sit here?

17 DR. BLANCO: Oh, please. Thank you.

18 DR. CARIGNAN: Thank you. It's a little bit
19 easier to spread out this way.

20 The first question that I'll respond to was the
21 one that Dr. Brown raised regarding the distribution in the
22 study of women according to race and ethnic background and
23 also with prior abdominal surgery. We have this
24 information for the pivotal trial. For the Phase II study,
25 we did not collect race information specifically. In the

1 pivotal trial for the entire study cohort, we had 5.4
2 percent black women, 6.4 percent Latin and then .4 Asian,
3 .4 American Indian, .8 percent of mixed race, .4 percent
4 other, and the remaining women were Caucasian. That was
5 for study sites in the U.S., Australia, and Europe.

6 If you look at the racial distribution just
7 within the U.S. study cohort, which is a little bit more
8 particular for these classifications, black women accounted
9 for 8.8 percent, with a range of 2 to 25 percent of
10 patients, depending on U.S. study site, Latin women were 10
11 percent, with a range of 2 to 32 percent of participants,
12 depending on study site, and Caucasian women were 79
13 percent, with a range of 43 percent to 92 percent,
14 depending on study site. So there was quite a bit of
15 variation by study site.

16 If you look at prior abdominal surgery, in the
17 pivotal trial, 19 percent of women had had prior abdominal
18 or pelvic surgery, and if you look at obesity as greater
19 than or equal to of body mass index of 30, 26 percent of
20 women would have been considered obese. First question.

21 The next question related to the animal studies
22 and the issue that was being discussed about the toxic
23 reaction of the device potentially if it were in the
24 peritoneal cavity. Just to review all of the
25 biocompatibility studies that we did of the implant, we did

1 cytotoxicity, sensitization, genotoxicity, an implantation
2 study, subchronic toxicity study that I'll speak about, a
3 mutagenicity study that was an in vivo mutagenicity study,
4 an irritation study and an acute systemic toxicity. So we
5 had quite a range looking at the components of the implant.

6 Specifically, the subchronic toxicity study was
7 conducted as a 26-week study in 20 rabbits. The rabbits
8 had two Essure devices placed in one side of the
9 perivertebral muscle and they had two control rods placed
10 in the other perivertebral muscle. When the implant sites
11 were excised, we had them embedded in the methylocrylate
12 similar to the process that we do for the intertubal
13 devices, so that we can again see the relationship of
14 surrounding tissues to the actual device, and they were
15 then evaluated to look at local toxicity. We also looked
16 at end organs for systemic toxicity, and there was no
17 evidence of either systemic toxicity or local irritancy
18 noted with the Essure devices when placed into the
19 perivertebral muscles as well and again within the fibers,
20 we did see what was the expected reaction to PET fibers.

21 The other issue that was raised related to long
22 trailing lengths, and in the pivotal trial, we had nine
23 women in whom one of the devices was rated to be greater
24 than or equal to 18 millimeters by the investigator
25 assessment. Of those, three resulted in expulsions and six

1 have been reliant, and as we pointed out in the data
2 before, we have no persistent pain with the exception of
3 one woman and that woman did not have one of these long
4 trailing lengths, and there's no difference in these women
5 who have a longer trailing length with women who had
6 different trailing lengths.

7 Thank you. I think that was all.

8 DR. BLANCO: Those were the big ones. Thank
9 you.

10 Any quick comments or questions from the panel?

11 (No response.)

12 DR. BLANCO: If not, we'll go ahead and proceed
13 with the panel deliberation portion. All right. What we
14 need to do at this point is we need to go over so that it's
15 on the record and also refreshed everyone's memory of some
16 of the definitions and the issues that will be discussing,
17 and essentially the first thing would be the definitions of
18 safety, effectiveness and valid scientific evidence, and
19 we'll go ahead and I will just read you. The panel has
20 these handouts in their packet.

21 The definition of safety. "There is reasonable
22 assurance that a device is safe when it can be determined,
23 based upon valid scientific evidence, that the probable
24 benefits to health from use of the device for its intended
25 uses and conditions of use when accompanied by adequate

1 directions and warnings against unsafe use outweigh any
2 probable risk."

3 The definition of effectiveness is "There is
4 reasonable assurance that a device is effective when it can
5 be determined, based upon valid scientific evidence, that
6 in a significant portion of the target population, the use
7 of the device for its intended uses and conditions of use,
8 when accompanied by adequate directions for use and
9 warnings against unsafe use, will provide clinically
10 significant results."

11 The definition of valid scientific evidence is
12 "Valid scientific evidence is evidence from well-controlled
13 investigations, partially controlled studies, studies and
14 objective trials without matched controls, well-documented
15 case histories conducted by qualified experts, and reports
16 of significant human experience with a marketed device from
17 which it can be fairly and responsibly be concluded by
18 qualified expertises that there is reasonable assurance of
19 the safety and effectiveness of a device under its
20 condition of use. Isolated case reports, random
21 experience, reports lacking sufficient details to permit
22 scientific evaluation and unsubstantiated opinions are not
23 regarded as valid scientific evidence to show safety or
24 effectiveness."

25 The next thing, and you should have all this in

1 your packet, is the discussion questions, and what we have
2 found to be useful in the past, rather than reading all of
3 the discussion questions at one time, is to go ahead and
4 deal with discussion questions and discussions by the panel
5 at the same time so that we can deal with it as we read it.
6 If we run over a little bit on time, we'll, I'm sure, use
7 some of the voting option panel deliberation time. So it
8 should be okay.

9 So let's go ahead and take a look at the first
10 discussion question that we have presented before us which
11 deals with effectiveness, and I'll go ahead and read this.
12 "The results for the single-arm clinical trials featuring
13 bilateral placement of the current (gamma) version of the
14 Essure Micro-Insert are provided below. How does the
15 effectiveness of the Essure Micro-Insert compare to other
16 available methods for female tubal sterilization?" I'll
17 let you look at the table there yourselves as well as the
18 comments on the table.

19 Unless someone objects, what I'd like to do at
20 this point, if I could, is have Dr. Costello, who presented
21 the information on the CREST Study, review for us a little
22 bit about some of the data from the CREST Study looking at
23 number of pregnancies, number of patients in terms of their
24 success rate and also look at from the viewpoint of this
25 device and other methods.

1 Is Dr. Costello back? Thank you for agreeing
2 to do this, by the way.

3 MS. COSTELLO: No problem.

4 All right. If you will, while I'm going over
5 the different methods and their failure rates, if you'll
6 look back at the handout that I used for this morning's
7 presentation, the Slide Number 6 has the cumulative
8 probability of pregnancies by year since sterilization for
9 all the different methods, and what you'll see -- not on
10 that graph -- is the overall cumulative probability of
11 pregnancy at one year following sterilization was 5.5 per
12 thousand procedures or about .6 percent by one year.

13 If you look at them by method, you'll see that
14 spring clip application was actually the highest risk for
15 pregnancy at one year following sterilization and only one
16 other method was actually statistically significantly more
17 at risk for pregnancy than the reference group postpartum
18 partial salpingectomy and this other method was silicone
19 rubber band application.

20 Does that answer your question?

21 DR. BLANCO: Yes.

22 MS. COSTELLO: What other questions do you
23 have?

24 DR. BLANCO: Well, let's bring you back if we
25 have it because it deals with this, if you wouldn't mind.

1 I think unless someone wants a clarification, we'll go
2 ahead and start the panel deliberations.

3 MS. COSTELLO: Okay.

4 DR. BLANCO: Thank you.

5 MS. COSTELLO: You're very welcome.

6 DR. BLANCO: Okay. Does anybody have any
7 comment on this question they'd like to begin? Please,
8 sir.

9 DR. LARNTZ: This is Kinley Larntz. I'm the
10 statistician.

11 If you look at the number of pregnancies
12 column, you'll see all zeroes. Statistically, you can't do
13 better than that.

14 (Laughter.)

15 DR. LARNTZ: And with respect to is this
16 adequate information, you have to look at the sample size
17 and the upper bounds of the Bayesian intervals, and by the
18 way, the Bayesian analysis is highly appropriate and very
19 useful for combining the two data sets, and so if you look
20 at the combined data set, which is what I'd look at, is you
21 have assurance, good assurance, that the rate at one year
22 is less than half a percent. That's what you have. Good
23 assurance is less than half a percent.

24 Is that good enough? Well, that's beyond my
25 statistical expertise, but it certainly looks consistent

1 with the rates that we saw in the figures.

2 DR. BLANCO: Thank you.

3 I guess implied, and I'll throw this out since
4 we're not getting a lot of other discussion, but I'll throw
5 this out, to some extent implied, I think, in this question
6 is also the issue that's also brought up in Question 8, the
7 post-approval study, and that has to do with the length of
8 time that we have of the data in terms of efficacy,
9 especially in light of data from the CREST Study showing
10 that the rate increases with time, and so I guess I'd like
11 someone, if they are interested in, I know someone is, to
12 talk a little bit about the one-year data and what they
13 think of that.

14 David, I think you wanted to address that
15 issue, didn't you?

16 DR. SEIFER: Well, I think the point's well
17 taken that at one year and with the Phase II trial at two
18 years, there are no pregnancies. It's hard to do better
19 than that. But what we've seen this morning, the
20 presentation from the CDC, sort of highlighting why the
21 CREST Study's such a landmark study and was used as a
22 benchmark for this presentation, the fact that when we look
23 at this Slide Number 6 that was just pointed out to us, if
24 someone might want to comment on not only does the failure
25 rate increase with time but it seems to accelerate in the

1 latter portion of the years that are followed here between,
2 say, five years and 10 years, and because of that, I wish
3 there was some kind of remark that somebody could make
4 regarding the likelihood that the success rate with this
5 particular device isn't going to accelerate, its failure
6 rate isn't going to accelerate with time, because here's
7 six other methods, all producing tubal ligation, failure
8 rate is supposedly due to recanalization of which it seems
9 we have very limited understanding of why that occurs, and
10 with age being such an important factor here because the
11 younger women are the greater the change they're going to
12 have recanalization, the greater change that they're going
13 to be recanalated, if you will, at a younger age when
14 they're still fertile and still able to conceive.

15 So I wish I had a better understanding of how
16 this method is going to hold up over the course of time and
17 with this five-year follow-up, I wonder if it begs the
18 question of is that long enough because here you have data
19 which is well illustrated by each of the six methods and
20 you can see that it increases between five and 10 years.

21 DR. BLANCO: Any comments from anyone else?

22 DR. O'SULLIVAN: Well, I think what we can say,
23 based upon the information that they did give us and based
24 upon what Kinley said, that the pregnancy rate, the highest
25 possible pregnancy rate at the end of one year, if I got

1 your terminology correct, would be .5 percent.

2 DR. LARNTZ: At most.

3 DR. BLANCO: Please speak into the microphone.

4 DR. O'SULLIVAN: He did. He said .5 percent at
5 most, and if I look at the CDC CREST Study that Dr.
6 Costello mentioned, the pregnancy rate at the end of one
7 year was .6 percent. So, they could be basically
8 equivalent and that's all we have. We have nothing beyond
9 that for this particular study, and I don't think that they
10 can give us anything more than that, other than what
11 they've already said, which is that the occlusion is one
12 and a half centimeters because of the device. They're
13 assuming that it's a one and a half centimeters.

14 DR. BLANCO: Go ahead.

15 DR. BROWN: Just one other possibility might
16 be, I don't know if what Dr. O'Sullivan is saying, this may
17 be that in the postmarket follow-up, would they consider
18 extending that follow-up period to be longer for the
19 patients that are already on it, since you see this bump.
20 It almost seems like starting at six to seven years, it
21 starts to accelerate again. So you know, could we consider
22 maybe having longer follow-up on those patients?

23 DR. BLANCO: I think there are several points
24 that we're discussing or that need to be looked at. I
25 think Number 1 is the issue which maybe bothers David a

1 little bit, if I'm reading things into what he's saying,
2 but is Number 1, is one-year and some two-year data
3 sufficient to be able to allow the device to be marketed,
4 and there, you have to weigh the short number of years that
5 we have versus to some extent the fact that this permanent
6 method has some benefits in terms of ease and safety and
7 other issues. Okay. So that, that's one issue that maybe
8 we should address, and then as a second issue is, if that
9 is sufficient information to say, well, we need to go out
10 and gather more to know for sure and that we can better
11 counsel our patients that are going to have this, knowing
12 what the information is for the first couple of years, then
13 what needs to be done and that may be more appropriately
14 Question 8, but maybe we can do it here as well. What
15 needs to be done and for how long and what's the need?

16 So maybe we can try to break that up. Does
17 that seem reasonable?

18 MS. LUCKNER: I think it does. Speaking as a
19 consumer rep here, I think when you use the word "permanent
20 sterilization" and we are showing a one-year level of great
21 compliance and great doing the job it's supposed to do, I
22 don't see how you can call this permanent. I don't think
23 there's a woman in the audience or here on the panel who
24 would like to buy into that system for just one year. It's
25 a little risky if you are going for permanent

1 sterilization.

2 DR. BLANCO: Well, but let me not let you off
3 the hook so easy. So then, do you think that more data
4 needs to be gathered in terms of length of time of efficacy
5 before you would want to see the device approved?

6 MS. LUCKNER: Or very, very careful labeling
7 that the permanent implies one year or restrictive labeling
8 so that people understand. The woman who elects it with
9 her gynecologist understands that his confidence is based
10 on the data that states X and Y.

11 DR. BLANCO: Gerry?

12 DR. SHIRK: Dr. Shirk. I guess I'd sort of
13 take some of the other view in that we do have some limited
14 data over a two-year follow-up that they presented that
15 basically showed similar prolonged success rate and in fact
16 the curves were, as the FDA showed, were going towards
17 closer to zero, you know, as far as their confidence rates
18 and what our statisticians decide how significant that is,
19 but this device is also different than the other means of
20 sterilization in that this device has built within it a
21 chronic irritant that basically causes continued scarring
22 and stuff like that. So it's not like, you know, you've
23 got a healing process that goes on and then over time, how
24 does the body repair that? This is an agent that has got
25 built inside it with the PET fibers that basically

1 continues to cause irritation and may prevent, you know,
2 recanalization over time.

3 DR. BLANCO: Go ahead, Nancy.

4 DR. SHARTS-HOPKO: I would disagree with doing
5 anything with the word "permanent" because you want women
6 to clearly understand that they're going down a one-way
7 street, even though we know some of them will change their
8 mind later on.

9 I also think that it's probably not reasonable
10 to expect longer than five-year follow-up by the company.
11 That's not been standard for any product in this category,
12 but I see that as a labeling issue. We have data for two
13 years, and for all other devices in this category, here's
14 what it looks like at five to 10 years. That's how I would
15 see that.

16 DR. BLANCO: So you would see it not as a need
17 for more data now. Some postmarket need for longer data,
18 but as a very specific labeling, which is what you what you
19 brought up as well, in terms of what is known about the
20 device at this point, and with obviously the proviso that
21 as more data appears, then that labeling can be resubmitted
22 to be changed.

23 DR. SHARTS-HOPKO: And we know that many
24 parties in World Health Organization and elsewhere are
25 going to be interested in the long-term results with this.

1 We know that data will be gathered.

2 DR. BLANCO: Anyone else? Any other comments
3 or statements? Awfully quiet panel.

4 Subir, I want to just call on you. What do you
5 think of the one-year and two-year? If you don't speak, I
6 start asking people to speak. So let's hear from you.

7 DR. ROY: As I think we've heard, zero
8 pregnancies is pretty great, and the likelihood that that
9 error is not going to be significantly different than .5
10 which certainly is as good if not better than any other
11 available method, so I don't know that we're being asked is
12 this as compared to other methods better, the same or
13 worse. We're just asking is it effective and by the
14 parameters we have available to us, this evidence, it is
15 effective.

16 So I would in the affirmative say that it is
17 effective on the basis of the available information we have
18 for one and two years of use. What will happen
19 subsequently, I sort of suspect, as Gerry suggested, that
20 it will continue to be effective because of the unique
21 features in its design, but time will tell us whether that
22 is in fact true or not. But I don't think we're being
23 asked to necessarily say is it going to remain the same or
24 somehow between eight and 10 years start drifting up. On
25 the basis of these other methods, those as Gerry pointed

1 out are different and permit a different healing of smaller
2 segments of separation.

3 DR. BLANCO: Thank you.

4 Dr. Noller?

5 DR. NOLLER: I think it's important for us to
6 compare the one-year data versus one-year data, and it
7 looks like it's as good as or better than all the other
8 techniques for those women who had bilateral placement.
9 Now that's coming up in other questions, but if we look in
10 the intent-to-treat, it's not nearly as good as
11 laparoscopic where the failure rate, inability to get
12 something you think are the tubes, is less than 1 percent.
13 Here, it's 8 to 12 or depending on what numerator and
14 denominator you look at, maybe 14 percent, but among those
15 that had them placed at one year and at two years, it's as
16 good as the other methods, probably better, looks like.

17 DR. BLANCO: David, you want to make any other
18 comments on this?

19 DR. SEIFER: I wonder what it would look like
20 if we had concurrent controls doing the tubal sterilization
21 with the same people, same investigators. Probably the
22 pregnancy rate would be close to zero as well.

23 DR. BLANCO: Well, I don't think that this
24 device is necessarily to be marketed to beat other devices
25 or whatever. I think it's basically this is the

1 information, and it's an option and it has these other
2 benefits and these drawbacks, and it's just part of the
3 labeling and counseling of patients, you know. I don't
4 know how necessarily -- you know, there are various methods
5 obviously being used by different people in different
6 settings and it just adds one more. So I don't know that
7 it has to necessarily beat every method.

8 DR. SEIFER: It adds one more option with one-
9 year follow-up, two-years follow-up.

10 DR. BLANCO: Go ahead.

11 DR. LARNTZ: I mean, I would have to say, what
12 I'm saying, I may get thrown out of the statistical
13 society, but, I mean, if we've got to concur in the
14 control, I don't think we'd have any different information
15 because zero is still zero and how much better could it
16 have done if we'd had a concurrent control? I don't think
17 it would have changed our thoughts about this at all. So I
18 think, I don't disagree that we don't know what's going to
19 happen in the future. That's one of the nice things about
20 the future. If we knew, then maybe we wouldn't like it so
21 much, but in fact I think the fact is that for the data
22 that we have for the one, and I'll have to say, I think
23 it's relatively limited two-year data. I don't want to
24 oversell the two-year data, but the two-year data is as
25 good as it can be, given the limited nature of it, and with

1 the plan I think that's in place to follow patients and
2 I'll argue later that I don't want to throw any patients
3 out for the follow-up, by the way, I want to follow
4 everybody, just to let people know where I'm going to stand
5 on that because these are small numbers of patients for
6 small rates, we hope are small rates of future pregnancies.

7 DR. BLANCO: All right. I think we've probably
8 done that one in, unless someone wants to throw in anything
9 else.

10 (No response.)

11 DR. BLANCO: If not, we'll go ahead and move to
12 Question 2. Question 2 is, "The ages of the women in the
13 pivotal study trial ranged from 21 to 40, with median age
14 32. The age distributions in the pivotal trial and in the
15 CREST Study are given below. Are these age characteristics
16 appropriate for a study of this type?" Again, I'll let you
17 look at the boxes of data yourselves.

18 Anybody want to address the issue? I mean,
19 obviously there's some difference in terms of the
20 percentages in looking at the age range, 21 to 27 and 18 to
21 27, 17 percent versus 33. Is there concerns over that by
22 anyone on the panel? Most people say no. I think the
23 point of this question is the issue of women who have it at
24 a much younger age group are going to have this device
25 implanted for many more years, and they may be more fertile

1 than the older women. So is the data applicable, and I
2 guess what I'm getting from everybody in the panel is that
3 it is.

4 DR. NOLLER: The other thing about younger
5 patients is that a bigger percentage of them either regret
6 or want reversal. So that's the other fact.

7 DR. BLANCO: Yes, and I think it is interesting
8 to point out when you bring reversal, that if you need a
9 corneal resection to remove this, reversal isn't going to
10 be much of an option in most patients. I think that's
11 probably safe.

12 DR. NOLLER: It certainly would require a C-
13 section then if the woman did get pregnant.

14 DR. BLANCO: And reanas most of the tube. It'd
15 be a lot more complicated than lots of other options.

16 DR. SHIRK: Well, I guess my answer to that
17 would be that very rarely do we do reversals now anyhow.
18 In vitro fertilization has gotten to the point where it's
19 statistically better than trying to reverse. So I think
20 it's sort of a mute point. I think the big question would
21 be basically are these patients a candidate for in vitro
22 fertilization which would be more on safety issue thing
23 than the issue of reversibility.

24 DR. BLANCO: All right. I guess the other
25 issue just to bring up would be, do you think that there

1 are any different results if they had included younger
2 patients with potential higher rates of fertility? Let's
3 try to hit all the different points of the answer.

4 DR. SEIFER: Only if we're going to follow them
5 out some significant period of time. You're not going to
6 see much of anything within 12 months. I think time is the
7 issue here.

8 DR. BLANCO: Okay.

9 DR. ROY: Just a different side of the points
10 that were just raised. I don't think everyone has IVF as a
11 viable option if they change their mind. I work at a
12 county institution and I would be somewhat fearful that
13 people might downplay the permanence of this procedure and
14 by ease of use use it in individuals who have every right
15 to change their mind and then they're over a barrel. So I
16 think counseling is going to be very crucial in many
17 settings.

18 DR. BLANCO: Well, take the opposite side of
19 that. I mean, I'm sorry, I didn't mean to interrupt, but
20 take the other side of that. So would you recommend some
21 form of labeling because of the information that's been
22 presented in terms of fibrosis, continued inflammation, not
23 something easily -- you know, would you recommend any
24 labeling over and beyond a typical permanent -- forgive me
25 -- method? Other permanent methods of sterilization

1 concerning reversal of this particular method, maybe
2 especially in younger women? I mean, do you feel that
3 strongly about it?

4 DR. ROY: I do, and I agree that some assurance
5 must be placed that because of the ease of use, out-patient
6 and the perception of saving health care dollars, which are
7 very precious, to accomplish a goal that we don't sort of
8 sweep under the table the importance of the permanence of
9 it and if one changes their mind.

10 I mean, the most frequently performed procedure
11 in practically every infertility service I know of at at
12 least a municipal center is tubal reanastomosis. I mean,
13 we do that every week and these are women who were
14 counseled and were told that tubal sterilization is
15 permanent, yet they change their mind. Now, if we're
16 putting these in and having to do cornual resections and
17 trying to reimplant fallopian tubes, I mean, you know,
18 that's an all together different kettle of fish and the
19 likelihood of them being successful is markedly diminished
20 over conventional tubal sterilization.

21 DR. BLANCO: Dr. Brown?

22 DR. BROWN: It already says in your discussion,
23 I was just looking at the labeling, and I would argue that
24 both the physician and the patient labeling be made
25 stronger. For example, the patient labeling actually says

1 something about if you want to have IVF in the future, I
2 would like to see some type of statement saying something
3 like because of the unique mechanism of action of this
4 device. You know, emphasizing more that it's not known to
5 be reversible. Just make that really stronger so that the
6 patient hears that.

7 Also, for the physician, it might be a good
8 idea maybe to include some data about age and rates of
9 changing your mind and maybe some suggestion, the same kind
10 of thing, that because of the unique mechanism -- well,
11 it's believed to be the mechanism of action -- you should
12 highly select patients who may be older and more sure about
13 not wanting any future fertility. To me, that's my concern
14 about them not having more young people, is that this might
15 be a device that really needs to be geared towards women
16 who are older and therefore more sure about their decision.

17 MS. LUCKNER: I just want to add that remember
18 we taught patients that having a tubal ligation was
19 permanent sterilization, tying the tubes. There is a
20 genre of understanding out there about these kind of
21 surgical procedures that have something to do with the
22 tubes, that if you put it in, you can take it out. So even
23 though labeling is going to be a part of it, I think
24 there's much more of a burden on a physician to explain
25 because they've heard their mothers and others talk about

1 it. You can untie it, and we spend hours teaching patients
2 before they go for tubal, remember what it means. Just
3 because you tie and untie a shoe, there's a lot of very not
4 well-informed women making decisions about sterilization
5 and then being surprised that it's not what they think it
6 is.

7 DR. BLANCO: Gerry?

8 DR. SHIRK: Well, I guess I'm going to bring up
9 an issue I brought up when I first asked the question, was
10 basically it's not a question of reversibility, but it's a
11 question of whether these patients really are even
12 candidates for in vitro fertilization. I think we have to
13 ask ourselves what these little metal devices coming out of
14 the fallopian tubes, what statistical problems are we going
15 to run into with pregnancies if the patient does get
16 pregnant? We've obviously got three pregnancies that went
17 to term in their study from luteal phase, things that
18 really showed no problems, but I don't think we have any
19 data to the panel that would suggest that we have any way
20 of guessing as to what kind of obstetrical complications
21 would be created by having these devices in the uterine
22 cavity.

23 DR. BLANCO: So the flavor that I'm getting
24 from the panel is that there's not much of a concern in
25 terms of the results of the data but much more concerns

1 again in terms of labeling and selection of patients with a
2 potential for the younger patients to want reversal later
3 on and this being much more difficult to accomplish with
4 this particular device. Is that kind of how people feel?
5 Okay. We'll be back to that.

6 Okay. Anything else on this particular
7 question?

8 (No response.)

9 DR. BLANCO: Let's move on to Number 3. "The
10 PMA presents results from a prehysterectomy 'proof of
11 concept' study with with 52 patients where fallopian tube
12 specimens were examined histologically 24 hours to 14-plus
13 weeks following device placement.

14 "A. What do the results of this study indicate
15 about the mechanism of action of the Essure device?

16 "B. Can results from this study shed any light
17 on the likelihood of tubal recanalization in a long-term
18 setting?"

19 Any comments to start off the discussion?
20 Anybody?

21 DR. SEIFER: Dr. Wright's opinion this morning
22 may have changed by this afternoon, but it seems that there
23 was very limited information or understanding about that
24 very topic.

25 DR. BLANCO: Dr. Brown?

1 DR. BROWN: I don't know. I would kind of take
2 the opposite tack. I mean, although again you can't know
3 what's going to happen in 10 years, it seemed to me that
4 we're talking about something that is a unique mechanism of
5 action compared to all these things that were in the CREST
6 Study in the sense that you have these two coils in between
7 which is this substance that has been shown in other
8 implants long-term to have this long-term fibrotic
9 reaction. So I thought the answers to this would be it
10 indicates that it's a fairly unique mechanism of action
11 that, although we don't have the proof of it, is probably
12 less likely to have recanalization, I mean, if you look at
13 what you're saying about the data with valvular grafts and
14 heart valves and that kind of thing.

15 DR. SEIFER: Well, I'd like to ask Dr. Wright,
16 what other tissues most similar to tubal epithelium that
17 would give us some analogous comparison?

18 DR. BLANCO: Dr. Wright, just introduce
19 yourself for the record.

20 DR. WRIGHT: Tom Wright from Columbia
21 University, a GYN pathologist.

22 One of the issues with this, and I hope I was
23 clear in my earlier presentation this morning, is, is that,
24 PET fibers have been used in a variety of implants which
25 are predominantly vascular grafts and settings different

1 than what we see with the fallopian tube because in the
2 fallopian tube, you have an epithelial line structure in
3 which you're placing this into, and I know of no analogous
4 situation where a device containing PET has been used to
5 actually occlude an epithelial line structure.

6 Having said that, though, what we see
7 histopathologically is an ingrowth of dense fibrosis
8 together with some smooth muscle growing into this, which
9 is very typical of the histopathological responses that we
10 see with PET at a variety of different body sites. That is
11 a very long segment. It's 1.2 sonometers which is the
12 region in which we're placing this device in. So if you
13 say is there an analogous situation where someone has tried
14 to occlude an epithelial line structure using a PET device
15 and looked at it 10 years later, the answer to that is I
16 have never heard of that application.

17 DR. SEIFER: How about more than three months?

18 DR. WRIGHT: We have not looked at these long-
19 term tubes. The whole purpose of the pre hysterectomy study
20 was specifically to look at mechanism of action and how
21 does occlusion take place. That study was not designed to
22 look at recanalization. I mean, it's a different study
23 design. It wasn't designed to do that.

24 DR. BLANCO: All right. Thank you.

25 DR. WRIGHT: Thank you.

1 DR. BLANCO: I think, and I can't read the mind
2 necessarily of everybody that wrote this study or wrote
3 these questions, but I wonder, again it seems to me to hark
4 back to the issue of the one-year, possibly two-year,
5 length of data and then saying, well, this is a mechanism
6 probably more recanalized, so we can believe that the
7 failure rates won't go up further down the line as well as
8 the issue of the permanence and the difficulty of trying to
9 change things if somebody changes their mind, and I don't
10 know if that's what they were looking at but I think we
11 kind of addressed that. So unless there's another
12 different angle, I don't know that we need to keep talking
13 about this one. Anybody else want to say anything?

14 (No response.)

15 DR. BLANCO: Well, let's move on. Doing great.

16 Number 4. "In the three months following
17 device placement, the patient is instructed to stay on
18 alternate contraception to allow for sufficient tissue
19 ingrowth to produce tubal occlusion.

20 "In the pivotal study, a hysterosalpingogram
21 confirming correct device placement and tubal occlusion was
22 needed before the patient stopped alternative
23 contraception. The pivotal study showed that the rate of
24 bilateral occlusion was 96 percent of the number of
25 correctly placed devices.

1 "The sponsor is proposing that in commercial
2 use, alternate contraception can be stopped three months
3 post-placement if a pelvic x-ray, not a
4 hysterosalpingogram, confirms position of the device.

5 "In view of the potential for placement to
6 overrepresent occlusion as well as the potential for
7 incorrect interpretation of pelvic x-ray, is the sponsor's
8 proposal adequate?"

9 I guess I'm going to start this one off because
10 one of the things that I saw from their data was that there
11 actually were 16 patients out of the 456 that had the
12 device placed correctly but the hysterosalpingogram showed
13 the tube to be still patent and therefore -- and please
14 correct me if my numbers are wrong, but I think I wrote
15 that down, but were still patent and they therefore
16 continued to use a different method of contraception and
17 then had a second hysterosalpingogram.

18 So I think this is an issue because 16 out of
19 the 456, if my math works out correctly and it may not be,
20 is 4 percent. So there was what I think is a sizeable
21 number of patients that had it in place. So even if the x-
22 ray shows is to be in place, they still could have ways for
23 those little sperm to get past that thing. Okay. You were
24 going to make a comment, please.

25 DR. LARNTZ: No, my comment was it's a concern

1 if you change the way the device is used from the way the
2 device is studied. That's simple procedure, and the 4
3 percent, admittedly if you went out further, I think you'd
4 go out another three months, if 15 of those are taken care
5 of but it looks like another one took nine months, if I
6 understand the timing, I may not understand it perfectly,
7 it seems like if we're getting rates down at under half a
8 percent with -- this is going to raise the risk
9 considerably for an additional period of time and I would
10 worry about that.

11 DR. BLANCO: Well, the problem is you don't
12 know how many of those 16 would have gotten pregnant or
13 might not have gotten pregnant, but we don't have that data
14 to really know whether this would have caused a higher
15 rate. I think that's what you're saying. So this is of
16 concern to me on here.

17 Any other comments? Dr. O'Sullivan?

18 DR. O'SULLIVAN: To do the x-ray alone once
19 again reinforces what you said, but wouldn't it be a lot
20 cheaper to do a sonogram and even a hysterosonogram?

21 DR. BLANCO: That would be a lot cheaper and
22 probably easier and less trauma to the patient.

23 DR. O'SULLIVAN: And more reliable.

24 DR. BLANCO: Any other comments?

25 DR. ROY: Could I just get clarification?

1 Those 16 who had non-occluded tubes, were they continued on
2 contraception until such time as they did demonstrate
3 occlusion?

4 DR. BLANCO: Ms. Domecus, could you come answer
5 that, please?

6 MS. DOMECUS: Yes. They all continued on
7 alternative contraception for an additional three months
8 and all were found to be occluded at that time.

9 DR. BLANCO: Dr. Brown?

10 DR. BROWN: Could I just ask, because I had
11 that same thought as Dr. O'Sullivan, and I know you
12 mentioned that in commercial uses, people were using
13 ultrasound, but has there been any standardization, even
14 though it was not in the study, in terms of how ultrasounds
15 can be interpreted to show that there's occlusion and so on
16 in the commercial uses that might be able to be provided to
17 the people using this device?

18 DR. BLANCO: Do you understand the question,
19 and we'll give you a little leeway, because I think we're
20 going to want to hear a little bit about your experience,
21 at least I would like to hear a little bit about your
22 experience with ultrasound for placement of this device. I
23 think it'd be worthwhile for the panel to hear about that,
24 although I will rein you in if you talk too long.

25 DR. CARIGNAN: Okay. The issue, just to

1 clarify, it's not the issue of placement with ultrasound
2 but follow-up at three months with ultrasound, correct?

3 DR. BROWN: Well, that was my question.

4 DR. CARIGNAN: Yes. As I mentioned in the
5 Phase II study, we initially were looking at ultrasound as
6 the modality to check device location at three months as
7 well as the women were undergoing hysterosalpingogram in
8 terms of the occlusion. When we looked retrospectively at
9 those x-rays, we could then see that the ultrasound
10 correlated well to the device locations. As you all know,
11 the ultrasound image is going to be somewhat different to
12 train to than a pelvic x-ray would be, where you can
13 clearly see here's the device.

14 We decided not to continue with that in the
15 pivotal trial, just to go with the one study, thinking that
16 if we could just demonstrate a consistency with device
17 location and occlusion, then that would be the endpoint and
18 that's what we tried to do with that, but of the
19 investigators who did perform the ultrasound, all felt that
20 they could visualize the devices with ultrasound. Again,
21 we weren't looking at the level of precision that we
22 thought we could see otherwise, and I'd just like to point
23 out that that's different than what we see with the prior
24 iteration as was mentioned before which is difficult to see
25 on ultrasound. This device was much easier to see

1 ultrasonographically.

2 DR. SEIFER: But even if you could confirm
3 adequate placement, would you be able to confirm occlusion
4 on an ultrasound?

5 DR. CARIGNAN: As was mentioned, it is possible
6 to do tests of occlusion via ultrasound if it's scaled up.
7 That probably is not as widespread currently as just basic
8 ultrasound looking at device location. You can see an
9 echogenic device in the area of the uterus and the cornua.
10 It is easier than trying to see flow through the tubes at
11 this point in time.

12 I would like to mention, if I could, just
13 regarding the patencies, I could clarify. We did have 15
14 women who proceeded to become occluded at between the
15 three-month and the subsequent HSG and the remaining
16 patient, the 16th, actually had an equivocal HSG at three
17 months where it really couldn't be ascertained by the
18 investigator whether or not what was seen was actually
19 venous or lymphatic filling for flow through the tube, it
20 was that minuscule, and that there's no pooling contrast
21 noted on the HSG films. They were reviewed by myself and
22 an independent radiologist. Neither of us could conclude
23 that it in fact was patent. To us, it appeared occluded.
24 So we do think that all 16 were occluded by the sixth-month
25 HSG.

1 The other thing of note is that there was one
2 investigator who was doing the HSGs himself, rather than
3 having the radiologist do it, and his technique one might
4 describe as a bit aggressive for this procedure, and in
5 fact was probably recanalizing past the device at that time
6 point because of the amount of pressure and the duration of
7 time that he was actually distending the uterus because he
8 was using as an endpoint basically the woman saying that
9 hurts too much, stop, and so at that point, he was probably
10 opening the tube as it's used in other applications with
11 HSG.

12 DR. BLANCO: Yes, but let me interrupt you for
13 a minute. But I don't think, see, that's the real issue.
14 I think the real issue is you got a great result because
15 everybody went in and you knew ahead of time that everybody
16 was occluded, okay, and that's great, but now you're asking
17 the panel to say that it's okay not to have that check for
18 occlusion.

19 I think most people will likely buy the
20 ultrasound or x-ray for placement, but you don't have that
21 occlusion, and now what we don't know is how many of those
22 16 would have gotten pregnant had they not been using some
23 other form of contraception, and therefore would your
24 results have been the same?

25 I don't know if our statistician could do it

1 very quickly, but, I mean, how many pregnancies would you
2 have had to have had in order to make your results not look
3 anywhere near as good as they do?

4 So the issue I don't think is whether the
5 device works and it occludes. I don't see that as an issue
6 at all. The issue is we've had data presented that says
7 nobody gets pregnant on this, but everybody got checked to
8 make sure they were occluded. Now, the question is,
9 nobody's going to get checked to make sure they're
10 occluded. Is the pregnancy rate going to be the same and
11 that's a little more difficult to believe, let's put it
12 that way, at this point.

13 All right. Thank you. That was just a
14 statement, not a question for you.

15 MS. MOONEY: Dr. Blanco?

16 DR. BLANCO: Yes, ma'am?

17 MS. MOONEY: One thing I think we should look
18 at in the packet which I think is relevant to this
19 discussion is the literature that the sponsor references
20 regarding patency rate versus pregnancy rate, and in our
21 panel packet, they did make mention of the fact that for
22 tubal ligation patients at a three-month time point, there
23 was a similar patency rate and obviously after we've seen
24 the CREST data, that does not automatically translate to a
25 pregnancy rate. So I think we have to factor that in,

1 also, as we think about this.

2 DR. BLANCO: Right. No, I'm not saying that
3 that invalidates it or whatever. I'm just saying the issue
4 is not the HSG, just that there's a change in technique
5 from the study to clinical use with a potential for
6 changing success rates, and I have a problem with that, and
7 I think other panel members do, too.

8 MS. MOONEY: They may be trying also to
9 standardize the post-procedure techniques to other types of
10 -- for example, I don't think HSG is standard for other
11 sterilization methods.

12 DR. BLANCO: No, I don't either.

13 MS. MOONEY: So I think they may be looking at
14 trying to standardize that, too.

15 DR. BLANCO: No, I know, and I understand that,
16 but I guess I keep going back that it's not standard, you
17 know. When you do a laparoscopic tubal ligation, you don't
18 go do an HSG, but the data for what the failure rate is
19 isn't limited only to the patient that had the HSG and
20 showed the occlusion. It's to everybody, so it's comers,
21 and I just wish in a way -- I mean, I wish that we had that
22 data to know if it does make a difference or not.

23 Am I stressing this too much? You guys agree
24 with this or somebody want to take me on? Go ahead.

25 DR. SHIRK: My question would be basically with

1 an x-ray and you've got no outline of the uterine cavity or
2 uterus itself because it's not going to show up soft
3 tissue, I mean, how can you absolutely be sure that they're
4 placed correctly? I mean, ultrasound obviously is going to
5 give you at least the outline of the uterus itself, so you
6 know that you're in the proximity. So obviously an HSG
7 gives you an idea of the uterine cavity, so you know where
8 the uterine cavity is. So I just have a hard time
9 visualizing that you'd see two, you know, sterilization
10 objects in a flat plate and say yes, they're placed
11 correctly. Who can really make that statement?

12 DR. BLANCO: Well, the thing, though, with that
13 is that -- I'm trying to look for the data, but my
14 recollection is that there were only three, and please, if
15 the company can put the number -- there were only three
16 patients where there wasn't the combination of incorrect
17 placement and recanalization.

18 Maybe I'm wrong. Do you all know in how many
19 patients you did the hysterosalpingogram and found
20 incorrect placement? How large a number of patients was
21 that? It was in your data. I just didn't write it down.

22 Do you see what I'm saying, Gerry? But it
23 wasn't a big number to begin with. So I think it's more
24 whether there's occlusion or not occlusion becomes the
25 issue.

1 DR. CARIGNAN: To that point, there were 19
2 women.

3 DR. BLANCO: Just say your name, please.

4 DR. CARIGNAN: Dr. Charles Carignan.

5 There were a total of 19 women who had on HSG
6 an unsatisfactory device location. However, the expulsions
7 were identified just on the flat plate portion of it. So
8 if the number was small, then we look at what was actually
9 diagnosed by the HSG.

10 DR. BLANCO: So let me make sure that -- wait.
11 Don't go away. Let me make sure that you're saying there
12 were 19 women that on hysterosalpingogram you identified
13 incorrect placement?

14 DR. CARIGNAN: That's true.

15 DR. BLANCO: Okay. Now, of those 19, did I
16 misread the slide or you also had concomitant lack of
17 occlusion or was that a separate group? You also had
18 another 16 women?

19 DR. CARIGNAN: Yes.

20 DR. BLANCO: We have proper placement but --

21 DR. CARIGNAN: Right.

22 DR. BLANCO: Okay. Thank you.

23 DR. SEIFER: Do you happen to know the age of
24 those 19 women?

25 DR. BLANCO: Repeat your question, David. I'm

1 sorry.

2 DR. SEIFER: Well, if we're concerned about
3 pregnancy rate after failure placement or incorrect
4 placement, I wonder if those are younger women or older
5 women.

6 DR. BLANCO: Yes. I'm not sure they're going
7 to be able to pull that data out that quickly for those
8 particular patients.

9 Dr. Brown?

10 DR. BROWN: Just sort of to the second -- and I
11 don't know if this is what was being brought up, but
12 besides the issue that you brought up, to me is the issue,
13 and maybe I'm wrong and you all can correct me, but to my
14 knowledge, the standard reading of a flat plate for uterine
15 anatomy is not a standard thing that most radiologists know
16 how to do, whereas in an institution that has a busy OB/GYN
17 practice, they probably do know how to read a
18 hysterosalpingogram. So my concern is that you're asking
19 radiologists, and again correct me, I didn't see any
20 training for radiologists in here about reading these flat
21 plates.

22 I mean, it's one thing if, yes, you have normal
23 uterine anatomy and antverted uterus and tubes are both
24 hanging off the side to tell symmetry, but what if the
25 woman has a retroverted uterus? What if it's distorted by,

1 you know, subcervical fibroid? Are you relying a lot on a
2 radiologist who may have never read a flat plate for
3 placement of these devices before, which obviously won't
4 have, so that the issue which is if I prepared the correct
5 interpretation of the pelvic x-ray I also think is of
6 concern in addition to -- because hysterosalpingogram is
7 something that is a standard radiologic test that
8 radiologists have been trained to read whereas this is
9 different.

10 DR. BLANCO: Dr. Noller?

11 DR. NOLLER: We're confusing a couple of
12 numbers here. The 19 bad placements, something like 14 of
13 them were in the uterus and those are not the same people
14 that had patent tubes, correct? If you saw the device in
15 the uterus just sitting there, it was out of the tube, you
16 didn't go ahead and do an HSG and look for occlusion, is
17 that correct? So they're different people? I'm leading to
18 a point, based on your answer here.

19 MS. DOMECUS: They are somewhat different
20 categories, but everyone had an HSG done. That was how the
21 expulsions --

22 DR. NOLLER: Even the expulsions.

23 MS. DOMECUS: Right. They all had the pelvic
24 x-ray and HSG done at three-month visit.

25 DR. NOLLER: So were the expulsions included in

1 those 12 women that were patent or 15 women?

2 DR. BLANCO: It's 16.

3 MS. DOMECUS: Yes.

4 DR. LARNTZ: The 16 had satisfactory device
5 location and then were patent.

6 MS. DOMECUS: Correct.

7 DR. NOLLER: Right. See, those are little
8 different. See, I would love to say let's just do an x-
9 ray. It's less trauma to the woman. But you didn't do
10 that study. If we say yes, it's okay just to do pelvic x-
11 ray, it's kind of on no data because that isn't the study
12 you did. I wish you would have done it, but you didn't.

13 DR. BLANCO: Well, let's follow up on that. So
14 what would you like to see in terms of data to satisfy you
15 that they can switch over either from a hysterosalpingogram
16 to a flat plate or from a hysterosalpingogram to an
17 ultrasound with or without liquid assistance to see if
18 there's recanalization? Do you understand my question?

19 DR. NOLLER: I certainly do.

20 Well, it would require a group of women that
21 had the device placed and you'd check them in three months
22 with flat plate and those that show good placement, you'd
23 take off whatever the other contraceptive method they're
24 using is and those that had bad placement, of course, then
25 you have to replace or something, but that wasn't done.

1 It would require really another study, I think.
2 I don't think there's any way to use the flat plate since
3 you went ahead and did HSGs and you didn't remove the
4 contraceptive, additional contraceptive, method from those
5 you found were wrong or tubes were opened by HSG. So we're
6 mixing apples and oranges. That study wasn't done.

7 DR. BLANCO: Well, Ken, let's pin it down even
8 more because what I'm saying is which issue -- Dr. Brown's
9 concern is one thing, and then there are two issues to
10 address. One is the patency issue, and the other one is
11 the correct placement issue, right? You would agree with
12 that?

13 DR. NOLLER: What I would love to know is among
14 those women who on flat plate had normal placement, if you
15 follow them for a couple of years, how many get pregnant,
16 if any?

17 DR. BLANCO: Well, by inference then, I guess
18 the question I'm asking is let's say that the patency
19 wasn't an issue. It was just placement. Do you think that
20 going from the study they did of the hysterosalpingogram to
21 a flat plate, that would be comfortable enough for you to
22 know that you had correct placement or would you want that
23 study and then we can deal with the patency issue?

24 DR. NOLLER: Actually, because of the anatomy
25 of the tubes and because of the length of the device, I

1 think you could be fairly sure on a flat plate that it was
2 correctly positioned. It would be nice to know if
3 ultrasound were better. We don't know that either, but
4 there might be, I should say, some way short of HSG of
5 determining whether it's okay and they can stop their birth
6 control pills, but we don't know that. Right now, we only
7 know that with HSG and if they're patent, you keep
8 following them and it's okay, but we don't know about flat
9 plate.

10 MS. LUCKNER: But if we're trying to find out
11 which modality is best to use to confirm the either
12 placement or patency at three months, we've discussed
13 three, but you're only now talking about only two
14 collecting data on. You have the flat plate with some
15 restriction about who can read them with the skill and that
16 has to be built into the study, and then you've used
17 ultrasound, and which one gives from patient acceptance,
18 cost and accessibility, which one is the most reasonable
19 one to collect data for that will be used in general
20 practice? I mean, we're now talking about lots of ladies
21 getting this done with their gynecologist. Which modality
22 at three months is most representative of what will be in
23 general practice?

24 DR. BLANCO: Gerry?

25 DR. SHIRK: I think the question is pretty

1 straightforward. Most gynecologists do ultrasound in their
2 office, so ultrasound's going to be the modality that
3 you're going to choose. It's also simple to do on
4 ultrasonic hysterosalpingogram just by putting fluid in the
5 uterine cavity and then putting some carbon dioxide gas in
6 behind it. I mean, you can watch the bubbles go through
7 the tubes, if they're going through the tubes. So I mean,
8 it's not standard. That's not standard.

9 That's sort of an investigational process right
10 now of looking at tubes ultrasonically, but it's certainly
11 possible to do that. It certainly would be easier to get
12 gas through a small hole than it is to get fluid through a
13 small hole, but I still think ultrasound is probably the
14 most reasonable modality.

15 DR. ROY: Well, the study was done with HSG. I
16 mean, what's the price you're going to pay? You got the
17 convenience of an out-patient procedure. You have the
18 inconvenience of three months of contraception and an HSG.
19 Well, until we have other venues, we shouldn't just assume
20 that other things are going to work. A flat plate will
21 only give you at best location, not patency, and ultrasound
22 with or without CO2 bubbling through and all of that could
23 be investigated in the meanwhile. Maybe downstream, they'd
24 have more data and they say, well, you can do something
25 less invasive, but at the present time, the only facts we

1 have are these facts.

2 DR. BLANCO: Dr. Dubey, did you want to say
3 something?

4 DR. DUBEY: No.

5 DR. BLANCO: Well, I'll throw something else
6 out just because I think trying to look at some guidance
7 for them. The other possibility is just that you don't
8 need any tests, okay, and then you look at raw pregnancy
9 rates at that point without any tests and then you're able
10 to talk about that and see how effective it is without any
11 kind of tests. Would you agree with that or would you guys
12 -- I mean, we don't do other tests for other methods of
13 sterilization, but we know that they have a failure rate and
14 we know without checking they have a failure rate. I don't
15 do tubals anymore very often, but when I did them, I put
16 them on birth control for awhile until I knew they weren't
17 going to recanalize.

18 DR. BROWN: But when other devices were
19 approved that had to be approved, were the criteria that
20 you had to have a test? For example, when the clips were
21 approved or whatever, were any of these devices approved
22 through this process, were they approved based on studies
23 that did use an HSG or were they based on studies that
24 just, as you said, provided the raw data?

25 DR. BLANCO: Well, I don't know that. I guess

1 what I was saying, I was just trying to give options
2 because the company's listening and FDA, and I'm just
3 saying, I mean, and obviously I'm the only one that thinks
4 that, but I mean, if they hadn't done anything, if they'd
5 just put the devices in and then just looked at raw
6 pregnancy numbers and it turns out to be very, very low or
7 low enough, you know, then do you really need anything
8 else? No. I mean, the question here is because they did
9 do the other things and we make sure it was occluded and
10 properly placed and so therefore that's going to affect the
11 rate. But maybe I'm just offbase here.

12 DR. LARNTZ: No, it's not. This is Larntz.

13 Obviously if they had not done any tests and
14 they'd gotten zeroes, we'd all be sitting pretty and not
15 having to worry about it, but they did have a confirmatory
16 test at three months and then if it didn't work out
17 continued, and from the company's point of view, if I were
18 advising them, I would say do everything you can to make
19 sure you do get the thing through in the sense of have
20 these confirmatory tests because what if they had gotten
21 two or three pregnancies in their thing? We wouldn't be
22 sitting here talking the same way.

23 DR. BLANCO: Okay. Any other comments?

24 (No response.)

25 DR. BLANCO: I think we probably beat that one

1 pretty good.

2 Let's move on then. Number 5. "There was a 12
3 percent failure rate of bilateral placement on the first
4 attempt.

5 "A. Do the failure rates experienced by the
6 investigators in this study provide an adequate indication
7 of the failure rate that might occur when this device is in
8 wider use?

9 "B. Is this failure rate acceptable?"

10 Gerry, why don't we start with you? You do a
11 lot of hysteroscopy. What do you think?

12 DR. SHIRK: Well, I mean, certainly there are
13 lots of reasons why you may not be able to visualize a
14 fallopian tube. One of the things is obviously the
15 question of just basically tubal plugs. We see
16 infertility, you see a lot of just plugs where the tubes
17 aren't really occluded, where there's just a plug in the
18 tube, and so and so the big question in these patients, and
19 I'm not sure whether the company's answered it or not, is
20 how do you deal with these patients where you can get
21 unilateral placement?

22 I mean, are they then supposed to be subject to
23 other means of sterilization if they want it? If you go
24 back and do a hysterosalpingogram and it shows bilateral
25 occlusion of the tubes, then do you assume that these

1 patients are basically then sterile? Certainly a good
2 portion of those are just going to have tubal plugs. You
3 can't really say that the procedure is then a success, that
4 these patients can use it as a contraceptive device. So I
5 think the big question is direction there.

6 My other question was basically again the
7 question of you get in there and find existing intrauterine
8 pathology, is it appropriate then to place the tubal plugs
9 or that first -- treating that intrauterine pathology, and
10 the intrauterine pathology may have -- it may preclude
11 putting the tubes in or putting the plugs in.

12 DR. BLANCO: Dr. Noller?

13 DR. NOLLER: This is one of the two areas I
14 have real problems with.

15 First of all, I don't see in any of the
16 labeling, particularly to the consumer, where it says you
17 have one chance in eight that we can't do this. The people
18 doing this also, I know some of the names. I don't know
19 all of them. The names I know are expert hysteroscopists.
20 When 35,000 gynecologists who do a little bit of
21 hysteroscopy have this available who are not experts, I
22 can't believe that the failure to implant rate will be
23 anywhere near as low as 12 percent. It's going to be
24 higher.

25 Also, none of the "non" except for some REIS

1 and occasionally generals, none of the 35,000 practicing
2 OB/GYNs have any experience doing hysteroscopy on an awake
3 patient. They do them all with the patient asleep. I
4 don't think that is going to change. I think they're going
5 to do these asleep. I suspect, based on my experience
6 being a department chair with 50 and 25 members, knowing
7 the hysteroscopic skills, that what's going to happen is
8 the patient's going to be put to sleep, we'll try it, see
9 if we can get in from below, and if we can't, then we'll do
10 a laparoscopy. That's what the patient's going to be told.
11 All along here, there are problems, and it all revolves
12 around the fact that at the very best, the failure rate to
13 get these in is 12 percent, and I suspect that it could
14 easily be 20 percent among people that don't do this very
15 often. So even with the 12 percent rate, if women are told
16 that up front, unless there's some fallback plan, like
17 laparoscopy at the same time, I don't know why they would
18 accept this.

19 DR. SEIFER: Twelve percent is probably a
20 conservative estimate. There were 20 investigators but
21 five of these investigators had more than 50 percent of the
22 cases. So there's an obvious learning curve, and in the
23 best of hands, that probably brought down the overall
24 failure rate.

25 DR. SHIRK: My argument would be that this

1 procedure's probably in the office equivalent to a
2 diagnostic hysteroscopy, and I've done thousands of them in
3 the office and have yet to have a major complication. I
4 mean, it's an extremely safe procedure and a lot of the
5 interuterine pathology I look at before I do an operative
6 hysteroscopy, I do a diagnostic hysteroscopy in the office.

7 DR. NOLLER: May I respond?

8 DR. BLANCO: Well, let him finish.

9 DR. SHIRK: So I mean, you know, I think you're
10 looking at it from the standpoint that this has the same
11 hazard as doing a hysteroscopy asleep. I mean, none of us
12 would not do an endometrial biopsy in the office. We
13 wouldn't even blink about doing an endometrial biopsy in
14 the office and diagnostic hysteroscopy is basically on
15 about the same level, once you get comfortable and get over
16 a learning curve, to basically do an endometrial biopsy.
17 So I don't see this nearly as a hazardous procedure to the
18 patient that a major operative procedure would be.

19 DR. NOLLER: I absolutely agree that office
20 hysteroscopy is possible, good, safe, but the fact is that
21 virtually no practicing OB/GYNs have an office
22 hysteroscope. When they do them, they do them in the OR
23 with the patient asleep. I think it would be great if they
24 were doing them in the office but they don't and your
25 skills and those you've done are way beyond the usual

1 practicing gynecologist.

2 DR. BLANCO: I guess at this point, I'd like to
3 remind the panel, though, that to some extent, almost all
4 studies of almost all devices are always done by people who
5 have an interest in the particular methodology being
6 performed. This is true for fetal heart rate monitoring or
7 any other type of monitoring or whatever. So that, I don't
8 think that it's a question that we say, well, it's 12
9 percent and when it gets in the hands of everybody else,
10 it's going to be horrible and whatever. I don't think that
11 that's fair to the company or fair to what we need to look
12 at.

13 I mean, basically, we can try to impact on that
14 by requiring appropriate labeling and appropriate
15 disclosure and I think the company has presented an
16 educational plan to try to ensure that there is some
17 education of the physicians who are going to be doing this
18 with a reasonable amount of experience, and I think that
19 you can break this question as FDA did in two parts. One
20 is the overall just failure rate to put the device in. The
21 other one is the issue of the experience of the
22 investigator.

23 I think their data does show that after about
24 five insertions, you may shorten the time of the
25 hysteroscopy but you don't really improve the failure rate,

1 if you will, if I read that data correctly, and you know,
2 the difference between 14 and 10 minutes on a hysteroscopy,
3 I mean, we sometimes waste five minutes doing other things
4 that aren't anywhere near as important with the patient in
5 that setting.

6 So I'm not as concerned about that. I think if
7 everybody has to be an expert before they use something,
8 before something's approved, nothing's ever going to be
9 approved. So I think the issue is labeling and appropriate
10 counseling and notification for the patient of what's going
11 on until more experience is gathered and as experience is
12 gathered, then that labeling can be changed to reflect what
13 the actual numbers are with larger numbers, Number 1, and
14 then Number 2, an educational program requirement for
15 physicians that are going to be inserting this device to
16 ensure that they have the appropriate training to at least
17 attempt to be as close to the lowest failure rate possible.

18 Yes, sir?

19 DR. NOLLER: I absolutely agree with that. I
20 guess where I started with my point was that I think that
21 we have things on labeling later, but it just doesn't say
22 now that there's a 1 in 8 chance that this won't work, and
23 I think women deserve to be told that up front in big
24 letters in a box, you know, this isn't perfect, and we may
25 find with experience that it's a whole worse or might be

1 even better with time, but that isn't in their labeling
2 currently nor is the general anesthesia problem.

3 DR. BLANCO: Go ahead, David.

4 DR. SEIFER: The training program, it was
5 proposed to have five cases of proctored surveillance, and
6 I think it was Dr. Pennello from FDA. He had a slide. I
7 think it was Slide 23. I don't know if he's still here,
8 but it showed the timing of the procedure being cut in half
9 from, I think it was --

10 DR. BLANCO: Eighteen to 14, and 14 to 10.

11 DR. SEIFER: Yes. Based on the number of cases
12 that were done, and I think there's a pretty good argument
13 that this five cases be extended to something more
14 meaningful than five because again we're trying to improve
15 the chances of this being effective, and at five cases, it
16 hardly seems that it's going to be useful, it's going to
17 have its most beneficial effect. The patient's going to be
18 under twice as long and everything that correlates with
19 time under anesthesia, even if it's IV sedation or local,
20 amount of volume will increase in terms of the media
21 exposure and risk to the patient.

22 DR. BLANCO: Anybody want to comment on that?
23 I'll make commentary. Well, go ahead.

24 DR. SHIRK: Well, I think the answer is that
25 basically what they said, if you have a person who's an

1 experienced hysteroscopist that within five cases you can
2 teach this individual to place these adequately and that
3 their learning curve will be fairly rapid, and I would
4 agree that that's probably true.

5 The big question you have is what about the
6 person who has limited hysteroscopic abilities and you're
7 trying to teach them essentially two things, hysteroscopy
8 and also placing these devices in the tubal ostia, and so
9 the big issue with the training process is basically what
10 criteria should there be before somebody's allowed to come
11 into a training session or should there be two different
12 levels of training, those people who have very limited
13 hysteroscopic experience and those people who are adequate
14 hysteroscopists, because I think the question about the
15 technical ability to do this rides more on the person's
16 ability to do hysteroscopy, rather than their ability
17 really to place the tubes.

18 DR. BLANCO: I think the thing is, and this is
19 something we wrestle with in this committee all the time in
20 terms of devices, and it has to do with once things are
21 approved, then they're out in the market and physicians can
22 use them in ways other than the intended way, but that's
23 still not, you know, something that we can fix or are going
24 to fix in this committee.

25 I think we need to come up with a reasonable

1 educational program with a reasonable number of interaction
2 of education so that the average physician who should be
3 getting into this will know how to do it and the ones that
4 shouldn't shouldn't. That doesn't mean they won't, but
5 that's, I think, the most that we can ask, you know, when
6 we approve something, and I guess to me, failure rates are
7 more important than the decrease of time for hysteroscopy
8 from 18 to 10 something minutes, and so with five failure
9 rate didn't seem to change. So I guess I'd be satisfied
10 with five proctored events at this point and maybe that's
11 wrong but we'll see.

12 Anybody else? Rebuttal? Go ahead.

13 MS. MOONEY: Yes, Dr. Blanco. I was going to
14 bring up that same statistic you just mentioned.

15 I think Dr. Pennello's slide showed a trend
16 towards decreasing time with experience but I think his
17 placement rate analysis for different experience didn't
18 show a difference and maybe that is partially explained by
19 the sponsor's evaluation of the reasons for failure which
20 seemed to be a majority of those related to proximal tubal
21 occlusions. So it may have been more anatomical limitation
22 as opposed to an actual level of experience of the
23 operators. So that may help explain Dr. Pennello's data
24 that didn't show a difference in success rates over
25 experience level.

1 DR. BLANCO: And I guess the thing is if you're
2 really going to go for that and go for the 10 minutes, and
3 I don't have the slide in front of me and I don't remember
4 that, but it became a significant number.

5 PARTICIPANT: Twenty.

6 DR. BLANCO: Thank you. You had to get over
7 20, you know, before you reduced the time from 18 to 10 and
8 that's a lot to ask, I think, to be proctored. Maybe
9 that's just my bias.

10 Anybody else? Gerry?

11 DR. SHIRK: I think it's always a problem when
12 you try to put numbers on a credentialing game. You know
13 what I mean? I mean, some people are going to in five have
14 it completely, some people in 60 are not going to be able
15 to accomplish it very well. So I think it's difficult.

16 DR. BLANCO: Well put.

17 DR. SHIRK: So I think five is adequate.

18 DR. BLANCO: Anybody else? Any comments?
19 Anything else on this particular question?

20 DR. NOLLER: We didn't really answer the
21 question.

22 DR. BLANCO: Oh, well, we often don't do that.
23 (Laughter.)

24 DR. BLANCO: Do you want to go ahead?

25 DR. NOLLER: I don't know the answer to is the

1 failure rate acceptable?

2 DR. BLANCO: Well, I think there are two issues
3 and you brought them up and I think you brought up a very
4 good issue. I think, one, I mean, it's always the labeling
5 and counseling. Clearly that needs to be strengthened, the
6 actual numbers that are known need to be told to the
7 physicians and to the patients. But I think your other
8 issue is actually a very good suggestion and that's the
9 issue of a fallback plan. If you do face that situation
10 whether that should be, you know, a repeated attempt at
11 introduction, depending on what the reason was for the
12 failure, or whether that's at that same time and place to
13 go into a different methodology. I think that's a good
14 suggestion that maybe needs to be considered as a
15 possibility in there.

16 DR. SHIRK: I guess that was a question I
17 initially brought up when you asked me the question, was
18 basically that tubal occlusion thing, and there's no
19 direction from the company as to which way, how to handle
20 that. Certainly you could say, well, just go straight to
21 other means. If you get one in, a unilateral one in, and
22 you can't but there's a lot of those patients that have
23 tubal plugs. If you go back and do a hysterosalpingogram,
24 you're going to blow the plug which they found out and were
25 able to go back and replace the second tube, you know, the

1 second device. So it's two procedures, but again you're
2 not doing it under general anesthetic. I mean, you're
3 basically saving a lot of cash and also you're obviously
4 protecting the patient from a general anesthetic and some
5 other risks. So I think that I'd like to see at least some
6 type of direction built into the physician labeling as to
7 how to deal with this, you know, from the company.

8 DR. BLANCO: Well, I wonder if you want to be
9 that specific, though. I wonder if it might not be better
10 just to say that you should have a discussion with your
11 patient of what's going to happen if you are unable to
12 insert, you know, the devices bilaterally as to what your
13 next move is because if it is utilized in a non-general
14 anesthesia-type setting, I mean, you may not necessarily be
15 in a situation where they're going to go do a laparoscopy
16 at that point nor do you necessarily need to. As you
17 pointed out, there may be other reasons to try it later.

18 I think the issue more is that the point of
19 what happens if we don't succeed which does happen at this
20 rate needs to be brought up, discussed and some plan that
21 is appropriate to that particular patient and to that
22 particular physician should be made.

23 Dr. Noller, you brought this up. You think
24 that's fair enough or would you be more specific?

25 DR. NOLLER: No, I think that's fair enough.

1 DR. BLANCO: All right. Anything else?

2 (No response.)

3 DR. BLANCO: All right. Well, let's move on.

4 Safety, Number 6. "The authors of the CREST
5 Study noted that sterilization failure rates should not be
6 considered in isolation but rather in conjunction with
7 safety and acceptability of the female sterilization
8 procedures evaluated. The following are known risks of the
9 Essure System placement: tubal perforation, hypervolemia
10 due to high volumes of distention fluid over a short time,
11 vaso-vagal response, discomfort, bleeding/spotting.
12 Potential risks, not observed in the study, include
13 sterilization failure, ectopic pregnancy and infection.

14 "Given the advantages of the Essure System
15 procedure (e.g., less anesthesia; avoidance of abdominal
16 incision; patient satisfaction and comfort) is the safety
17 profile of this device acceptable?"

18 Dr. Brown?

19 DR. BROWN: Well, in reading through in detail
20 the adverse events, even though I think tubal perforation,
21 I guess that was one of the more frequent adverse events, I
22 just think it's interesting that in terms of the sequelae
23 of that seem to be nothing or very little, and I guess
24 that's probably not surprising when you actually look at
25 the diameter of this device, and the fact that if you are

1 perforating, you're perforating with something that is so
2 tiny and its non-reactive effects if it does get extruded
3 into the peritoneal cavity, but what I thought was more
4 concerning was reading, I guess, the two cases of
5 hypervolemia and maybe that's because I come from a city
6 where a patient actually died from this, was very well-
7 publicized case. So I was just interested in terms of the
8 labeling.

9 Reading those two cases, it's almost like the
10 data we looked at with the vacuum. Why would you put a
11 vacuum on 16 times, and I guess I might say why would you
12 infuse, you know, whatever it was, several liters of fluid
13 in? I mean, I would never do that, but given that that is
14 a potential risk, maybe there should be something in the
15 labeling just in terms of the life-threatening nature to
16 the patient. That's the one thing to me that seems to have
17 a potential to be really the biggest risk to patient
18 safety. So maybe there should be a little more emphasis in
19 the labeling that even though that's a rare complication
20 just to re-emphasize you have to monitor the ins and outs,
21 you know, kind of thing in the labeling so the physicians
22 keep that in mind.

23 DR. SEIFER: I agree with Dr. Brown, and I
24 would go one step further and there is some discrepancy
25 about the amount of time that was delineated in this

1 calling it not successful. I think in one piece there, it
2 said after 10 minutes and one tube but 30 minutes total.
3 So if we could have a consistent message about it's 20
4 minutes for total procedure or 30 minutes for total
5 procedure and perhaps some discussion about Is and Os input
6 and output deficits, if the deficit exceeds 1,500 ccs of
7 normal saline, and then for those who do hysteroscopy in
8 what I read in terms of the temperature of the saline
9 media, it's that I think it said to have it at body
10 temperature and I know that there are other methods or
11 other approaches to that. You could have it at room
12 temperature and perhaps lower your chances of
13 intravasation.

14 So I agree with Dr. Brown. I think that in the
15 labeling, it would be helpful to have some guidelines as to
16 how to reduce the risk of fluid overload because that
17 probably is the most serious complication.

18 DR. SHIRK: Well, I guess I could speak to this
19 since I've got two or three papers in the literature about
20 fluid overload.

21 I mean, first of all, saline is fairly safe as
22 we learned with when we did laser ablation and some of the
23 newer devices were used and obviously it's not innocuous
24 because you can drown somebody with it as I proved, but
25 probably the half-lethal dose is three liters for the