

1 wanted to just demonstrate that in the before picture there  
2 is non-coaptation of the bladder neck and such that the  
3 leakage or urine can be pretty significant.

4 [Slide.]

5 Where the bulking agent is used, essentially, you  
6 fill in the gap at the bladder neck and proximal urethra,  
7 thereby increasing resistance at this area and affecting  
8 continence, and as you know, there are several agents that  
9 have been tried in the past and are currently being  
10 investigated for the use of continence in these patients.

11 I would like to take any questions if there are  
12 any.

13 DR. A. KALLOO: Thank you, Dr. Foote.

14 DR. FOOTE: Thank you.

15 DR. A. KALLOO: Next, we will proceed with the FDA  
16 presentation. I would like to remind the panel that they  
17 may ask for clarification of any point included in the FDA's  
18 presentation, but the discussion should not go beyond  
19 clarification.

20 The first speaker for the FDA is Dr. Rao  
21 Nimmagadda.

22 **FDA Presentation**

23 **FDA Lead Reviewer**

24 **Rao Nimmagadda, Ph.D.**

25 DR. NIMMAGADDA: My name is Rao Nimmagadda. I am

1 a chemist in the Urology and Lithotripsy Devices Branch and  
2 the Lead Reviewer for the Durasphere PMA.

3 My presentation is an overview of the Durasphere  
4 PMA and does not go into the details as the sponsor has  
5 already made a detailed presentation. In my presentation, I  
6 shall only outline the various aspects covered in the PMA  
7 and point out some of the issues that are still under  
8 review.

9 [Slide.]

10 The PMA was first submitted in December 1998 to  
11 document the safety and effectiveness of Durasphere, and  
12 updated in June 1999 to include additional clinical data.  
13 The PMA contains information about: the device description  
14 and how the device improves or cures incontinence,  
15 manufacturing and device specifications, preclinical testing  
16 including a two-year dog study, clinical studies, summary of  
17 safety and effectiveness, device labeling, post-approval  
18 study proposal.

19 Let me now briefly discuss each section to draw  
20 your attention to some important points and issues.

21 [Slide.]

22 Durasphere is a sterile, nonpyrogenic, injectable  
23 bulking agent composed of pyrolytic carbon-coated zirconium  
24 oxide beads suspended in an aqueous beta-glucan carrier gel.  
25 The pyrolytic carbon-coated beads have a size range of 212

1 to 500 microns. The carrier gel is approximately 97 percent  
2 water and 2.8 percent in beta-glucan.

3 When Durasphere is injected submucosally in the  
4 periurethral tissue at the bladder neck, it increases the  
5 tissue bulk and produces coaptation of the bladder neck  
6 and/or urethra. By increasing urethral resistance to urine  
7 flow, this coaptation reduces and in some cases even  
8 eliminates urine leakage.

9 Durasphere is formulated Advanced UroScience from  
10 the components, pyrolytic carbon-coated zirconium oxide  
11 beads and beta-glucan powder received from the vendors.

12 The sponsors prepares the beta-glucan gel, adds  
13 the pyrolytic carbon-coated beads to the gel to produce the  
14 desired concentration of the beads, fills 1 ml syringes with  
15 the material, packages each syringe and steam sterilizes the  
16 packages.

17 [Slide.]

18 The manufacturing of the pyrolytic carbon-coated  
19 zirconium oxide beads reproducibly according to  
20 specifications (212 to 500 micron size range) to ensure the  
21 absence of small particles below 80 microns by sieving the  
22 beads and removing carbon soot on the beads by washing and  
23 to ensure the purity of beta-glucan gel is critical for the  
24 safety of Durasphere.

25 If there are particles below 80 microns in

1 Durasphere, they may migrate to distant sites, such as  
2 liver, kidney, and lung, and cause serious complications.  
3 If beta-glucan has higher levels, that is, greater than 2.5  
4 percent of impurities such as protein, it may increase the  
5 risk of sensitization reaction in patients.

6           The carbon-coated beads account for a specific  
7 percentage of Durasphere's volume and the sponsor maintains  
8 the bead concentration within narrow limits. If the beads  
9 occupy less than the specified volume, the bulking effect  
10 per ml of Durasphere would be less than that found in the  
11 clinical study.

12           Since Durasphere is a permanent implant, it has to  
13 be sterile and nonpyrogenic. The firm's manufacturing  
14 procedure is designed to ensure conformance to these  
15 specifications.

16           [Slide.]

17           Biocompatibility testing. The firm had conducted  
18 both short-term and long-term biocompatibility studies. The  
19 short-term studies include: pyrogenicity, Guinea pig  
20 sensitization, cytotoxicity, systemic toxicity, hemolysis,  
21 muscle implantation (45 days) and Ames mutagenicity tests.

22           These tests showed that Durasphere is not toxic.  
23 Other tests include 7-day and 28-day dog studies, as well as  
24 a 2-year dog study, in which Durasphere was injected in the  
25 periurethral tissue.

1           The injection sites revealed mild to moderate  
2 granulomatous inflammation/subacute inflammation in the 7-  
3 day dog study and trace to mild granulomatous inflammation  
4 in the 28-day dog study.

5           Dr. Herrera will address a possible consequence of  
6 this inflammation in his presentation. After this initial  
7 phase, the tissue response from the carbon-coated zirconium  
8 oxide particles was found to be a normal tissue response to  
9 the presence of foreign material.

10           The sponsor has adequately addressed any potential  
11 concerns regarding the migration of carbon-coated beads to  
12 distant sites and organs, providing reasonable assurance of  
13 the safety of these beads.

14           The clinical section covers various topics: study  
15 objectives, study design, study protocol, description of  
16 patient population, effectiveness and safety results,  
17 summary and conclusion.

18           You may remember from the sponsor's presentation  
19 that a total of 578 patients were tested for skin  
20 sensitivity at 9 U.S. sites and 1 foreign site, and 355 were  
21 treated. All of these patients I am referring to here are  
22 female patients, and my presentation discusses the study  
23 results only on females, because there were very few males.

24           Eighty percent of the patients treated are  
25 Caucasian and 19 percent of the patients are Hispanic,

1 primarily from the Costa Rican site. Afro-Americans  
2 accounted for only 1 percent of the treated population.

3           Of the 355 patients found eligible and treated,  
4 178 patients were treated with Durasphere and 177 with  
5 Contigen, the control. The patients are well matched  
6 between Durasphere and Contigen arms in regard to a number  
7 of baseline characteristics.

8           The protocol required at least a 12-month follow-  
9 up. Although several parameters, like pad weight urine  
10 loss, incontinence episodes, change in Quality of Life, were  
11 used to monitor the effect of treatment on the patient's  
12 incontinence, improvement of greater than or equal to 1  
13 grade at 12 months by Stamey incontinence grade scoring  
14 system was chosen as the primary endpoint for effectiveness.

15           For this primary endpoint, 115 patients in the  
16 Durasphere arm and 120 patients in the Contigen arm had 12-  
17 month follow-up. All adverse events observed or reported by  
18 patients were considered in the safety analysis.

19           Although there are still some issues that require  
20 clarification or explanation by the sponsor, we are in  
21 general agreement with the firm that the clinical  
22 performance of Durasphere is equivalent to that of Contigen.

23           I would now like to draw your attention to the  
24 following information presented in the PMA.

25           [Slide.]

1 Skin sensitivity testing. In the skin sensitivity  
2 test, none of the 485 U.S. patients tested positive to  
3 Durasphere, that is, to beta-glucan. In contrast, 19 of the  
4 93 Costa Rican patients tested positive to Durasphere in the  
5 initial testing, but only 1 tested positive on retesting  
6 using a revised protocol by an allergist/immunologist sent  
7 from the Mayo Clinic.

8 The sponsor attributes the initial high  
9 sensitivity rate to the desire of the Costa Rican medical  
10 personnel to be overconservative in rating the skin test  
11 results. The protocol used in retesting is a valid  
12 protocol. FDA is in the process of reviewing whether there  
13 were any differences in the purity of beta-glucan lots used  
14 in the testing and retesting that could have caused the  
15 variant results.

16 However, based on Dr. Herrera's clinical review,  
17 which will be presented later, hypersensitivity to  
18 Durasphere does not appear to be a significant clinical  
19 concern.

20 In contrast to the low reactivity of Durasphere,  
21 Contigen exhibited a positive skin reaction rate of 15  
22 percent in the Costa Rican patients, although the overall  
23 rate of 3.5 percent observed in the U.S. patients is within  
24 the limits of 1 to 5 percent reported in the literature for  
25 Contigen. A potential advantage of Durasphere is that it

1 may not require skin testing.

2 [Slide.]

3 In regard to effectiveness, as you have seen from  
4 the sponsor's presentation, both Durasphere and Contigen has  
5 the same effectiveness profile at 12 months. Sixty-six  
6 percent improved by one grade with 31 percent reporting  
7 dryness. Similar decrease in pad weight urine loss, and  
8 similar decrease in incontinence episodes per week, similar  
9 change in Quality of Life scores.

10 [Slide.]

11 Durasphere performed obviously equally well when  
12 the improvement of incontinence grade at 12 months was  
13 analyzed as a function of the number of treatments.

14 [Slide.]

15 With 1 treatment, Durasphere showed 83.7 percent  
16 improvement versus 71.4 percent improvement. In regard to  
17 dryness, 46.9 percent dryness versus 51.9 percent.

18 With the 2 treatments, 54.4 percent showed  
19 improvement for Durasphere versus 65.4 percent for Contigen.

20 For dryness, 21.7 percent for Durasphere versus 15  
21 percent for Contigen.

22 With 3 treatments, 60 percent of Durasphere  
23 patients improved versus 33 percent for Contigen. The  
24 dryness rate is 20 percent for Durasphere versus zero  
25 percent. You should note that there were very few patients

1 who received 3 treatments.

2 [Slide.]

3 Issues under review regarding effectiveness.

4 Improvement and dryness should be evaluated as a function of  
5 baseline incontinence grade since most patients had a  
6 baseline grade of 1 and 2. Very few patients at Grade 3.

7 Improvement should be evaluated as a function of  
8 baseline urine loss by pad weight, and there is very little  
9 data available regarding improvement and dryness beyond 12  
10 months.

11 Dryness observed by Stamey incontinence grade of  
12 zero at 12 months should be correlated with other criteria  
13 such as pad weight urine loss, number of incontinence  
14 episodes and change in the Quality of Life.

15 Did the patients who were dry by Stamey grade  
16 scoring have zero urine loss and zero number of incontinence  
17 episodes at 12 months? If not, what was the average urine  
18 loss and average number of incontinence episodes for these  
19 dry patients?

20 There is also a pooling issue for the primary  
21 effectiveness endpoint. Significant differences among  
22 centers were observed for the primary endpoint of  
23 improvement equal to or greater than 1 grade at 12 months.

24 In conjunction with significant differences found  
25 between centers regarding a number of baseline

1 characteristics such as incontinence grade, pad weight urine  
2 loss and incontinence episodes, the center to center  
3 differences in the primary endpoint may require further  
4 justification for pooling.

5 Dr. Herrera will note in his talk that there are  
6 of no clinical concern, these differences are not of  
7 clinical concern.

8 [Slide.]

9 Safety/adverse events. All adverse events were  
10 separately categorized, depending on whether they lasted  
11 less than or greater than 24 hours. A comparison of the  
12 adverse events lasting more than 24 hours shows that the  
13 rates for a variety of complications, such as non-acute  
14 retention, frequency, respiratory, and other infections,  
15 musculoskeletal, and cardiac events, outlet obstruction,  
16 allergic reactions were comparable for Durasphere and  
17 Contigen. However, as you heard before, for urgency and  
18 acute retention, the rates were higher for Durasphere and  
19 statistically significant.

20 Thirteen of the 44 patients with urgency in the  
21 Durasphere group required medical intervention with drugs  
22 and antibiotics.

23 [Slide.]

24 In the transient symptoms category notable rates  
25 of hematuria, retention, urgency, and dysuria were reported



1 The first issue that I would like to discuss is the  
2 demographics.

3 [Slide.]

4 Nearly all patients enrolled and treated in the  
5 study were females, all of which were over 25 years of age.  
6 Since there were too few men treated to statistically  
7 evaluate, my discussion is limited to the female population.  
8 After my discussion, you will be asked to address this issue  
9 as pertains to the device indication.

10 Regarding the racial make-up in the study  
11 patients, there were 81 percent for the Caucasians, 18  
12 percent for Hispanics, and only 1 percent for the Afro-  
13 Americans. Based in the demographics of the general United  
14 States population, Afro-Americans appears to be under-  
15 represented. However, the clinical significance of this  
16 disparity is not clear, but not appears a significant issue.

17 Next, I would like to touch upon the issue of  
18 pooling that Dr. Nimmagadda discussed in this presentation.  
19 As pointed out, differences among centers were observed for  
20 the primary endpoint of improvement of 1 grade or more at 12  
21 months.

22 Likewise, several key baseline characteristics,  
23 such as incontinence grade, pad weight urine loss, and  
24 number of incontinence episodes, were significantly  
25 different between sites. While these differences are worth

1 noting, I believe that they are due to the natural  
2 variability among these groups of patients, and, therefore,  
3 are not of clinical concern.

4 [Slide.]

5 As described in the presentations of the  
6 manufacturer and Dr. Nimmagadda, the effectiveness of the  
7 two products were similar at one year in: improvement of  
8 continence 1 grade, changes of continence grade, achieving  
9 continence, improvement in pad weight, and changes in the  
10 number of incontinence episodes per week.

11 The safety of the two products was also similar,  
12 except in the incidence of urgency and acute retention. One  
13 possible reason for this urgency rate is the larger size of  
14 the needle needed for injection.

15 The vast majority of these cases were resolved  
16 with the administration of antispasmodics. The retention,  
17 as mentioned by Dr. Nimmagadda, could be the result of  
18 inflammatory reaction as was seen during the early periods  
19 in the dog study.

20 After self-catheterization the retention was  
21 resolved on average in four days. There were no trends in  
22 laboratory values noted for either Durasphere or Contigen  
23 patients or differences seen between the treatment groups.

24 In the 12-month KUB, no evidence of significant  
25 migration was observed in Durasphere patients at 12, 18, and

1 24 months.

2 Dr. Foote's detailed overview of the treatment of  
3 urinary stress incontinence was very illustrative. As a  
4 reminder of the present modalities of treating, I am  
5 presenting this slide.

6 [Slide.]

7 Treatments are behavioral, pharmacological,  
8 periurethral bulking agents, and surgical.

9 [Slide.]

10 The advantages of the Durasphere are: no need for  
11 skin test prior to injection, no apparent risk for  
12 hypersensitive reactions, to the coated beads are non-  
13 absorbable, the beads are not prone to migration due to  
14 their large size, significantly less volume of Durasphere as  
15 compared to the control material was injected. However, I  
16 do not believe that this difference in the amount of  
17 material injected clinically is significant.

18 [Slide.]

19 My main concern is the durability of the implant  
20 past one year is largely unknown at the present time.

21 This is an issue which the panel will be asked to  
22 address during your deliberations.

23 [Slide.]

24 Durasphere has equivalent effectiveness to the  
25 only legally marked injectable bulking agent and similar

1 safety profiles. There is an increased risk of urgency and  
2 retention, both of which were resolved. This difference  
3 must be balanced against Durasphere's benefits.

4 The fact that the injection of both products can  
5 be performed as an outpatient is an important feature for  
6 the patients considering a surgical approach for their  
7 incontinence.

8 For urologists, the injection procedure for  
9 Durasphere is familiar. This fact is evidenced by the short  
10 learning curve observed in this study.

11 The beads permanently reside at the injection  
12 site. Therefore, reabsorption may be less of an issue.  
13 However, some Durasphere patients needed reinjection, and  
14 this re-treatment rate was similar to that of the Contigen.  
15 As I stated earlier, the long-term effectiveness of  
16 implantation of these non-resorbable beads is not yet known.

17 No skin testing is necessary, and there is less  
18 risk for long-term immunological complications.

19 In light of all the available treatments for  
20 stress urinary incontinence, Durasphere's risk-benefit ratio  
21 appears to be comparable.

22 Thank you very much.

23 DR. A. KALLOO: Thank you.

24 Are there any questions from the panel at this  
25 time?

1 DR. DIAMOND: I have two questions for Dr.  
2 Nimmagadda and I have one for Dr. Herrera.

3 Last week in Detroit, we had a patient --  
4 actually, we didn't have a patient, it was another hospital  
5 -- had a patient, a 57-year-old delivered a baby, and while  
6 most of the patients in this group are menopausal, the age  
7 range went into the premenopausal range. So, it caught my  
8 eye that when you looked at the biocompatibility testing,  
9 reproductive toxicity was not mentioned.

10 Was that done and it wasn't on the slide?

11 DR. NIMMAGADDA: I can't really -- the  
12 biocompatibility testing I already mentioned, but the tests  
13 showed Durasphere to be nontoxic.

14 DR. DIAMOND: What about reproductive toxicity?

15 DR. NIMMAGADDA: Yes.

16 DR. DIAMOND: Was that tested, to your knowledge?

17 DR. NIMMAGADDA: Right.

18 DR. DIAMOND: And did not show any?

19 DR. NIMMAGADDA: No.

20 DR. DIAMOND: The second question was in the  
21 presentations given today, and what I saw here, I didn't see  
22 any breakdown on patients who either had had, on the outcome  
23 specifically, the patients who had a prior suspension  
24 procedure, of which there were about 10 or 15 percent in  
25 each group, or any breakdown as a function whether women had

1 had hysterectomies.

2           Were there data like that available for your  
3 review?

4           DR. NIMMAGADDA: Maybe the company can answer that  
5 question.

6           DR. A. KALLOO: Company, do you have the  
7 information on the question about previous surgery?

8           DR. HOLCOMB: I am not sure that we have really  
9 looked that, so that we can't address what impact, if any,  
10 prior hysterectomies or prior suspensions would have caused.  
11 They weren't exclusions for the study, so to the extent that  
12 they were represented in the normal patient population, they  
13 would have been included in the study.

14           DR. DIAMOND: I would think they would be sizable,  
15 and I would think that would be something worthwhile looking  
16 at, because it may have impact one way or the other on  
17 outcomes that you observed.

18           DR. HOLCOMB: Only through, you know, as a  
19 surrogate, we have examined the effect of age on outcomes,  
20 and didn't find any effect there.

21           DR. DIAMOND: That's a good issue, but it's  
22 probably a different one in my mind.

23           The last question I had for I think probably more  
24 for Dr. Herrera, was it started out each group had about 230  
25 patients, and ends up -- sorry -- about 170 in each group,

1 and ends up each group having about 120 patients.

2           So, basically, there is only one year follow-up on  
3 about two-thirds of the original patients in the group or  
4 one-third of the patients were lost, and primary endpoint  
5 analysis and secondary endpoint analysis not available.

6           Are there ways to try to statistically correct for  
7 that, or how do you -- when you do a statistical analysis, a  
8 relevant statistical analysis, how do you control for that  
9 large loss of patients in your study population?]

10           MR. BAXLEY: I am John Baxley. I am Acting Branch  
11 Chief in the Urology and Lithotripsy Devices Branch.

12           I think that a lot of those patients hadn't  
13 reached 12-month follow-up, and if the firm could comment on  
14 that.

15           DR. HOLCOMB: Well, that is exactly right. They  
16 weren't really lost, they just haven't reached the follow-up  
17 time.

18           DR. DIAMOND: Maybe you can enlighten me then  
19 about the rate of enrollment. I thought the study started  
20 in '96, is that right?

21           MS. PETERSON: Yes.

22           DR. DIAMOND: I don't know when enrollment closed  
23 and you put together your package, but it would seem one-  
24 year follow-up, you should have had a lot more patients,  
25 unless you had a ballooning of enrollment at the very end of

1 the study.

2 DR. HOLCOMB: The study was not atypical in that  
3 respect. It started slow and ramped up with the majority of  
4 the patients in the latter part of the study. As has been  
5 alluded to earlier, some of the patients actually we have  
6 two-year data on, so those early patients in the study, we  
7 do have long-term follow-up on.

8 There were also two phases for the study, and that  
9 should be pointed out. The first group of patients that  
10 were done, were done in the early part of the study, prior  
11 to starting the pivotal, so only a small number are out at  
12 that longer period of time.

13 DR. STEINBACH: A question for Dr. Herrera. Is  
14 there a controlled clinical trial in the literature on men  
15 and Contigen or not?

16 DR. HERRERA: Yes, there is, but there were not  
17 enough patients in this particular trial for evaluation.

18 DR. N. KALLOO: Excuse me. Dr. Herrera, I had a  
19 question about your advice about not skin testing. My  
20 concern would be certainly if this is done in America, and  
21 you do it on more African-Americans, and there is a history  
22 of keloid formation with skin healing, does that apply, or  
23 does anybody know if that applies internally, as well, and  
24 would they tend to get more or a different type of healing  
25 with the biosphere as compared to, say, whites?

1           The other question is would that apply to Asians  
2 or other groups of Hispanics, as well? I am wondering if  
3 excluding skin testing overall, in all groups, is  
4 necessarily a good idea.

5           DR. HERRERA: I cannot answer that question.  
6 Really, in this study, we didn't have enough patients, Afro-  
7 Americans. As you can see, there was only 1 percent of the  
8 population, so it is something that is a question for the  
9 panel to decide.

10          DR. A. KALLOO: Just from the company, was there a  
11 reason why there was such a disparity in the accrual? Was  
12 it because of the sites of recruitment? Do you know?

13          DR. HOLCOMB: I don't think so. I think it is  
14 difficult. There was an attempt to enroll a cross-section  
15 of patients, as you can see from the description of where  
16 the centers were, there is a variety of geographic  
17 locations, urban/rural. It just happened that way, and  
18 unfortunately, happens that way in many studies.

19          DR. N. KALLOO: I had one other question. You did  
20 KUBs only? Were there any chest x-rays that were done to  
21 look for migration?

22          DR. HERRERA: Yes, there were patients that they  
23 had the KUB and chest x-ray.

24          DR. N. KALLOO: So, it was both, the KUB and --

25          DR. HERRERA: Yes.

1 DR. A. KALLOO: Any other questions?

2 DR. N. KALLOO: I have one more question, I am  
3 sorry.

4 My question is sort or directed to the Grade III  
5 stress urinary incontinence, and I notice that in Appendix  
6 A, they have about 40 percent achieved a Grade zero, and  
7 maybe Dr. Foote could address this, as well.

8 What is the cure rate or roughly the cure rate for  
9 Grade III stress incontinence, with, say, a sling procedure?

10 DR. FOOTE: That's a good question, because I  
11 think when we look at new technology, we have got to compare  
12 it to what we have got in regards to traditional technology,  
13 and the cure rates for Grade III incontinence, I can't quote  
14 specifically, but as you can see from the meta-analysis that  
15 was done at the AUA, all comers, keeping in mind that most  
16 of those patients did have Grade III incontinence, was about  
17 80, 85 to 90 percent, so that the success rates in regards  
18 to sling would be higher.

19 DR. N. KALLOO: And from what I can recall, at our  
20 institution, most people with sling procedures are actually  
21 out in less than 24 hours. I am not sure if they are all  
22 outpatient, if you consider that outpatient, but I think for  
23 billing and DRG, I think less than 24 hours is considered an  
24 outpatient procedure, so actually, the injection is done as  
25 an outpatient procedure and also the slings at our

1 institution I know are done as an outpatient procedure.

2 DR. FOOTE: That's true. Certainly, the  
3 postoperative recovery period would be longer for an  
4 individual having a sling although there are some newer  
5 technologies that are allowing the slings to be done with  
6 less and less morbidity on the part of the patient.

7 The postoperative period to return to full  
8 activity may be on the order of three to six weeks depending  
9 on the type of procedure, the type of methodology used for  
10 performance of the sling.

11 DR. N. KALLOO: So, for surgery it would be three  
12 to six weeks, and for the injection, are they going right  
13 back to work?

14 DR. FOOTE: I can only speak -- I am not familiar  
15 with the current study product. The company may want to  
16 respond. I am familiar with the use of GAX collagen, and  
17 these patients are back to work the following day.

18 DR. SNYDER: I just want to point out, if I may,  
19 that you are comparing success rates of Grade zero on these  
20 patients, but we are talking about, in the index, five  
21 patients, and two of five patients, so the sample is  
22 extremely small, and so it really isn't a comparative group.  
23 It's not fair to compare 200 sling patients to 5, because  
24 here, two of five achieved a Grade zero, giving you 40  
25 percent. So, I think the sample size really doesn't make

1 that comparison quite fair.

2 MS. NEWMAN: Also, the success rate in what you  
3 showed was cure, dry, or improved, correct?

4 DR. FOOTE: Yes.

5 MS. NEWMAN: So, we are not still talking about  
6 dryness in that end either, okay?

7 DR. SNYDER: In the literature, the cure means  
8 many different things.

9 MS. NEWMAN: That's right.

10 DR. SNYDER: And that's fair, yes.

11 DR. HOLCOMB: Chairman Kalloo, we do have someone  
12 here that might be able to shed some additional light on the  
13 issue of ethnic background and immunogenicity. If I could  
14 introduce him, he is Dr. Roy Ritz, who may be familiar to  
15 some of you. He is a former head of the Immunology Panel,  
16 Advisory Panel for the FDA.

17 DR. A. KALLOO: If you could please state your  
18 name.

19 DR. RITZ: Yes, it's Ritz [phonetic]. I am an  
20 emeritus Professor of Microbiology and Oncology at the Mayo  
21 Clinic. I am emeritus Executive Director of the King Faisal  
22 Specialist Hospital in Riyadh, Saudi Arabia, and I have no  
23 financial interest in the company, but a desire to have my  
24 hotel room paid and perhaps get a Ferrari.

25 As to the question you addressed, Dr. Foote, about

1 the skin testing, the first thing is that nonliving, aqueous  
2 antigens in blacks and whites, in my experience of about  
3 over 30,000 patients, probably shows no significant  
4 difference. A difference would be in the living antigen,  
5 such as smallpox, where you do see keloid formation.

6 In the case of this particular product, the issue  
7 of immunogenicity and antigenicity arose by someone either  
8 misreading or misunderstanding a paper on beta-glucan  
9 written by Nick DeLusio in the seventies, and no theoretical  
10 or practical immunologist would suspect that glucan would be  
11 immunogenic, but the company has done a series of studies  
12 which show that it is not. The skin test material would not  
13 in any event contain the beads since their immunogenicity  
14 are antigenicity is not a question.

15 The beauty of having a nonimmunologic reactive  
16 material, such as this, and I can tell you this from many of  
17 our oncology studies, is that you eliminate a two-day period  
18 that brings patients and brings extra cost to the patient,  
19 extra expense of personnel to put down the skin test, read  
20 them, when very often, and unless someone is fairly expert,  
21 there is a lot of ambiguity to begin with.

22 So, I think the cost saving and the economic  
23 aspects, as well as the lack of nuisance factor to both  
24 physicians and patients is a positive aspect of this.

25 DR. A. KALLOO: Could you explain the discrepancy

1 with the Costa Rican patients in terms of the initial  
2 testing and then subsequent?

3 DR. RITZ: It was my view when I looked at the  
4 data sent to me by E-mail, I guess, or maybe before I left  
5 Minnesota, that the responses were being wildly overread,  
6 and I think that is reflected in the rate of responses read  
7 in Costa Rican patients for Contigen, which is about three  
8 times my understanding of what has been in the literature,  
9 and I might point out that how can I, in the fifties, were  
10 the first to demonstrate antigenicity to tropocollagen, so I  
11 think there was reading, and Dr. Adele Taylor, from Mayo,  
12 went and reviewed those patients, and the only one that she  
13 did find who was positive, she ascribed a variant of the  
14 hypersensitivity to, which is her opinion.

15 My opinion is that that doesn't exist, but the  
16 opportunity to address one patient that seemed to have what  
17 I believe is a factitious or an idiosyncratic reaction would  
18 have been to take a biopsy. So, we don't know about that  
19 one patient, but I believe that the non-physician reader of  
20 the test was extravagant.

21 DR. A. KALLOO: Was that one patient of African  
22 origin?

23 DR. RITZ: I am not able to tell -- Hispanic? I  
24 don't know if it was African origin or not.

25 DR. A. KALLOO: Any other questions?

1 DR. NIMMAGADDA: I am clarifying the question  
2 about the genotoxicity testing. I believe they did, but I  
3 want to doublecheck. I don't want to be on the record that  
4 they did, but even if they didn't, considering that these  
5 are a pyrolytic carbon-coated zirconium oxide beads, and the  
6 other component is beta-glucan, I don't see any reason or  
7 rationale of requiring genotoxicity testing. That is what I  
8 wanted to say.

9 DR. DIAMOND: I am sorry. Genotoxicity is a good  
10 question. Reproductive toxicity is what I was asking.

11 DR. A. KALLOO: Dr. Hawes.

12 DR. HAWES: I would sort of like some advice,  
13 maybe from Dr. Foote. There were a few people who were in  
14 this study reported that were Type III, and you mentioned in  
15 your meta-analysis that most of the people undergoing a  
16 sling operation were Type III.

17 Is there a reason to believe that these  
18 implantable bulking agents will be less effective in Type  
19 III patients, and should the panel, in your opinion,  
20 consider that group separately? Is there not enough data in  
21 the Type III's, I guess specifically?

22 DR. FOOTE: That is a very good question. It is  
23 also a very complex question, and I am going to go back to a  
24 slide that I showed earlier in the discussion that I had to  
25 show that as clinicians and as researchers, we are impressed

1 that there is a lot of overlap, you know, a pure Type III  
2 patient, you know, is really in the minority now in terms of  
3 what we are thinking now as opposed to what we thought years  
4 ago.

5           So, when you talk about a patient who is pure  
6 intrinsic sphincteric deficiency without any problems with  
7 prolapse, for example, that patient is really in the  
8 minority now in terms of what we are thinking, and because  
9 of that, I think it would be difficult and I think  
10 inappropriate to try to pin down a therapy based upon a  
11 designation which as time goes on is going to be used less  
12 and less.

13           In regards to one of the points of information  
14 that I found interesting was the fact that for these groups  
15 of patients -- and by the way, that we have also found for  
16 Contigen -- is that the leak point pressure, which is a  
17 quantification of the amount of pressure that it takes to  
18 allow your leak from the bladder was not significantly  
19 different between responders and non-responders, and you  
20 might say, well, if leak point pressure can let you know to  
21 what degree the individual has incontinence, is that  
22 predictive, well, that has not been really predictive  
23 either.

24           So, you know, it would be wonderful if we did have  
25 something in regards to a diagnostic test or in regards to

1 something in regards to the history to be able to allow us  
2 to predict which patients were going to be responders and  
3 which patients would not be responders, but I am afraid that  
4 the level of our understanding at this point in regards to  
5 the diagnosis of the different classes, if you will, of  
6 incontinence, is not to the point that it really would be  
7 beneficial to do so at this time.

8 DR. HAWES: As a point of clarification for the  
9 company, you are asking for approval for all, irregardless  
10 of the grade scores?

11 DR. SNYDER: If I may just address your previous  
12 query, one of the things that makes discussion, as Dr. Foote  
13 stated just now, difficult is that one creates a mixup  
14 between grade and type, and using two different systems and  
15 measuring two different processes.

16 In reality, when one does a study of stress  
17 urinary incontinence due to intrinsic sphincter deficiency,  
18 one is including 100 percent of the patients are Type III  
19 patients, so Type III would include all the grades of what  
20 we are grading.

21 So, all patients in the study who received  
22 implantation are Type III patients. Now, within the Type  
23 III intrinsic sphincter deficiency, we have different  
24 gradations of how much activity causes it.

25 So, we are looking at a new definition of

1 intrinsic sphincter deficiency at a time when Type III  
2 didn't -- there was no intrinsic sphincter deficiency for  
3 Type III. We now acknowledge or are in general agreement  
4 that Type III urinary incontinence includes stress urinary  
5 incontinence with mild activity, with moderate activity, and  
6 severe.

7           So, the Grade III of Type III are what you  
8 classically I think are talking about, but they are actually  
9 all Type III patients. It is my feeling that the company is  
10 talking about all types of Type III urinary incontinence.

11           DR. HAWES: But my question was on the grade. I  
12 understand the Type III. There were very few Grade III in  
13 your trial, very, very few, and my question is are you  
14 asking, are you making any discrepancy about their grade in  
15 terms of the efficacy of your treatment.

16           DR. SNYDER: No.

17           DR. HAWES: So, you are asking for approval for  
18 all grades within Type III patients?

19           DR. SNYDER: Yes.

20           DR. HAWES: Again, I would bounce it back to you.  
21 That seems reasonable?

22           DR. FOOTE: Well, in regards to that specific  
23 point, I personally feel the numbers were not high enough to  
24 contraindicate the use of this therapy for patients with  
25 those most severe types of incontinence, and generally, what

1 happens is that the market tells the tale. I mean as the  
2 numbers get more, and you have more investigators using it,  
3 it will become apparent what grades, if you will, of  
4 incontinence are best treated by this device.

5 DR. HOLCOMB: Dr. Hawes, maybe I could just add  
6 one additional comment. There is a table in Appendix A, the  
7 very first table, which shows improvement by baseline grade.

8 DR. HAWES: I was looking for that.

9 DR. HOLCOMB: Page A-1. Two things are worthy of  
10 note. The classification in the Grade II or Grade III, as  
11 Dr. Foote mentioned, had in our patients a significant  
12 overlap. There were people who fell sort of in the gray  
13 area potentially between, and could have gone one way or  
14 another in terms of the grade that they were assigned.

15 The other thing that you will notice there is that  
16 even among those people that were classified as the most  
17 severe in Grade III, they had comparable success rates, all  
18 small numbers aside, they had comparable success rates to  
19 what we saw with Grade II.

20 The last thing that I think is worthy of note in  
21 that table is that that effect was also present in both  
22 groups, both Contigen and Durasphere had a similar profile.

23 DR. A. KALLOO: Any other questions?

24 DR. DIAMOND: Could I just get clarification, were  
25 genotoxicity and reproductive toxicity tests done?

1 MS. PETERSON: Genotoxicity was done in our  
2 biocompatibility.

3 DR. DIAMOND: But not reproductive toxicity?

4 DR. HOLCOMB: Related to ability to become  
5 pregnant?

6 DR. DIAMOND: And outcome of fetuses that are  
7 conceived or that are carried by a woman who has these  
8 implants in place.

9 MS. PETERSON: No, we didn't do that.

10 DR. DIAMOND: Or I mean animal equivalent studies,  
11 obviously.

12 DR. HOLCOMB: Those studies were not done.

13 DR. BENNETT: Jenelle, you may want to magnify on  
14 this, but it is rare for a urologist to treat a childbearing  
15 person with a bulking agent.

16 DR. A. KALLOO: But it is also important to know  
17 whether or not that --

18 DR. BENNETT: But it is not commonly done because  
19 you don't want to deliver a child through the vagina with a  
20 bulking agent because you are going to let it go every which  
21 way, and it will destroy whatever effect you are going to  
22 have on the treatment.

23 MS. NEWMAN: But you have a cross-section of quite  
24 of quite a few young subjects in the study. Your age span  
25 here was these came to urology offices, and they decided

1 that they should enter into the study, so it seems like that  
2 there are urologists who are doing that, correct, on  
3 childbearing women?

4 DR. FOOTE: Yes, correct.

5 MS. NEWMAN: And not just in the 50s, which is an  
6 aberrant, I hope, but women who are 40 or maybe 30, who are  
7 coming in with this type of incontinence, that may have  
8 babies, and they decided they would get a bulking agent.

9 DR. FOOTE: Yes. As a matter of fact, and I will  
10 speak for my clinical experience, for women who are still  
11 interested in having children, of childbearing age, a  
12 bulking agent may look more attractive than doing something  
13 like a pubovaginal sling, although there would be the  
14 possibility that either procedure may be affected by a  
15 vaginal delivery, clearly, the effect on the surgical  
16 procedure, like a retropubic suspension or pubovaginal sling  
17 would be greater than in a bulking agent.

18 DR. HOLCOMB: Just one specifically in the  
19 inclusion/exclusion criteria, Ms. Newman, it was a patient  
20 who had been pregnant in the past 12 months or was scheduled  
21 to become pregnant in the succeeding 24 months was excluded  
22 from the study.

23 MS. NEWMAN: But there are women who become  
24 pregnant that don't schedule it. Okay?

25 DR. A. KALLOO: Any other questions?

1 DR. N. KALLOO: Is there any indication that this  
2 would prevent surgery in the future if it was unsuccessful?

3 DR. SNYDER: There is no concern regarding this.  
4 Prior bulking agents, most urologists have fairly good  
5 experience in using a more conservative therapy, such as  
6 bulking agents, and then going in and either doing a sling  
7 procedure with autologous or non-autologous tissue, as well  
8 as other procedures, such as an artificial urinary sphincter  
9 in men post-prostatectomy, and there appears to be no  
10 contraindication for this and no further fibrosis that  
11 occurs.

12 DR. N. KALLOO: So, basically, similar to the  
13 collagen.

14 DR. SNYDER: Very analogous.

15 DR. A. KALLOO: We will now take a lunch break for  
16 45 minutes and return at 1:15.

17 [Whereupon, at 12:32 p.m., the proceedings were  
18 recessed, to be resumed at 1:15.]

## 1 AFTERNOON PROCEEDINGS

2 [1:20 p.m.]

3 DR. A. KALLOO: Good afternoon and welcome back.

4 **Panel Discussion**

5 We will now reconvene the open committee  
6 discussion with the FDA charges; while this portion of the  
7 meeting is open to public observation, public attendees may  
8 not participate except at the specific request of the panel.

9 We have had a fair amount of discussion. I think  
10 Dr. Diamond has a couple more questions he wants to ask, and  
11 then we will move along to the specific questions that we  
12 are charged with by the FDA, and then answer these questions  
13 in turn.

14 DR. DIAMOND: I would presume after the agent is  
15 placed, if you did a pelvic exam, you would be able to feel  
16 the bulking agent when you palpated the interior vaginal  
17 wall vaginally, is that correct?

18 DR. SNYDER: I would presume so.

19 DR. DIAMOND: Is there any discomfort women have  
20 with intercourse, any dyspareunia once it has been done, was  
21 that reported by any of your patients?

22 DR. A. KALLOO: Would you step up to the  
23 microphone, please.

24 DR. SNYDER: You can if you inject and implant  
25 enough of the device, you can feel it through the anterior

1 vaginal wall. We had no reports of dyspareunia, and  
2 patients were asked if they had pains, vaginal pains at all,  
3 and this was not reported, so this was not a concern for us.

4 DR. DIAMOND: Presumably, all the surgeons that  
5 were participating in the study had lots of experience with  
6 prior bulking agents that were on the market. For surgeons  
7 that were not that experienced with those, is there going to  
8 be a steep learning curve there?

9 DR. SNYDER: Tina, can you just describe the  
10 population of surgeons? Not all surgeons were  
11 overqualified, some had minimal experience with bulking  
12 agents. Can you just define the groups a little bit?

13 DR. DIAMOND: Would less experienced physicians,  
14 if you had some, did they have greater failure rates?

15 MS. WITTCHOW: We did not see that. Our Costa  
16 Rican physician had no experience with Contigen whatsoever,  
17 and he had, as you see in the report, had a nice success  
18 rate with both products.

19 DR. SNYDER: I must say personally I who have had  
20 huge experience with bulking agents was in the middle of the  
21 pack, and sometimes my stuff looked good, and it was just --  
22 I had a 0.64, and I was right in the middle of the pack of  
23 all sites.

24 DR. DIAMOND: The last question I had is when  
25 actually were patients randomized? First, they were given

1 the forms, they saw who was included and excluded, you did  
2 the skin testing, but when in the process were the patients  
3 actually randomized to the treatment or control groups?

4 DR. SNYDER: That's a great question. Patients  
5 were randomized in the operating room. Patients were  
6 prepared for surgery or if the procedure was done in the  
7 office, they were prepared at the time.

8 A monitor was present for every single  
9 implantation case, a sealed envelope was present, and at the  
10 time the patient was up in position, the seal was broken,  
11 and at that point we knew, the implanting surgeon knew what  
12 he or she was going to implant.

13 DR. DIAMOND: You were ready to go with either  
14 one, you had them both available, and whichever one?

15 DR. SNYDER: Exactly.

16 DR. DIAMOND: That's great.

17 DR. SNYDER: And just normally, we would do more  
18 than one procedure often on the same day, so we would have  
19 all product available.

20 DR. N. KALLOO: These were all urologists?

21 MS. WITTCHOW: We had one gynecologist. That is  
22 our Seattle site.

23 DR. A. KALLOO: Thank you.

24 The first question is based on the patient  
25 population enrolled in the clinical investigation of the

1 Durasphere Implant and reported in the PMA, should the  
2 intended use statement be limited to adult women, that is,  
3 exclude men and/or patients under 21 years of age?

4 Question 2. Given the rates of improvement in  
5 effectiveness outcome measures and the rates of adverse  
6 events observed during the clinical trial and reported in  
7 the PMA, does the panel believe that the Durasphere Implant  
8 has a favorable risk/benefit profile?

9 Question 3. Is the post-approval study outlined  
10 in the PMA adequate to document the long-term safety and  
11 effectiveness of the Durasphere implant?

12 Question 4. Should physician training be required  
13 prior to use of the Durasphere Implant?

14 Question 5. Are the proposed "Directions for Use"  
15 accurate and comprehensive?

16 We will go back to Question 1. What we will do is  
17 to have each panel member comment on the question, at the  
18 end of which Dr. Donatucci will summarize the panel comments  
19 at the end of each question.

20 We will start with Dr. Foote on the first  
21 question.

22 DR. FOOTE: I personally feel that the product  
23 should not be restricted. Although the study did not  
24 include a significant number of male patients, there  
25 certainly may be male patients in the clinical situation

1 that that may potentially benefit from the device, and I  
2 would say the same thing for pediatrics. It does not appear  
3 to me that there had been any contraindications that I could  
4 see for use in the pediatric age group.

5 DR. A. KALLOO: Dr. Diamond.

6 DR. DIAMOND: I would make basically the same  
7 observations, but I would probably come to the opposite  
8 conclusions. I would think since there is a paucity of data  
9 on men and a paucity of data on children, that its use  
10 should be restricted to not include those groups. Once it  
11 were approved, if it were approved for adult women, a  
12 physician and a patient would have the option of going ahead  
13 and using it off-label, and I think that would probably be a  
14 better way of going than approving its use for something  
15 where we don't have data or a large enough volume of data to  
16 show that it is safe and effective.

17 That might be something in a postmarketing study  
18 that if the company wanted those specific indications, they  
19 could enroll additional patients to do that.

20 The other caveat that I would throw in here is  
21 about the use in women who are either of reproductive age or  
22 desiring further reproductive potential, and whether in  
23 those individuals, there ought be labeling to that degree or  
24 even excluding its use in women in those situations who  
25 potentially desire future childbearing is one way of

1 phrasing it, or otherwise who are of reproductive potential,  
2 natural reproductive potential.

3 DR. A. KALLOO: Ms. Newman.

4 MS. NEWMAN: I don't think there is data in men,  
5 but I really do think it can be used in adult women and men.  
6 I am not sure about pediatrics because I don't think there  
7 is enough data, and they don't have enough long-term data on  
8 this product yet.

9 But I agree that I think its potential in  
10 premenopausal or childbearing women is of concern, and if  
11 women, even though they may not be pregnant in the next 12  
12 months, but can possibly become pregnant, you know, in the  
13 next so many years, I have a concern about this injection.

14 DR. A. KALLOO: Dr. Vertuno.

15 DR. VERTUNO: I have no objection to it being used  
16 in men, but I think it should be clearly labeled that what  
17 modest data there is shows it to be less effective. I would  
18 like to see some data before it is approved in the pediatric  
19 age group. I am concerned about that.

20 DR. STEINBACH: I do not object to using it in  
21 men, but I agree with Dr. Vertuno that the labeling should  
22 reflect that it doesn't seem to be as effective.

23 DR. A. KALLOO: Dr. Bennett.

24 DR. BENNETT: Yes, I concur to what Dr. Foote has  
25 already said.

1 DR. A. KALLOO: Dr. Hunter, to comment on this  
2 question.

3 DR. HUNTER: Handle it with labeling.

4 DR. A. KALLOO: Dr. Deitrick.

5 DR. DEITRICK: I would agree with what has already  
6 been stated. I think that we need to handle with labeling  
7 as far as men are concerned, and I would still, until we had  
8 more documented evidence, that I would restrict it to those  
9 women of reproductive age.

10 DR. A. KALLOO: Dr. Hawes.

11 DR. HAWES: My opinion would be that we should  
12 manage the male population with labeling, that it should not  
13 be restricted. I personally don't think that it should be  
14 approved for the pediatric population since there is no  
15 data, and I am concerned about the long-term situation with  
16 this.

17 I would agree that in terms of women of  
18 childbearing age, my own personal feeling is that it would  
19 be managed by labeling, that it shouldn't be automatically  
20 restricted, but that labeling should be appropriately made  
21 in that regard.

22 DR. N. KALLOO: I agree with what everyone else  
23 has pretty much said, that labeling should take care of the  
24 male population. It can be used, but definitely mention  
25 that it is not effective, and again long-term studies before

1 it is approved for pediatrics.

2 DR. A. KALLOO: Dr. Donatucci, can you summarize  
3 the comments of the panel?

4 DR. DONATUCCI: Well, it appears that the panel in  
5 summary feels comfortable with handling the paucity of data  
6 in men by addressing that in the labeling. I think, in  
7 summary, that the panel feels that the pediatric population  
8 should not be included in the intended use because of the  
9 paucity of data, and at least my read of the panel here is  
10 that there is a little bit of a difference in terms of women  
11 with reproduction.

12 Several panel members feel fairly strongly that  
13 that should be stated, that it should not be used in that  
14 population until data are available. Others feel that that  
15 precaution can be included in the labeling.

16 DR. DIAMOND: I was probably the most vocal about  
17 the women of reproductive age, but the way you phrased that  
18 was actually not the way I was intending. The way you  
19 phrased it was that women of reproductive age should not be  
20 using it, and I am not in favor of that. I am just in favor  
21 of the indication being in women who are beyond reproductive  
22 age as opposed to putting the negative there for that group  
23 because I don't know anything that says it is bad, I just  
24 don't know anything, this is not an issue.

25 DR. A. KALLOO: Dr. Hunter.

1 DR. HUNTER: I would handle it a different way. I  
2 would say there is no data on it, which is what you see in  
3 the PDR on any drugs, and so forth. There is no data on it,  
4 so safety has not been proven.

5 DR. DONATUCCI: I would point that actually that  
6 is exactly how it is handled in the directions for use. It  
7 says there are no data.

8 DR. A. KALLOO: Do you need to resummarize that  
9 last point?

10 DR. DONATUCCI: I think the feeling of the panel  
11 is that the problem in terms of reproductive women is a  
12 problem that is addressed in the labeling, that the  
13 indication should be for women who are beyond reproduction,  
14 but the precaution could be handled in the labeling.

15 DR. BENNETT: Craig, could you repeat what your  
16 concept is concerning pediatric age group? The reason I  
17 bring that up is bulking agents are often the court of last  
18 resort for urologic disasters in the pediatric age group,  
19 and very small amounts sometimes produce a remarkable  
20 improvement in symptoms, and there is no immunologic data  
21 that we have seen that there is any danger in giving this  
22 product to anybody.

23 So, I just want to hear what you --

24 DR. DONATUCCI: Well, let me first give you my  
25 opinion, which I didn't give it, I just summarized what the

1 panel felt. My personal opinion about pediatrics is that  
2 there are two issues. First, the bulking agent can be used  
3 for incontinence in the pediatric population. There is also  
4 a potential use as a bulking agent for reflux.

5 DR. BENNETT: But the indication is ISD, so that  
6 is different.

7 DR. DONATUCCI: But that has to be clear.

8 DR. BENNETT: Well, it will be clear in the  
9 labeling I would assume. It's not an anti-reflux product.

10 DR. DONATUCCI: You want me to restate --

11 DR. BENNETT: I just want to hear what you think  
12 the opinion of the panel is concerning the pediatric. I  
13 would also like to know the pediatric age group, I would  
14 like you to define the age of a pediatric age group, as  
15 well.

16 DR. A. KALLOO: Dr. Kalloo, any comments?

17 DR. N. KALLOO: Pediatrics can go all the way up  
18 to 21, but again, you can buy beer at 18, and you can vote  
19 at 18, and you can use sometimes puberty as the cutoff. If  
20 you have got an adult body, then sometimes you can do adult  
21 things. I know for certain hospitals, if they are over a  
22 certain weight, they can be 14 and 110 pounds, but if you  
23 are over a certain weight, you can go on the adult ward.

24 So, the definition sort of can be skewed.

25 DR. A. KALLOO: What about the use of bulking

1 agents in the pediatric --

2 DR. N. KALLOO: For the use of bulking agents, I  
3 would probably say puberty.

4 DR. DONATUCCI: But the summary of the panel  
5 appears to be -- and this is my concept of the summary of  
6 the panel -- I will restate it now taking into account what  
7 Dr. Diamond said.

8 The indication should be for adults and there  
9 should be no comment about excluding children. There should  
10 be a comment about the absence of data with children.

11 DR. A. KALLOO: Good.

12 DR. HUNTER: And pregnancy.

13 DR. DIAMOND: Women desiring.

14 DR. A. KALLOO: Question 2. Given the rates of  
15 improvement in effectiveness outcome measures and the rates  
16 of adverse events observed during the clinical trial and  
17 reported in the PMA, does the panel believe that the  
18 Durasphere Implant has a favorable risk/benefit profile?

19 Dr. Foote.

20 DR. FOOTE: I think yes although the rates of  
21 bladder irritative symptoms and urinary retention were  
22 higher in the Durasphere arm, those effects were self-  
23 limited and did resolve in a reasonable period of time.

24 DR. HUNTER: Yes.

25 DR. A. KALLOO: Dr. Diamond.

1 DR. DIAMOND: In most cases I don't think there  
2 was much difference with the control group other than two  
3 items that were mentioned, so I would say that it does, yes.

4 MS. NEWMAN: Yes.

5 DR. VERTUNO: Yes.

6 DR. STEINBACH: Yes.

7 DR. BENNETT: Yes.

8 DR. DEITRICK: Yes.

9 DR. HAWES: Yes.

10 DR. N. KALLOO: Yes, for the short term.

11 DR. DONATUCCI: Yes as an individual, and yes for  
12 the committee. In summary, I think the panel believes the  
13 answer to the question is that the profile is favorable and  
14 in favor of it.

15 DR. A. KALLOO: Question 3. Is the post-approval  
16 study outlined in the PMA adequate to document the long-term  
17 safety and effectiveness of the Durasphere implant?

18 Dr. Foote.

19 DR. FOOTE: I would have to defer on this because  
20 I didn't have the chance to read the entirety of that, and I  
21 would like to review that while you are going around.

22 DR. HUNTER: I would match the control. Whatever  
23 the control did historically with the FDA -- and I can't  
24 remember what that was -- but I would match that.

25 DR. DIAMOND: I have a couple thoughts. First of

1 all, I think it is hard to know, to be able to answer this  
2 until we know for sure what the labeling and full  
3 indications that we are going to approve are going to be.

4 But with that caveat, I think 188 patients is  
5 probably too small. I think it also needs to be segregated  
6 into different populations, such as women who have had prior  
7 surgical procedures, women who have had hysterectomies, and  
8 perhaps some other groups, as well, that if we had further  
9 discussion, we can identify.

10 DR. A. KALLOO: Ms. Newman.

11 MS. NEWMAN: I think it is adequate.

12 DR. VERTUNO: I think it's adequate, as well, but  
13 I would like to see some data on the populations that we  
14 have discussed.

15 DR. A. KALLOO: Specifically?

16 DR. VERTUNO: Men, women of childbearing age, and  
17 young people.

18 DR. STEINBACH: I agree with Dr. Vertuno.

19 DR. BENNETT: I wasn't privy to the post-approval  
20 study because I am the industry rep, but I would not  
21 recommend what Dr. Hunter recommended because that study,  
22 number one, was designed because of the potential  
23 immunologic aspects of GAX collagen, and that does not  
24 apply, and the bar to the Contigen study is a totally  
25 different study. It's looking for rheumatologic disease, et

1 cetera, so it certainly has no application whatsoever to  
2 this product. So, those are my comments.

3 DR. DEITRICK: I think it's adequate.

4 DR. HAWES: I think it is adequate with again the  
5 comments that were made regarding the specific groups that  
6 we are concerned with, i.e., the question of whether they  
7 should address the pediatric population and women of  
8 childbearing age. Otherwise, I think it is adequate.

9 DR. N. KALLOO: I think my concern still lies with  
10 those patients who have total incontinence, and I think we  
11 need more numbers and more long-term data on those specific  
12 patients.

13 DR. FOOTE: After my review of the PMA, I would  
14 say yes with the comments that were made earlier.

15 DR. DONATUCCI: I think it's adequate personally  
16 and I think that, in summary, in terms of the safety  
17 question, I think the panel's feeling is that the post-  
18 approval study is adequate, but there is definitely a  
19 feeling that the panel would like to see more data on  
20 subpopulations in that study.

21 DR. A. KALLOO: Would you just go over the  
22 subpopulations?

23 DR. DONATUCCI: The subpopulations that have been  
24 mentioned earlier are patients with Grade III incontinence,  
25 we previously mentioned -- that's in terms of effectiveness,

1 we want more data on the Grade III population in terms of  
2 safety -- we previously mentioned pediatric population and  
3 women of reproductive age.

4 DR. STEINBACH: And men.

5 DR. DONATUCCI: Men, yes.

6 DR. HUNTER: Dr. Donatucci, so you think there  
7 should be more study, a long-term study on patients that  
8 really aren't even indicated for use of the drug, you are  
9 asking the company to do studies that they didn't really try  
10 to get approval for?

11 DR. DONATUCCI: I was just summarizing the panel.

12 DR. HUNTER: Oh, okay.

13 DR. DONATUCCI: In fact, I think it's adequate as  
14 it is personally.

15 DR. A. KALLOO: Okay. Question 4. Should  
16 physician training be required prior to use of the  
17 Durasphere Implant?

18 DR. FOOTE: My answer is yes, I think as an  
19 initial requirement, physicians should have evidence of  
20 training and expertise in the use of the cystoscope, and  
21 then there should be some documentation of their ability to  
22 perform the injection. Although many urologists are  
23 familiar with the use of Contigen, for example, not all  
24 physicians are, and I think if a physician does not have  
25 that type of experience, some type of training should be

1 documented.

2 DR. HUNTER: Well, I guess I am biased because I  
3 am a urologist, but this is a very easy technique and maybe  
4 if they could look at a video, let's say they looked at a  
5 video, that would be sufficient. It's not a difficult  
6 procedure.

7 DR. DIAMOND: I would be in favor of training.

8 MS. NEWMAN: I think that if they are trained in  
9 cystoscopy, I feel that is adequate, too.

10 DR. VERTUNO: I will defer to my urologic brethren  
11 on this one, but I think anybody trained in urology should  
12 be able to do this quite readily.

13 DR. A. KALLOO: Dr. Diamond.

14 DR. DIAMOND: Part of the reasons I think training  
15 is required is that all these procedures, once this product  
16 were to be approved, would not necessarily be done by  
17 urologists. Many might be done by gynecologists, and while  
18 there are some urogynecologists who are extremely familiar  
19 with other bulking agents and maybe others who are not, and  
20 for them I think training aids would be important.

21 I think another question that might come up at  
22 some point in the future, would this be a thing that a  
23 physician assistant or a nurse practitioner might do, and  
24 again, then, the level of training of individuals who are  
25 going to be utilizing the device, I think is important.

1 DR. A. KALLOO: But specifically, we are asking  
2 about physician training, number one, and secondly, do you  
3 think that the ability to do cystoscopy qualifies in itself  
4 as was mentioned? Dr. Diamond, do you?

5 DR. DIAMOND: Well, I would like someone to be  
6 able to do more than diagnostic cystoscopy.

7 DR. FOOTE: And I would agree, because there are a  
8 lot of, for example, gynecologists who do do diagnostic  
9 cystoscopy, but are not familiar at all with doing things  
10 therapeutically through cystoscope, and I think that having  
11 a requirement for -- and it's hard to be specific about  
12 that, but clearly, for someone who has not been trained in  
13 Contigen, for example, there were specific training  
14 protocols for Contigen injection, for example, and if  
15 someone had passed that, I think that that would be  
16 adequate, but if someone did not go through that, I think  
17 that it would be prudent to make sure that the success rates  
18 that are experienced in the community are the same ones that  
19 were experienced in the study to have some type of training  
20 documented.

21 DR. STEINBACH: I have no competence with this  
22 question.

23 DR. BENNETT: I would hate to see us revisiting  
24 what happened probably seven or eight years ago with the  
25 anger and the angst that occurred both at the AUA level and