

1 minutes as I review the safety and effectiveness  
2 profile of the transitional Class III absorbable  
3 hemostatic devices manufactured by Integra  
4 LifeSciences Corporation, and recommendations for a  
5 guidance document for special controls for  
6 absorbable hemostatic agents if reclassified to  
7 Class II.

8           Transitional Class III devices--the  
9 hemostatic agents manufactured by Integra  
10 LifeSciences, PMA products are Collastat absorbable  
11 collagen hemostatic agent, a PMA that was approved  
12 in December, 1980's, and Helistat absorbable  
13 collagen hemostatic agent, approved in November,  
14 1985. The Helistat PMA is a direct cross-reference  
15 to the Collastat PMA.

16           The indications for use for both products  
17 are indicated in surgical procedures, other than  
18 ophthalmological and urological surgery, as an  
19 adjunct to hemostasis when control of bleeding by  
20 ligature or conventional procedures is ineffective  
21 or impractical.

22           Currently, hemostatic agents, absorbable  
23 hemostatic agents used in surgery are classified as  
24 Class III, requiring a premarket approval  
25 application. In the European Union they are

1 classified as Class III under two different rules,  
2 Rule 8, any products that have a biological effect  
3 or be wholly or mainly absorbed, and the collagen  
4 hemostatic agents, because they are derived from  
5 animal tissue, are also considered Class III.

6 In Canada they are Class III or Class IV.  
7 Under Rule 1, Class III if they are wholly  
8 absorbed, and Rule 14, again, if they are products  
9 of animal origin.

10 In Japan, similar classification and data  
11 requirements as the FDA and European Union.  
12 Australia, similar classification and data  
13 requirements; In the rest of the world, most  
14 countries have the similar classification and data  
15 requirements as FDA and European Union, and there  
16 are some countries that do classify these agents as  
17 pharmaceuticals.

18 Safety profile--we concur with FDA when  
19 this first came out there is a long history of  
20 safety and difference of these products. There is  
21 a 21-year history of these absorbable collagen  
22 hemostatic agents, and estimated over 10 million  
23 surgical procedures. The adverse event rate or  
24 Medical Device Report rate is less than 0.0001  
25 percent. For the products manufactured by Integra

1 LifeSciences, in 21 years there have been no  
2 product recalls in the history of this product  
3 line.

4           But I would like to draw your attention to  
5 the data that we submitted in the PMA and also  
6 various PMA supplements for both of these PMAs.  
7 For biocompatibility studies the list is very  
8 lengthy: intracutaneous toxicity, dermal  
9 sensitization, cytotoxicity, acute subchronic and  
10 chronic toxicity, intramuscular toxicity, hemolysis  
11 studies, pyrogenicity studies, genotoxicity  
12 studies, immunogenic potential, implantation  
13 studies, absorption studies, mechanical testing  
14 looking at swellability, compression, stiffness and  
15 swelling and viral safety studies.

16           Animal studies looking at rate of  
17 absorption, foreign body reaction, incidence of  
18 infection, incidence of adhesion formation,  
19 incidence of any other tissue reaction; hemostatic  
20 studies in animal spleen models compared to control  
21 agents; infection model study looking at infection.

22           Multicenter clinical trial, randomized,  
23 controlled study at 10 investigational sites. This  
24 was the original PMA with a total of 550 patients  
25 in the areas of general, cardiovascular,

1 neurosurgical, obstetrics/gynecology, urological,  
2 burn and plastic surgery procedures. The control,  
3 other marketed hemostatic agents. The parameters  
4 evaluated were time to hemostasis; adherence to  
5 site; pliability; handling; overall procedure and  
6 postoperative evaluations, adverse events.

7           Manufacturing of these products is very  
8 critical. Products are manufactured in compliance  
9 with FDA quality system regulations, good  
10 manufacturing practices. At our last FDA  
11 inspection, which was last year, 2001, we had what  
12 is called FDA 483 observations. The facility is an  
13 FDA registered ISO 9001 certified facility. As  
14 part of the PMA process there is a pre-approval  
15 inspection prior to manufacturing these products,  
16 and routine inspections for compliance with FDA  
17 regulations, and annual reporting requirements for  
18 any changes in the manufacturing or quality  
19 procedures that aren't required to be submitted  
20 under a PMA supplement and, of course, PMA  
21 supplements.

22           Some of the conditions of approval:  
23 restriction on the sale and distribution of the  
24 device; requirement to add a prominent display of  
25 warnings, hazards and precautions necessary for

1 safe and effective use to labeling and advertising;  
2 medical device reporting requirements, which is  
3 common to most medical devices; and submission of  
4 annual reports to FDA.

5           Recommendations to FDA regarding  
6 reclassification: We recommend strongly that if  
7 FDA reclassifies absorbable hemostatic agents from  
8 Class III to Class II that it includes special  
9 controls. Class II devices are defined in section  
10 5133 of the Food, Drug and Cosmetic Act to include  
11 any device for which reasonable assurance of safety  
12 and effectiveness can be obtained by applying  
13 special controls.

14           Only general controls will apply to Class  
15 II devices until special controls are established  
16 by regulation. Special controls can include  
17 special labeling requirements, mandatory  
18 performance standards, patient registries and  
19 postmarket surveillance.

20           Reclassification should only occur with  
21 the issuance of an FDA guidance document to assure  
22 continued safety and effectiveness profile. The  
23 current FDA approved PMAs, PMA supplements remain  
24 in place and viable, and confidential information,  
25 specifically manufacturing data, remain

1 confidential.

2           Guidance document recommendations for an  
3 absorbable hemostatic agent--Basic information on  
4 the company, name, address, FDA establishment  
5 registration; description of the device, all  
6 significant components of the device; principle of  
7 action of each of the device components.

8           If the device is collagen, to use FDA  
9 guidance document, medical devices containing  
10 materials derived from animal sources, looking at  
11 the type of collagen, tissue and species, country  
12 of origin, processing, viral inactivation studies,  
13 BSE/TSE risk analysis.

14           Biocompatibility testing in accordance  
15 with FDA guidance, G95-11, use of international  
16 standard ISO 10993, biological evaluation of  
17 medical devices, part I, evaluation and testing,  
18 looking at the following testing: dermal  
19 irritation; sensitization assay; cytotoxicity;  
20 acute subchronic and chronic toxicity because these  
21 products are absorbed and left permanently in the  
22 body; hemocompatibility, hemolysis; pyrogenicity;  
23 mutagenicity studies; immunogenic potential;  
24 absorption; implantation studies and any other  
25 studies dependent on the biomaterial being

1 evaluated; in vitro hemostasis studies.

2 For animal studies the device should be  
3 evaluated in implantation studies to look at rate  
4 of absorption; foreign body reaction; incidence of  
5 infection; incidence of adhesion formation;  
6 incidence of any other tissue reaction.

7 Hemostatic studies in an animal spleen model should  
8 evaluate hemostatic properties compared to control  
9 agents.

10 Clinical experience--summary of any  
11 clinical experience. The sponsor must demonstrate  
12 that the hemostatic agent will perform as safely  
13 and effectively as another legally marketed  
14 absorbable hemostatic device. Clinical data for  
15 hemostatic agents composed of a material which has  
16 not been previously used as an implantable,  
17 absorbable, hemostatic agent should be provided  
18 from a multicenter clinical trial. Clinical data  
19 should demonstrate that the hemostatic agent  
20 performs similarly when compared to another legally  
21 marketed absorbable hemostatic device.

22 If a clinical trial is required, clinical  
23 studies should evaluate time to hemostasis;  
24 adherence to site; ease of handling and  
25 application; postoperative evaluations such as

1 postoperative bleeding, infection, hematoma  
2 formation, wound dehiscence and adverse events.

3           Device sterilization information should  
4 include the method of sterilization; validation  
5 method for the sterilization cycle; sterility  
6 assurance level to be achieved; the method for  
7 monitoring the sterility of each production lot;  
8 and description of the packaging to be used to  
9 maintain sterility.

10           If radiation sterility is used, the dose  
11 should be specified. If the method of  
12 sterilization is ethylene oxide, the maximum levels  
13 of ethylene oxide, ethylene chlorohydrin and  
14 ethylene glycol residues which remain on the device  
15 should be identified. Residual levels of ethylene  
16 oxide, ethylene chlorohydrin and ethylene glycol  
17 which remain on the device following EtO  
18 sterilization should comply with the maximum limits  
19 proposed in the Federal Register of June 23, 1978  
20 or ANSI/AMI/ISO guidance 109993-7, 1995, biological  
21 evaluation of medical devices, Part 7, ethylene  
22 oxide sterilization residuals. A sterility  
23 assurance level should be achieved because these  
24 products are left in and are absorbed.

25           For pyrogenicity testing the pyrogen

1 levels of the final sterilized device should be  
2 less than 0.06 endotoxin units/ml.

3 For product expiration dating, the data  
4 supporting the expiration date for the product  
5 should be submitted. Data should be collected from  
6 three lots of product. Stability studies should  
7 monitor the critical parameters of a device to  
8 ensure that it will perform safely and effectively  
9 during the entire shelf life.

10 Manufacturing should be in compliance with  
11 FDA quality system regulations. The submission  
12 should contain information on all device reagents  
13 and processing steps; packaging of the device;  
14 final device release specifications; product  
15 release testing specifications; residual levels of  
16 manufacturing agents; residual levels of heavy  
17 metals; pyrogen levels; and sterility.

18 In summary, absorbable hemostatic agents  
19 manufactured by Integra LifeSciences have a 21-year  
20 history of safety and effectiveness.  
21 Reclassification from Class III to Class II should  
22 only be with special controls and an FDA guidance  
23 document in place to ensure continued safety and  
24 effectiveness profiles. Current approved FDA PMAs  
25 for absorbable hemostatic agents should remain in

1 place. Thank you.

2 DR. WHALEN: Questions from the panel for  
3 Ms. O'Grady? Just to reemphasize your conclusion,  
4 somewhat significantly different from your other  
5 colleagues from industry, you are making the  
6 recommendation that you would find it acceptable to  
7 reclassify it as long as the appropriate controls  
8 were in place and with a guidance document?

9 MR. O'GRADY: That is correct. I think  
10 there is an extensive history of safety and  
11 effectiveness for these products, however, I do  
12 feel strongly that if they are reclassified to  
13 Class II there are very important considerations,  
14 and that reclassifying to Class II these products  
15 will only have general controls unless there is an  
16 issuance at the same time of a guidance document.  
17 These are left in the body and are absorbed and  
18 very critical postoperative reactions can occur.  
19 There has been a long safety and effectiveness  
20 profile, I do believe, due to the careful studies  
21 that have been conducted on these procedure lines,  
22 and careful manufacturing of the products, and  
23 monitoring of these processes.

24 DR. WHALEN: Any other questions?

25 [No response]

1 Thank you, Ms. O'Grady.

2 MS. O'GRADY: Thank you.

3 DR. WHALEN: We will continue now with the  
4 presentation from the FDA, to be done by Dr.  
5 Krause.

6 **FDA Presentation**

7 DR. KRAUSE: Good afternoon, Mr. Chairman,  
8 distinguished panel members and members of the  
9 industry. Thank you for taking this time to advise  
10 the FDA in regards to the reclassification of  
11 absorbable hemostatic agents and dressing devices.

12 We are asking your recommendation  
13 regarding our proposal to down-classify absorbable  
14 hemostatic agents and dressing devices from Class  
15 III to Class II. First, I will review the products  
16 and rationale for our proposed reclassification.  
17 Then, I will ask the panel several questions for  
18 discussion. After my presentation and your  
19 discussion, Ms. Shulman will take you through the  
20 formal reclassification work sheet.

21 This is the present definition of an  
22 absorbable hemostatic agent or dressing. An  
23 absorbable hemostatic agent or dressing is a device  
24 intended to produce hemostasis by accelerating the  
25 clotting process of blood. It is absorbable and,

1 at the present, it is a Class III.

2 We refer to the absorbable hemostatic  
3 agents as transitional devices. We call them  
4 transitional devices because at the time that the  
5 Medical Device Amendments were added to the Food,  
6 Drug and Cosmetic Act, in 1976, these products were  
7 regulated as drugs. They were then transferred to  
8 device regulations since these were felt to be more  
9 appropriate for these types of devices. The  
10 absorbable hemostatic agents, sutures, a number of  
11 other products fit into this transitional product  
12 classification. All transitional products were  
13 automatically classified as Class III medical  
14 devices. This includes suture, which was  
15 previously reclassified to Class II about ten years  
16 ago.

17 I hope you all have your magnifying  
18 glasses! These are absorbable hemostatic agent and  
19 dressing products which were submitted for approval  
20 as drugs. The first one on the list is Oxycel,  
21 which Dr. Paulson alluded to in his discussion of  
22 Surgicel. It was approved as a drug in September  
23 of 1945. Surgicel was then approved in 1960.  
24 Avitene was approved in 1976, actually I think by  
25 Center for Devices. Gelfoam was also approved by

1 Center for Devices in 1983. However, Gelfoam has  
2 been on the market since 1945, or pretty close to  
3 that.

4 Other products which were approved under  
5 device regulations and were submitted as devices  
6 are a second form of Avitene, which was approved in  
7 1980. Collastat, which Ms. O'Grady discussed, was  
8 approved in 1981. The Superstat, which is no  
9 longer marketed, was approved in 1982. Instat,  
10 which is still marketed by Ethicon, in 1983.

11 I might add that all of these products, up  
12 until Novacol, were taken to the General and  
13 Plastic Surgery Devices Panel for review. That  
14 includes Helistat which, as Ms. O'Grady said, was  
15 approved in 1985 but referred to the 1981 PMA for  
16 Collastat. Novacol was approved in 1986.  
17 Hemostagene, I think was originally marketed under  
18 the name of Actafoam but is not presently marketed  
19 in the United States, was approved in 1985. This  
20 was the first of these products that did not go to  
21 the General and Plastic Surgery Devices Panel for a  
22 recommendation. Surgifoam was approved in 1999, as  
23 you heard from Ms. Bobak.

24 Recently we have approved two other  
25 products as absorbable hemostatic agents. These

1 products include licensed bovine thrombin as a  
2 component. They are considered combination  
3 devices. One was FloSeal, which was approved in  
4 December of 1999 and the second was CoStasis, which  
5 was approved in June of the year 2000.

6 Adverse events--I don't know if anybody  
7 can see these but I can go through them real quick.  
8 The thing that is important here is that I asked  
9 our MDR people to give me a list of MDRs that were  
10 listed for these devices. I got a list of 115.  
11 MDR reporting has been required since 1996. Before  
12 that it was voluntary since, I think, about 1992.

13 I would say that in the last six years, as  
14 these products have been used in, you know, a  
15 million surgical procedures and that is a  
16 conservative estimate, of the 115 adverse events  
17 that were reported, 66 of them were for a device  
18 that is not an absorbable hemostatic agent and were  
19 put in the wrong place. They were for a femoral  
20 artery closure device that was used following  
21 femoral artery catheterization procedures. A  
22 number were for collagen products that are injected  
23 under the skin for wrinkle control. Some of them  
24 were for other collagen-containing devices. Of all  
25 the ones that I went through, 38, which is that

1 number up there which probably nobody can read,  
2 were for what we would call the absorbable  
3 hemostatic agents.

4           If you look up there, you can see that 21  
5 were for the products which we are looking to  
6 reclassify, which are those without licensed bovine  
7 thrombin; and 17 were with licensed bovine  
8 thrombin. So, of all the multitude of procedures  
9 where these devices have been used, there were 21  
10 MDR reports since, let's say, 1996. Now, we know  
11 that MDR reports are under-reported but this is  
12 still a very substantial number, or lack of a  
13 substantial number.

14           Going through the MDR reports and also  
15 through the literature which is published, I sent  
16 you some articles but there are hundreds of  
17 articles on these products. I have listed what are  
18 the most common potential risks and the potential  
19 control that we are looking for. These controls  
20 would be listed in a guidance document which would  
21 direct manufacturers as to how we would like to see  
22 the data presented to us.

23           The first potential risk would be  
24 uncontrolled bleeding, which could be controlled  
25 either with animal studies and/or clinical data.

1 The second risk would be hematoma. The third risk  
2 would be infection with fever; wound dehiscence.  
3 For some of these, if you look at the labeling for  
4 these products, you will notice that there is very  
5 specific labeling and that wound dehiscence can  
6 easily be avoided if you follow the instructions in  
7 the labeling. Foreign body reaction, inflammation,  
8 edema, granuloma and these could be controlled with  
9 animal studies, product labeling perhaps, clinical  
10 data.

11 Adhesion formation; failure to be  
12 absorbed. Again, most of these or many of these  
13 would be controlled using a guidance document which  
14 would direct for animal studies, potentially  
15 clinical studies, clinical data and also product  
16 labeling. I don't want to belabor these and go  
17 through them all individually.

18 There are some additional risks for  
19 products which include the licensed bovine  
20 thrombin. You notice that I am specific about  
21 licensed bovine thrombin. since we can't predict  
22 what new products are coming, we can only address  
23 products that have come through the PMA process.  
24 The only ones that have come through the PMA  
25 process that include anything besides the

1 absorbable hemostatic device are two products which  
2 we have approved, which include licensed bovine  
3 thrombin. The additional risks with those products  
4 include allergic reactions, such as antibodies to  
5 collagen; gelatin thrombin, etc. and potential  
6 antibody cross-reactivity to bovine Factor Va,  
7 which cross-reacts with human Factor Va, which can  
8 result in coagulopathy. This is specifically  
9 mentioned in the thrombin labeling and the  
10 information can be obtained there.

11 The second problem in some of the MDR  
12 reports that I found is that people sometimes have  
13 difficulty assembling products which include bovine  
14 thrombin, or deploying them because if they don't  
15 prepare the apparatus correctly there can be  
16 clogging because the thrombin fairly quickly causes  
17 coagulation and can clog the device.

18 The FDA's proposal is that the agency is  
19 proposing that the absorbable hemostatic agents and  
20 dressing devices that do not contain bovine  
21 thrombin may be reclassified into a lower  
22 classification, which is Class II, special  
23 controls, and that the special control employed, in  
24 this case, would be a detailed guidance document.

25 The present CFR, which is Code of Federal

1 Regulations, listing for absorbable hemostatic  
2 agents and dressings are an absorbable hemostatic  
3 agent or dressing as a device intended to produce  
4 hemostasis by accelerating the clotting process of  
5 blood. It is absorbable; presently Class III. It  
6 requires PMA or PDP.

7           What we are proposing is an absorbable  
8 hemostatic agent or dressing as a device intended  
9 to produce hemostasis by accelerating the clotting  
10 process of blood. It is absorbable. That has not  
11 changed. The classification would be Class II for  
12 those that do not include licensed bovine thrombin  
13 and Class III that do contain licensed bovine  
14 thrombin.

15           Again, we cannot predict what products are  
16 coming in the future so we cannot include them in  
17 this reclassification. Those that do include the  
18 licensed bovine thrombin, we continue to require  
19 PMA and those that are reclassified to Class II  
20 would now require a 510(k).

21           That is the end of my presentation. I  
22 just wanted to read to you the indication for use  
23 that we normally apply to these products, which is  
24 that they are for use as an adjunct to hemostasis  
25 when ligature and other conventional methods are

1 ineffective or impractical, and there can be some  
2 variations on that but it is the same as the slide  
3 that Ms. O'Grady put up for you to see. Are there  
4 any questions?

5 DR. WHALEN: Dr. Krause, you speculated  
6 conservatively that a million surgeries may have  
7 been done over the period that these adverse events  
8 were recorded, with roughly equivalent, 21 versus  
9 17, without thrombin and with thrombin. Do you  
10 have any idea what the breakdown denominator would  
11 be without thrombin and with thrombin among those  
12 million operations?

13 DR. KRAUSE: The products with thrombin  
14 have only been approved since '99. We had one in  
15 '99 and one in 2000. So, I would say that the  
16 denominator for those products would be quite a bit  
17 smaller than for the products without thrombin.

18 DR. WHALEN: Although the incidence of the  
19 adverse events reported is low for both, it might  
20 be substantially higher for those with thrombin in  
21 view of that.

22 DR. KRAUSE: Yes, except that, again, 17  
23 out of--maybe Debbie can give us an idea of how  
24 much FloSeal is on the market, but 17 would still  
25 be a fairly small number, less than one percent I

1 am sure.

2 MS. BROWN: Let me just comment, I haven't  
3 been with the company for a year so I am not  
4 current on the statistics but I was with the  
5 company that manufactured FloSeal. But one of the  
6 things I noticed is that one of the MDR categories  
7 looked like it was sinus usage and I know that  
8 FloSeal was used in ENT maybe more than the other  
9 use allocations. So, it is possible that it just  
10 has to do with the area of the body where it is  
11 being used.

12 DR. KRAUSE: Right, there were about five  
13 FloSeal MDR reports for sinus infection.

14 DR. WHALEN: Dr. Choti?

15 DR. CHOTI: Dr. Krause, if you would just  
16 clarify for me the distinction between these. I am  
17 stuck a little bit on the bovine thrombin. Is that  
18 because it is a biologic? You say it is a combined  
19 product device and why the bovine thrombin? Why  
20 not the fibrinogen or whatever other things in  
21 these new? Why is this the one thing that you have  
22 kind of categorized as distinctive?

23 DR. KRAUSE: Sure, fibrin sealant is  
24 considered a biological. It is regulated by the  
25 Center for Biologics. We don't regulate those.

1 So, that would be something that they would take  
2 care of. Aprotinin is a part of a fibrin sealant.  
3 We have focused on the licensed bovine thrombin for  
4 the simple reason that the only products we have  
5 seen that are combinations included only licensed  
6 bovine thrombin, nothing else. We have never seen  
7 anything with aprotinin. We have never seen  
8 anything with coagulation Factors V, VI, VII or  
9 VIII or any of those types of things. We have only  
10 seen product with the licensed bovine thrombin and  
11 we got a co-review on those from the Center for  
12 Biologics.

13 DR. CHOTI: Then I am confused. The  
14 FloSeal product has the gelatin?

15 DR. KRAUSE: Yes, it is bovine gelatin  
16 combined with licensed bovine thrombin and a  
17 determination was made that it was a medical device  
18 so it was reviewed here, or Center for Devices.

19 **Panel Discussion and FDA Questions**

20 DR. WHALEN: Other questions for Dr.  
21 Krause? Seeing none, we will proceed to have Dr.  
22 Krause read the FDA questions, keeping in mind once  
23 again as we did earlier this afternoon that the  
24 panel will not immediately respond to them. We  
25 will have a brief general discussion of the issue

1 at hand and then follow with our deliberations with  
2 answering the questions. Dr. Krause?

3 DR. KRAUSE: We have three questions for  
4 you regarding the reclassification for absorbable  
5 hemostatic agent and dressing devices.

6 The first question says, please discuss  
7 the proposed reclassification of the absorbable  
8 hemostatic agent and dressing. Please also discuss  
9 what descriptive information and intended use  
10 should be included in the classification  
11 identification.

12 Second question, please discuss the risks  
13 to health for the absorbable hems agent and  
14 dressing devices.

15 Third question, are there any other risks  
16 to health for these devices that have not been  
17 identified? Thank you.

18 DR. WHALEN: Thank you, Dr. Krause. The  
19 panel will now start with general deliberation with  
20 a brief review of the entire topic at hand before  
21 directly addressing the FDA questions. Certainly  
22 all surgeons find hemostasis important. The  
23 surgical oncologist is at the top of the table, so  
24 Dr. Choti?

25 DR. CHOTI: Well, just to summarize again,

1 this is a class of devices that is absorbable, that  
2 achieves hemostasis. I think it has an extremely  
3 long history of use. The safety record, it appears  
4 to me as though it is quite good.

5           The one issue is that these are different  
6 products that are kind of grouped together. The  
7 processing is different. The products are  
8 different. Some are bovine; some are porcine; some  
9 are cellulose and the manufacturing processes are  
10 different. Perhaps the definition that we have  
11 come up with, which is absorbable hemostatic  
12 products, is somewhat non-specific. So, I think  
13 that it is important that new similar products as  
14 they are developed need to be carefully regulated  
15 if they are to be placed in this class. That would  
16 be one concern, that these are not all really the  
17 same devices.

18           Saying that, I do think that this is a  
19 long track record. I think it makes a lot of sense  
20 to reclassify them as we are discussing today.

21           DR. WHALEN: Dr. Dubler?

22           DR. DUBLER: As long as the controls were  
23 specific to the different sorts of materials that  
24 we are addressing, if there was the flexibility in  
25 reclassifying from Class III to II to take into

1 account the huge variability in structure of these  
2 and manufacturing, then it seems to me to be  
3 justified to move from III to II.

4 DR. WHALEN: Dr. McCauley?

5 DR. MCCAULEY: I agree with the two  
6 comments. I think the two points that I kind of  
7 get stuck on, and the first really relates to the  
8 variability in the structure and nature of these  
9 products and I think if we, indeed, classify them  
10 to Class II products then we have to have something  
11 that is very specific, not necessarily for each  
12 product but for each subgroup of products that  
13 comes through with similar structure.

14 The second issue really still relates to  
15 the thrombin. At this point, looking at the data,  
16 even if the N is a little smaller for the group  
17 that uses the bovine thrombin, I am not sure that  
18 really poses such a tremendous risk.

19 DR. WHALEN: Dr. Doyle??

20 DR. DOYLE: I am interested in the  
21 manufacturers' desire. All of them seem to wish  
22 them as classification of III, at least two of them  
23 said specifically with guidelines. I guess I don't  
24 understand why we would wish to classify it less  
25 restrictively. I don't understand their reticence

1 to have them reclassified, I guess.

2 DR. WHALEN: Do you just wish that to be a  
3 comment or do you want a specific question of  
4 another panel member or manufacturer?

5 DR. DOYLE: If someone could explain to me  
6 why they are reticent to have them reclassified.

7 DR. WHALEN: Is there anyone on the panel  
8 that wants to?

9 DR. MCCAULEY: I have a theory. It is  
10 possible that if you make it less regulated that it  
11 will make it more possible for competing products  
12 to be generated. So, there is a little bit of a  
13 protective situation with keeping it Class III.

14 MS. BROWN: I would like to make a comment  
15 about that. The clinical programs that have gone  
16 along with these products have been pretty big  
17 clinical programs. In general, they have been  
18 large randomized studies of 300 patients. The  
19 manufacturing processes are detailed and carefully  
20 reviewed in premarket applications that come in to  
21 FDA for the products. So, the track record that is  
22 being reviewed here is a track record that comes  
23 from pretty extensive review of the manufacturing  
24 and the preclinical and clinical work that is done.  
25 So, I think it is fair to say that the

1 manufacturers that commented on that are coming  
2 from the perspective of the reason their track  
3 record is good is because of that history.

4           Having said that, one of the manufacturers  
5 is saying that if there are adequate controls put  
6 in place and adequate guidance documents, she can  
7 probably achieve that same level of control with a  
8 510(k) process.

9           DR. WHALEN: Dr. DeMets?

10           DR. DEMETS: Well, the problem I am having  
11 is not seeing what the guidance document might look  
12 like, I am not familiar with those, but I think  
13 before I would be favorable to change something I  
14 would like to know what the content, the rigor and  
15 the details of that would be.

16           DR. WHALEN: Any response by FDA in that  
17 regard?

18           DR. WITTEN: Well, I will just say two  
19 things. One is that Dr. Krause listed risks to  
20 health and special controls. Those would be some  
21 of the things that would be expanded upon in the  
22 guidance document.

23           The other question, of course, is really a  
24 question for the panel, which is, based on what you  
25 know about these products, how they work, what the

1 risks are, etc., do you think special controls can  
2 be identified and can you make any recommendations  
3 about special controls? In other words, part of it  
4 is we have sketched out what in our minds would be  
5 a guidance document, and then the second half of it  
6 is we would like to know whether controls can be  
7 identified and what your view is on what they would  
8 be.

9 DR. WHALEN: Dr. Chang?

10 DR. CHANG: I have similar sentiments to  
11 Dr. DeMets' in that in a guidance document can  
12 these controls be as rigorous as that which is  
13 required from manufacturers or sponsors submitting  
14 a PMA? We like the track record; it is impressive.  
15 Even though the makers of Gelfoam had it available  
16 from 1945 and just had the PMA in the 1980's, they  
17 did get around to making the documentation of their  
18 safe manufacturing practices. So, the question  
19 remains if written guidance documents are rigorous  
20 to ensure continued high standards, then it would  
21 seem logical to reclassify to Class II for these  
22 products.

23 My other question, and I don't know if  
24 there is an answer, is what about the monitoring?  
25 What about companies that submit an address in

1 Thailand or an address in Tibet? I mean, some  
2 place where it is not as easy to have a site visit,  
3 how easily would they get a 510(k) through FDA for  
4 marketing in the U.S.? There is that kind of  
5 question.

6 DR. WHALEN: Dr. Miller?

7 DR. MILLER: I think I have to  
8 congratulate the companies that have created these  
9 products and done such a great job in validating  
10 their effectiveness and safety. I think after all  
11 these years that is very well demonstrated, and I  
12 think it is reasonable to shift the product to a  
13 lower level as long as we can ensure that any other  
14 new products meet the standards that these have  
15 met.

16 DR. WHALEN: Dr. Newburger?

17 DR. NEWBURGER: I guess I am having  
18 trouble conceiving the application of these  
19 standards to new products because it is not clear  
20 to me what these standards are. These do have  
21 different mechanisms of action and even in products  
22 that have a similar mechanism of action they are  
23 used in different situations. I am concerned since  
24 these are used in critical situations  
25 intraoperatively that the slightest variation could

1 have really much more profound impact than we  
2 think. So, I am wondering how clear the guidelines  
3 really would be.

4 DR. WHALEN: Thank you, all. At this time  
5 we can begin to focus our discussion on the  
6 specific three FDA questions. If someone could  
7 again put them on the screen so everyone can see  
8 them at the same time? We will not yet refer to  
9 the reclassification questionnaire. That will be  
10 done later, after the open public comment period.

11 Considering safety and effectiveness for  
12 the devices, we will deliberate upon the answers to  
13 these three questions, the first of which is to  
14 discuss the proposed reclassification of the  
15 absorbable hemostatic agents and dressings. Also,  
16 discuss what descriptive information and intended  
17 use should be included in the classification  
18 identification. Dr. Dubler?

19 DR. DUBLER: I am having trouble  
20 understanding how to frame our choice. So, I would  
21 like to ask the FDA why did they think it would be  
22 a benefit to move it from a Class III to a Class  
23 II, and what do you think we lose if it stays as a  
24 Class III?

25 DR. WHALEN: Dr. Witten?

1 DR. WITTEN: Well, just in general, we try  
2 to regulate things in the lowest classification  
3 that we think we can reasonably do because the  
4 burden, both upon the sponsor and the agency, in  
5 terms of what we review and the amount of paperwork  
6 is, is different. So, it just part of our general  
7 mission to look at things in the class that has the  
8 lowest regulatory burden.

9 DR. DUBLER: I see. So, there is nothing  
10 about this that singled it out but in the general  
11 review of Class III devices?

12 DR. WITTEN: I didn't understand your  
13 question perhaps. You mean why these products?

14 DR. DUBLER: Exactly.

15 DR. WITTEN: These products because, as  
16 Dr. Krause has described, there is a long history  
17 and in our minds the risks are identified. Dr.  
18 Krause listed what the risks and what the controls  
19 would be. So in our mind there is an understanding  
20 of what we would need to do to put in a guidance  
21 document and the area appeared to be right for that  
22 kind of discussion.

23 DR. WHALEN: Dr. Witten, am I wrong in  
24 saying it is not just the way FDA usually does  
25 things, but it is actually a legislative mandate to

1 keep it at the lowest possible level?

2 DR. WITTEN: Right, the least burdensome  
3 as possible.

4 DR. CHANG: And the second part of Dr.  
5 Dubler's question was is there anything lost by  
6 changing from Class III to Class II in terms of  
7 safety and effectiveness?

8 DR. WITTEN: Well, it is a different  
9 regulatory process, and I think as the  
10 manufacturers pointed out, we look at the details  
11 of the manufacturing. What we look at for a Class  
12 II is substantial equivalence. That is, is the  
13 device as safe and effective as the predicate in  
14 comparison to a product proposed for market? The  
15 way we would make that determination in terms of  
16 whether it is as safe and effective as the  
17 predicate device would in part be by looking at the  
18 guidance document and what types of consideration  
19 the guidance document suggest that we take into  
20 account in our review, and also the sponsor that  
21 they take into account in preparing their  
22 submission. So, what we would look at would be the  
23 guidance document plus any other information. You  
24 know, we look at the guidance document and a number  
25 of things and the marketing information which would

1 be a comparison of that device to a predicate  
2 device. In general, we would expect to see more or  
3 less information depending on how different that  
4 product was from the predicate. Whereas, for a  
5 Class III device the manufacturer needs to provide  
6 ground-up information describing their product as  
7 safe and effectiveness.

8 Now, there are some other differences  
9 also. I don't want to go into them in a lot of  
10 detail, but I will just mention that, for example,  
11 what the inspectional schedule would be could be  
12 different for the two products. That is, for a PMA  
13 the manufacturing site has to be inspected within a  
14 certain amount of time prior to approval, and the  
15 510(k)s are on a schedule. Also, we don't get the  
16 same annual reports. I mean, there certainly are  
17 reporting requirements for adverse events for  
18 510(k)s, just as for PMAs, but there aren't the  
19 same reporting requirements.

20 Actually, if you don't mind, it may be  
21 that our industry rep can probably add to this  
22 answer and that might also be able to help you.

23 MS. BROWN: I have taken gelatin- and  
24 collagen-based products through both the 510(k) and  
25 the PMA process, and probably the biggest

1 difference has been the level of clinical study  
2 that is required. The absorbable hemostatic agents  
3 went through a 300 patient clinical study, the  
4 510(k) products went through something more like  
5 30-50 patient clinical study. There tends to be  
6 more precedent--well, actually there is precedent  
7 with both. I think the FDA gets to apply more  
8 judgment to the 510(k) process than they do the PMA  
9 process. For the PMA process they are much more  
10 restricted in holding a higher standard and making  
11 sure that they do the same thing the next time that  
12 they did the last time. So, maybe with an  
13 absorbable hemostatic agent they think that a  
14 smaller clinical study would be appropriate but  
15 their hands may be tied if they have to do the  
16 large clinical study because that is what they did  
17 the last time. So, I think it is the clinical  
18 process. With these products, it is very possible  
19 that animal studies would be perfectly appropriate  
20 in determining effectiveness.

21 DR. DUBLER: Those are very helpful.

22 Thank you.

23 DR. WHALEN: Dr. Choti?

24 DR. CHOTI: A question regarding the  
25 exclusion of the bovine thrombin, in the future

1 510(k)s, if this is a Class II in which other  
2 combined products without bovine thrombin come down  
3 the market, how would that be handled or how would  
4 it be different? Let's say human thrombin or some  
5 other, would that be handled any differently if  
6 this is excluded? How would it be handled  
7 differently depending on how we look at it, or  
8 should we not be thinking about the future?

9 DR. WITTEN: Well, the short answer is,  
10 yes, we are not here to discuss future products.  
11 The slightly longer answer is that in general in a  
12 510(k) process if there is something in Class II  
13 and there is a new product that comes along, the  
14 sponsor could make their case--I mean new in terms  
15 of new technology, new material--the sponsor could  
16 make their case about substantial equivalence and  
17 then we would evaluate it. If a product is  
18 specifically in Class III, obviously, that product  
19 is already classified as a Class III product and  
20 wouldn't have the opportunity to submit a 510(k).  
21 But the short answer is we are not discussing other  
22 potential hypothetical products.

23 DR. WHALEN: Dr. DeMets?

24 DR. DEMETS: I am puzzled about something  
25 that has been said regarding the Class IIs. If

1 this was reclassified as Class II and a new product  
2 comes along that you compare to the predicate, and  
3 there were 30-50 patient studies as compared to 300  
4 patient studies, what puzzled me about that is that  
5 you can compare a new product to an existing  
6 product with, say, 50 patients for the sake of  
7 argument, and you know a lot less about that new  
8 product. In fact, the way we think about it in  
9 drugs is we call it control creep. That is, you  
10 keep approving products with slightly inferior  
11 results and pretty soon you are down to almost  
12 nothing. So, I am sitting here, puzzling how is  
13 this not getting into some of that same trap.

14           You asked whether we lose by this process.  
15 To me, so far, I am thinking we are losing rigor in  
16 the definitiveness of the new product being as good  
17 as or even perhaps better than what is out there if  
18 it winds up with smaller trials. Trying to show  
19 you are equivalent or as good as is the hardest job  
20 in clinical trials.

21           MS. BROWN: I would like to make a comment  
22 about that. There may be some history, however,  
23 with some of the absorbable hemostatic agents that  
24 don't have thrombin in them that have gone through  
25 the PMA process without that large trial. Maybe

1 David can comment on that.

2 DR. KRAUSE: To the best of my memory and  
3 looking at the previous PMAs, they all had fairly  
4 large trials. Surgifoam was the last one approved  
5 without thrombin and that had, I think, 300  
6 patients or more. The one before that was  
7 Hemostagene. That was about 300 patients and I  
8 think the one before that was Novacol and I think  
9 that had upwards of 300 patients. So, I don't  
10 remember any that had substantially less than 300  
11 patients.

12 MS. BROWN: Hasn't there been a Gelfoam  
13 equivalent that came through not too long ago?

14 DR. KRAUSE: The Gelfoam product that we  
15 looked at most recently was for a very specific  
16 indication of bone hemostasis. In other words,  
17 this was a product that was on the market that was  
18 approved for general use. The company wanted a  
19 specific indication for bone hemostasis and I  
20 believe they did 200 patients for that specific  
21 indication.

22 DR. WHALEN: Just to refocus the matter  
23 again, we are going to try to go around the panel  
24 to come up with answers to FDA's questions  
25 sequentially. Do you have something before that?

1 DR. MCCAULEY: Just a comment. I wonder  
2 if I could get some input from industry, from Dr.  
3 Paulson and Ms. Bobak. Ms. O'Grady gave a fairly  
4 detailed guidance document recommendation for  
5 absorbable hemostatic agents, which really kind of  
6 reads to me closer to a PMA than a 510(k), but I  
7 wanted to get your opinion, after reading this, is  
8 this the type of guidance document that would be  
9 acceptable in your eyes?

10 DR. WHALEN: Dr. Paulson?

11 DR. PAULSON: I think it is a very good  
12 start. Dr. DeMets I believe made a comment earlier  
13 that I would like to go back to, that it is hard to  
14 think about reclassification without knowing the  
15 specifics of it and then understanding how  
16 different products might perform to those  
17 standards. So, would it weed out some of the  
18 products that are manufactured under less stringent  
19 conditions? Would it weed out some of the products  
20 that are less effective than those currently on the  
21 market? So, while I think that is a good outline  
22 of types of considerations that should be  
23 addressed, it is hard to know whether they are  
24 really good enough without knowing how other  
25 products, that we would all agree might be

1 inferior, would perform against those standards.

2 But I think that is a good place to start.

3 DR. WHALEN: Ms. Bobak?

4 MS. BOBAK: Unfortunately, I have only  
5 known about this guidance from Ms. O'Grady for less  
6 than two hours so I don't feel safe about saying  
7 that that is adequate. What I would like to do is  
8 to go in depth with that suggestion and then see  
9 whether it is adequate. So, it is a good start  
10 but, from my point of view as a manufacturer of an  
11 animal-originated product, it is very important  
12 that the raw material has a requirement for  
13 endotoxins; that it has a requirement for level of  
14 microbes; that the manufacturing site has specific  
15 requirements and so forth. When Ms. O'Grady went  
16 through it I didn't have a good enough impact of  
17 all of these things that were mentioned. So, I  
18 would very much appreciate having time to look at  
19 it more in depth.

20 DR. WHALEN: Yes, Ms. Brown?

21 MS. BROWN: I have a question about the  
22 exclusion of the thrombin-containing products  
23 specifically from the definition. I understand  
24 that it is based on what is available currently.  
25 The concern I would have is that five years from

1 now, when this is the classification that stands,  
2 the thing that will stand out there is that  
3 thrombin-containing products have to stay in Class  
4 III and if another biologic agent came along and  
5 made the case to be substantially equivalent to  
6 those that are in Class II, what would happen?  
7 Would there be some kind of creep in the Class II  
8 area and then the FDA's hands would be tied but it  
9 is only the thrombin-containing product?

10 DR. WHALEN: Let me just interject before  
11 anybody answers that. There is one thought that I  
12 would like you to hold, and that is that what we  
13 are trying to get to is to sequentially have  
14 everybody comment upon reclassification. So, if we  
15 could do this maybe in a more orderly fashion and  
16 try to make sure we are out of here before 2100, it  
17 would probably go a little bit smoother. So,  
18 starting with Dr. Dubler, if you could comment upon  
19 the reclassification and, indeed, if you feel there  
20 should be reclassification, what elements of  
21 descriptive information should be in classification  
22 identification.

23 DR. DUBLER: I am not able to suggest,  
24 given my own expertise, what should be included in  
25 the classification specifically. I would assume

1 that if it shifted from Class III to Class II and  
2 if the guidance adequately addressed the specifics  
3 of manufacture, then it would be fine. I am just  
4 not sure if that is a question that we should move  
5 from III to II unless it were quite certain and  
6 unless industry agreed that, in fact, the shift  
7 from III to II would permit the maintenance of  
8 quality, I would be reluctant to make that shift.  
9 So, I would urge the FDA to establish some  
10 collaborative process in which they and industry  
11 would agree on the impact of the specific controls,  
12 and if that were agreed upon then I wouldn't oppose  
13 a shift from III to II. But simply to examine in  
14 the natural course of things what is in category  
15 III, with the idea that regulation should be  
16 limited as a matter of legislative intent, seems to  
17 me interesting but not dispositive.

18 DR. WHALEN: Forgive me but I am a surgeon  
19 and I think in very simple terms. You are against  
20 reclassifying at the present time?

21 DR. DUBLER: I am against reclassifying at  
22 the present time.

23 DR. WHALEN: Thank you. Dr. McCauley?

24 DR. MCCAULEY: I have to agree. I think  
25 that given the long history of safety and efficacy

1 of these products, if we reclassify these products  
2 without a rather stringent guidance document that  
3 is actually presented to these companies prior to  
4 classification, we are obligated to leave them as  
5 Class III.

6 DR. WHALEN: Very well. Dr. Doyle?

7 DR. DOYLE: I have the sense of buying a  
8 pig in a poke. I would like to see the guidelines  
9 too. I feel very much the same way as the others.  
10 I think it is sort of the chicken and the egg, and  
11 I would feel more comfortable, before we  
12 reclassified, if we knew what is going to be in  
13 place.

14 DR. WHALEN: Ms. Brown, your earlier point  
15 is being diminished by the current thread of  
16 thought, but assuming that doesn't continue, it  
17 would certainly be appropriate to reemphasize now  
18 the inclusion of the bovine thrombin.

19 MS. BROWN: I am not suggesting to include  
20 the thrombin-containing products in the  
21 classification process. I was more questioning the  
22 long-term implications of naming thrombin  
23 specifically just because down the road it is going  
24 to make it harder for the FDA--well, let's see, it  
25 may make it so the FDA can include other agents but

1 just exclude thrombin. So, I would just be  
2 concerned about that. I don't know how to fix it;  
3 I would just raise the concern. With respect to  
4 the down-classification, it sounds to me like the  
5 industry is concerned about having a good guidance  
6 document.

7 DR. WHALEN: If I could again try to get a  
8 more sharply focused question, understanding, of  
9 course, that you are representing industry, both  
10 the people who now have the manufacturing purview  
11 on this as well as those who might enter the  
12 market, would you favor reclassifying if we could  
13 assume for the moment, as the second step of the  
14 question, that we could come to an adequate  
15 guidance document for it?

16 MS. BROWN: I think I will abstain from  
17 answering that question. I think there is sort of  
18 a mixed response to that.

19 DR. WHALEN: Dr. DeMets?

20 DR. DEMETS: I have to say I am sort of  
21 feeling my way through this reclassification  
22 process. This is my first experience so I am  
23 working out of more ignorance than I normally do.  
24 If there were a group of devices that should be  
25 considered from a III to II, I think this is

1 probably one of those. However, as one who spends  
2 hours haggling over details of protocols and  
3 informed consent language, I just find it  
4 impossible to sign off on moving something without  
5 knowing the subtleties of the language and what the  
6 subtleties of language might imply. So, I am in  
7 favor of moving ahead with a process where the FDA,  
8 industry and perhaps this committee, with further  
9 comment, begin a process, some process with some  
10 language written down so we can look at it and say,  
11 aha, this will do the trick and we are comfortable  
12 moving from a III to a II under those conditions.  
13 Short of that, I just can't find myself making a  
14 recommendation to move.

15 DR. WHALEN: I would just take the  
16 privilege of the chair to interject briefly that we  
17 need to keep in mind that we can say that FDA ought  
18 to work with industry and that makes perfect sense  
19 I think to everybody in the room. But what we are  
20 about today is either saying yes or no to  
21 reclassification. As everybody knows, if we do  
22 reclassify to a II there is no way in heck it is  
23 going to go to a III any time soon.

24 DR. DEMETS: Since you are a surgeon, my  
25 answer is no.

1 [Laughter]

2 MS. BROWN: But we can say II and it can't  
3 be effective until there is a guidance document.  
4 Isn't that correct?

5 DR. WHALEN: That is correct, yes.

6 DR. KRAUSE: If I could just say any  
7 guidance document that we would come up with would  
8 go up on the web or in the Federal Register for  
9 comment.

10 DR. WHALEN: Dr. Chang?

11 DR. CHANG: In the presentation by Dr.  
12 Paulson, he did mention one device that did not  
13 appear to be effective. There was no hemostasis in  
14 one product after 12 minutes. So, if the guidance  
15 document, when in place, could ensure that such a  
16 product would not go on the market or the 510(k)  
17 would not be approved without a show of efficacy,  
18 or showing equivalence in terms of setting a  
19 standard of what is an efficacious product--it is  
20 not stated whether it is eight minutes for  
21 hemostasis, or ten minutes, or beyond twelve  
22 minutes if you haven't got a clot, forget it--I  
23 mean, that is the level of detail that I think is  
24 going to be needed for a guidance document to be  
25 protective for the public.

1           So, given that, if a guidance document  
2 were in place that could screen for products that  
3 don't work, even though they say that they are  
4 equivalent, then I would not object to classifying  
5 to II. So, my answer is yes, with conditions;  
6 classify to II with conditions.

7           DR. WHALEN: Dr. Miller?

8           DR. MILLER: I agree with the comment that  
9 Dr. Chang just made, and I think that if any device  
10 would qualify for being moved from III to II it  
11 should be these because their safety and their  
12 efficacy is without question. I mean, the device  
13 in and of itself should be moved. The questions  
14 that are being raised are do we create the  
15 possibility that inferior devices will be marketed  
16 and sort of be brought in under this class, and how  
17 do we protect against that. Well, we have the  
18 guidance document. We have all the tools in place  
19 to do this properly. Just to keep it Class III is  
20 like saying we are not sure it is safe yet, and we  
21 are keeping it in Class III because we are afraid  
22 of other products that may be introduced and we  
23 don't have any way to protect from that, but we do  
24 have a way to protect from that; we have the  
25 guidance document.

1           So, I think if we can create a Class II  
2 but veto the Class II if a proper guidance document  
3 isn't created, then that would be one way to go, or  
4 just to table it until we have a guidance document  
5 that we can vote on to go to a Class II. But I  
6 think we should move to a Class II somehow,

7           DR. WHALEN: Dr. Newburger?

8           DR. NEWBURGER: If the mandate to the FDA  
9 is to reduce burden of the approval process and  
10 paperwork, I think designing this guidance document  
11 is going to actually add to it. I am thinking  
12 about this and find it very difficult to define it.  
13 Wouldn't you then have to include things like the  
14 time that you see the volume of the material being  
15 resorbed, and so many other variables besides the  
16 time it takes for the material to clot? I am  
17 concerned that it wouldn't be detailed enough and I  
18 am in favor of keeping it in Class III.

19          DR. WHALEN: Dr. Choti?

20          DR. CHOTI: I would favor reclassification  
21 to Class II, as discussed, with appropriate  
22 documentation. I think that we know the industry.  
23 We know the class of product and how it behaves.  
24 We can come up with guidelines. I think we don't  
25 have to know eight minutes versus ten minutes. I

1 think there are good benchmarks of comparable  
2 product. So, I think it is not that difficult to  
3 come up with guidelines and I think, as Dr. Miller  
4 suggested, this is a class of products with an  
5 excellent track record.

6 The two concerns that I have, as I  
7 expressed initially, is that I think part of the  
8 guidelines should somehow state the product itself,  
9 that is, whether it is the gelatin sponge. The way  
10 it is currently defined, absorbable hemostatic  
11 product, in itself is quite non-specific and if it  
12 is a totally new material, then it certainly needs  
13 to be more rigorously tested and approved. But if  
14 a product is very similar or is manufactured  
15 similarly, then I think the guidelines, as much as  
16 they have been outlined with biocompatibility,  
17 animal studies, some clinical data is fairly  
18 straightforward.

19 The other thing is I agree with Dr. Brown  
20 regarding the clause regarding the bovine thrombin.  
21 Perhaps phrasing that a little differently, rather  
22 than specifically stating bovine thrombin but  
23 something like excluding any combined provide, or  
24 any product that is combined with biologics is  
25 excluded, something to that effect. Because, first

1 of all, it may allow the entry of other combined  
2 products which, at least based on the analysis of  
3 bovine thrombin suggests that this panel has some  
4 concern about or the FDA has some concern about,  
5 one way to do it is to actually broaden that  
6 exclusion to include combined with any biologic.

7 DR. WHALEN: Dr. Witten, in regards to  
8 FDA's first question, I think it is very clear that  
9 there is not a strong consensus among the panel as  
10 to whether or not there should or should not be  
11 reclassification, and it will be interesting to  
12 see, when we get to the reclassification document,  
13 how that goes down. Part of the biggest reason  
14 that I perceive from the thread discussion we have  
15 just had on this first question is that what makes  
16 people reticent to wish to reclassify is the  
17 potential enormity of what would be perceived as an  
18 adequate description for a document in this regard.  
19 With that less than an entirely clear answer, does  
20 that satisfy FDA on the first question?

21 DR. WITTEN: Yes, thank you.

22 DR. WHALEN: I think the next two are a  
23 bit easier. The second question is to please  
24 discuss the risks to health for the absorbable  
25 hemostatic agent and dressing devices. Dr.

1 McCauley?

2 DR. MCCAULEY: That is not quite as easy  
3 as you made it sound. I think that the  
4 presentation by Dr. Krause listed a number of  
5 parameters or risk factors that we need to look at,  
6 and certainly part of the guidance document that  
7 Ms. O'Grady brought forth also lists those issues.  
8 In general, I think those are all very good issues  
9 that need to be brought up in terms of  
10 risk/benefit.

11 DR. WHALEN: Dr. Doyle?

12 DR. DOYLE: I think that the years of  
13 evidence, as Dr. Miller was saying, certainly point  
14 out that there are minimal, and I think the figures  
15 that Dr. Krause gave out too point out that the  
16 risks seem to be minimal for the number of cases  
17 where it has been used.

18 DR. WHALEN: Ms. Brown?

19 MS. BROWN: Having put together a PMA for  
20 a hemostatic agent myself, I compliment Dr. Krause  
21 on the excellent job he did of putting together the  
22 potential risks both in his table and summary of  
23 the MDRs. I think it is a very complete job of  
24 describing the risks, and they are all there.

25 DR. WHALEN: Dr. DeMets?

1 DR. DEMETS: I don't think I have anything  
2 new to add. I think the track record is very good  
3 and the risks that we have learned about over all  
4 these years in surgery I think are identified. So,  
5 I am comfortable.

6 DR. WHALEN: Dr. Chang?

7 DR. CHANG: I think the list is complete  
8 as presented by FDA.

9 DR. WHALEN: Dr. Miller?

10 DR. MILLER: I agree with that. I think  
11 the list looks pretty complete to me.

12 DR. WHALEN: Dr. Newburger?

13 DR. NEWBURGER: I concur.

14 DR. WHALEN: Dr. Choti?

15 DR. CHOTI: I agree, the current products  
16 that were looked at are very safe.

17 DR. WHALEN: Dr. Dubler?

18 DR. DUBLER: I agree.

19 DR. WHALEN: And I would have to add that  
20 since I started my internship 26 years ago and I  
21 have used two of these products for over a quarter  
22 of a century, I think about giving an aspirin a  
23 heck of a lot more than I do these in terms of  
24 risks to my patients, and they are highly  
25 effective. So, in answer to number two, Dr.

1 Witten, we feel that the data has demonstrated, as  
2 presented by FDA, that the risks are quite low for  
3 these devices. Does that satisfy?

4 DR. WITTEN: Yes, thanks.

5 DR. WHALEN: Thank you. The third and  
6 final question is sort of a clairvoyant question,  
7 are there any other risks to health for these  
8 devices that have not yet been identified? Dr.  
9 Doyle?

10 DR. DOYLE: Well, I should say not yet  
11 identified by us but identified by someone else.

12 MS. BROWN: Not that I am aware of.

13 DR. WHALEN: Dr. DeMets?

14 DR. DEMETS: No comment.

15 DR. WHALEN: Dr. Chang?

16 DR. CHANG: I have no other additions.

17 DR. WHALEN: Dr. Miller?

18 DR. MILLER: Nothing to add.

19 DR. WHALEN: Dr. Newburger?

20 DR. NEWBURGER: Nothing else.

21 DR. WHALEN: Dr. Choti?

22 DR. CHOTI: No.

23 DR. WHALEN: Dr. Dubler?

24 DR. DUBLER: No.

25 DR. WHALEN: Dr. McCauley?

1 DR. MCCAULEY: None.

2 DR. WHALEN: No.

3 DR. WITTEN: Thanks.

4 Open Public Comment

5 DR. WHALEN: Very well, we can now begin  
6 the open public comment session. I would ask at  
7 this time that all persons addressing the panel  
8 come forward, speaking clearly into the microphone  
9 as the transcriptionist is dependent on this means  
10 of providing an accurate record of the meeting. We  
11 are requesting that all persons making statements  
12 during this open public comment period disclose  
13 whether they have any financial interests in any  
14 medical device company, and before making your  
15 presentation, in addition, state your name and  
16 affiliation and the nature of that financial  
17 interest or none, if that case exists. Yes, sir?

18 MR. IVEY: My name is Michael Ivey. I  
19 work at Pharmacia Corporation, manufacturers of  
20 Gelfoam. Yes, I do have a financial interest  
21 simply because my 410K has a lot of Pharmacia stock  
22 in it. I originally was approached by Dr. Krause  
23 to give a presentation, leaning one way or the  
24 other, as to how this determination should be  
25 reached and, honestly, until about an hour ago I

1 really hadn't decided which side to lean on.  
2 Sitting on my chair, realizing the efficiency of  
3 the panel in addressing the questions that I was  
4 writing down in my urgency to want to jump and say  
5 something inappropriately, to say, well, what about  
6 this--you guys have covered it all in great detail  
7 and have addressed any and all concerns.

8 I can understand the position of the  
9 industry, being that they have already gone through  
10 the painstaking effort of composing a PMA, as we  
11 had in the early '80's. If you had asked me the  
12 question two years ago I would have then been  
13 dead-set against reclassification because that  
14 would have given Mrs. Bobak an opportunity to just  
15 duplicate our product, and you guys have done a  
16 fantastic job; I am very proud. But now that we  
17 have several manufacturers of hemostats out there,  
18 and cumulative data, as I count, 20 years by one  
19 company, 40 by another and our product has been  
20 available to the American public since during the  
21 war even as it was invented during a necessity of  
22 dealing with bleeding in the battlefield, I am  
23 convinced we have sufficient data to say it is a  
24 safe product.

25 However, in understanding the complex

1 manufacturing process, as you have realized, there  
2 is a lot to it. There are a lot of indications,  
3 things to be aware of as far as the items that Mrs.  
4 O'Grady has pointed out that perhaps a 510(k)  
5 wouldn't address by itself. I am leaning now with  
6 your panel understanding of putting together a  
7 guidance document that says, well, not quite as  
8 easy as a 510(k) but not as hard as a full-fledged  
9 PMA because, yes, there are issues that need to be  
10 addressed.

11           You are using this product in a critical  
12 area of surgery. I mean in any general surgery  
13 where hemostasis is desired this product can be  
14 used. And, if some hodge-podge company comes  
15 forward and says, well, we have a product just like  
16 Gelfoam and we would like a 510(k) application,  
17 essentially just a "me too" product, I am not  
18 convinced that that would address all of the  
19 concerns. With this established guidance document  
20 I am, however, convinced that the wise panel here  
21 will lay forth the appropriate guidances that need  
22 to be followed. To say you are going to have to  
23 follow certain practices GMP-wise is almost like a  
24 Class III simply because there are problems that we  
25 discovered over the 60 years, and even in our

1 recent indication approval by FDA for bone  
2 hemostasis we had 200 patients and even from the  
3 results of that study realized that there are risks  
4 involved and a 510(k) won't cover them all if you  
5 are just going to manufacture a "me too" product.

6 If need be, would I use a hodge-podge  
7 product in my mom if she were on the operating  
8 table or would I choose one of the products  
9 manufactured by my competitors? I am convinced  
10 with PMA requirements--and looking at the size of  
11 our PMA, it must be more than my hand spread, I am  
12 convinced we have addressed all the concerns and I  
13 would be confident to use any of these three  
14 products.

15 With your wisdom, I understand that you  
16 would apply the same criteria to new products that  
17 would come about. I say that with heart pounding  
18 because that means that any competitor can come  
19 along and start stealing my market share, as some  
20 of my industry colleagues have already done, but  
21 that is okay; it opens up the door for new and more  
22 innovative products that would meet the same needs.  
23 I am confident that would also ease up the  
24 requirements by us to come up with different  
25 applications of our own product, whether it be

1 bovine thrombin that is currently a big issue or  
2 whether it is some new-fangled application for a  
3 drug that would benefit you, surgeons, who have  
4 clearly used it for many years of your surgical  
5 careers. Thank you.

6 DR. WHALEN: Thank you. Any other public  
7 members who wish to address the panel?

8 [No response]

9 Very well, now that the panel has  
10 discussed the FDA questions and our deliberations  
11 seem complete and the public has had an opportunity  
12 to comment, I would like to ask the FDA if they  
13 have any additional comments.

14 DR. WITTEN: No.

15 DR. WHALEN: Thank you. Is there anyone  
16 from the absorbable hemostatic agent and dressing  
17 industry that would like to make any final  
18 comments? Dr. Paulson?

19 DR. PAULSON: No.

20 DR. WHALEN: Ms. Bobak?

21 MS. BOBAK: No.

22 DR. WHALEN: Ms. O'Grady?

23 MS. O'GRADY: Again for the record, Judith  
24 O'Grady for Integra LifeSciences Corporation. My  
25 final comment is in regard to my proposal for the

1 guidance document, if there were to be a  
2 reclassification, is that all the items in this  
3 guidance document that I recommended are actually  
4 right from other guidance documents from FDA. So,  
5 it is very achievable to have a guidance document  
6 as part of the reclassification, and all those  
7 items listed, even though it may sound very  
8 thorough, are all part of other guidance documents  
9 that FDA has issued for products that need special  
10 controls because the products on the market are  
11 safe and effective, and we want to ensure that any  
12 new products coming on the market are as safe and  
13 effective and have the critical type of data that  
14 is needed to ensure that.

15 **Reclassification Questionnaire and Vote**

16 DR. WHALEN: Thank you. We will now  
17 proceed to the completion of the classification  
18 questionnaire and supplemental data sheet. Again,  
19 Ms. Shulman, the coordinator from the Office of  
20 Device Evaluation Classification and  
21 Reclassification will assist us. After the panel  
22 discussion of each of the questions on this form we  
23 will note the answer for each blank on the data  
24 sheet and it will be recorded on the overhead for  
25 all to see. We will then vote on the completed

1 questionnaire and supplemental data sheet, and this  
2 will constitute the panel's final recommendation to  
3 the FDA. Are there any questions by any of the  
4 panel members on how we are next to proceed?

5 DR. MILLER: Mr. Chairman, I just want to  
6 be clear how this process will occur. If we vote  
7 to make it a Class II, then we leave the formation  
8 of the guidance document to the FDA and basically  
9 our job is over? How does that work?

10 DR. WITTEN: Well, after you all make your  
11 recommendation, we will talk it over internally.  
12 If you make a recommendation for Class II and we  
13 decide to move forward with that, then we would  
14 write up a guidance document and put out a notice  
15 of proposed reclassification and publish that in  
16 the Federal Register and on the web, along with the  
17 draft guidance document. Then, after we receive  
18 the comments back, we evaluate the comments and  
19 decide what our next step is which, in general,  
20 would be to then move on to reclassify but it  
21 depends on what kind of input we get. But in the  
22 general course of events we wouldn't bring it back  
23 to this panel.

24 DR. MILLER: If the guidance document is  
25 for some reason found to be not satisfactory, there

1 is no going back? My sense from all of this, or at  
2 least my feeling personally is that it should be  
3 shifted, however, it is critical that the guidance  
4 document be a good one. Do we need to reserve the  
5 right to review the guidance document at this  
6 committee before we vote to shift it and,  
7 therefore, keep it as a Class III until we see the  
8 guidance document?

9 DR. WHALEN: I don't believe we have the  
10 right to reserve there, do we, Dr. Witten?

11 DR. WITTEN: Well, you can certainly  
12 recommend that it stay in Class III and make the  
13 comment that you would be happy to revisit this  
14 issue sometime in the future. Or, you can  
15 recommend that it is Class II, one or the other.

16 DR. WHALEN: If we recommend that it is  
17 Class II, then we are entrusting a body other than  
18 this committee to create the guidance document to  
19 their satisfaction and not ours.

20 DR. WITTEN: That is correct. Of course,  
21 we always have the option to bring it back to the  
22 panel but I don't want to tell you that that would  
23 be our plan because we will probably follow our  
24 normal procedures. Although we could; it would be  
25 within our ability to do that.

1 MS. SHULMAN: Marjorie Shulman. You also  
2 could recommend that we do bring it to the panel  
3 for comment as a recommendation before issuance.

4 DR. WHALEN: With a vote to change to  
5 Class II? Is that what you are stating?

6 MS. SHULMAN: I am looking at Nancy for  
7 help.

8 DR. WHALEN: The question I am raising is  
9 if we vote that it is going to be Class II today  
10 the die is cast and that recommendation will go  
11 forward. Maybe you can show it to us or maybe you  
12 won't but we will have voted to make this Class II  
13 today.

14 MS. SHULMAN: Correct, you will recommend  
15 it to be Class II.

16 DR. WHALEN: Is that right?

17 DR. CHANG: To clarify the question, even  
18 if the panel had these reservations about not  
19 seeing a final guidance document and said, well, we  
20 are so worried about whether it will be adequate or  
21 not that we want to leave it at III, if FDA feels  
22 they had a very, very comprehensive guidance  
23 document--I mean, it is still within the purview of  
24 the FDA to go ahead and change the classification.

25 DR. WITTEN: You are all making a

1 recommendation to us and we will take your  
2 recommendation back and consider it and try to, you  
3 know, do the right thing.

4 DR. WHALEN: Ms. Pluhowski, any input?

5 MS. PLUHOWSKI: Nancy Pluhowski, panel  
6 coordinator in the Office of Device Evaluation. If  
7 you feel that you cannot give us a recommendation  
8 today because there isn't, for example, a guidance  
9 document and one of the key special controls is  
10 unavailable to you, you could request that we bring  
11 this back to you at another time. In other words,  
12 table the recommendation today and we could come  
13 back at another time.

14 DR. MCCAULEY: I have a question.

15 DR. WHALEN: Dr. McCauley?

16 DR. MCCAULEY: If one makes a  
17 recommendation that it stays in Class III provided  
18 an adequate guidance document is developed, does  
19 that guidance document have to come back to this  
20 committee or can that guidance document be drafted  
21 by the FDA and industry, and with approval,  
22 automatically switch it to a Class II? Is that  
23 reasonable?

24 MS. PLUHOWSKI: I don't really understand  
25 that question.

1 DR. MCCAULEY: Does the document have to  
2 come back to the panel, basically?

3 MS. PLUHOWSKI: No.

4 DR. WITTEN: No.

5 DR. MCCAULEY: It does not?

6 MS. PLUHOWSKI: No, it does not. But when  
7 it is available in a draft form, when we are  
8 getting comments, of course, the panel can be  
9 invited to also make comments on the guidance  
10 document.

11 DR. KRAUSE: Excuse me, Nancy, on question  
12 seven it says, is there sufficient information to  
13 establish special controls to provide reasonable  
14 assurance of safety and effective? If yes, check  
15 the special control needed to provide such  
16 reasonable assurance for Class II. Couldn't the  
17 panel, under "other" say, yes, a guidance document  
18 agreed on by this panel as being appropriate?  
19 Couldn't that be their recommendation, and wouldn't  
20 that then require that it come back to this panel  
21 for their review?

22 MS. PLUHOWSKI: Yes, that could be a  
23 recommendation, that the guidance document be  
24 developed and that the panel be part of the review  
25 of that guidance document, but it is still a

1 recommendation.

2 DR. WHALEN: Are there other panel members  
3 who have procedural questions? Yes, Dr. Dubler?

4 DR. DUBLER: If we were to vote to put  
5 this off to come back to the panel at another time,  
6 the understanding being that this guidance document  
7 would by then be in existence, is that a vote we  
8 take before we do these specifics?

9 DR. WITTEN: I think Nancy Pluhowski is  
10 recommending that you all could choose to table  
11 responding to this reclassification questionnaire.

12 DR. DUBLER: So, that vote on tabling  
13 would then make these specifics not relevant to  
14 today's discussion?

15 DR. WHALEN: Right. I have to interject  
16 one thing before we proceed, and if it is  
17 inappropriate I will apologize but this is my last  
18 meeting so you can't fire me!

19 [Laughter]

20 What I have heard today from all the  
21 manufacturers and from all the panel members and  
22 from FDA is that we are looking at a class of  
23 agents which are extremely effective, which are  
24 extraordinarily safe, which have been used annually  
25 in millions of instances with almost nothing going

1 wrong, and with all due respect to the excellent  
2 representatives that we have from industry, the  
3 reason we have expressed such extraordinary  
4 consternation is that they have basically said it  
5 is that wonderful because we make it and maybe  
6 nobody else can do as well, and you could say that  
7 about anything. You could say that about any  
8 product that we use in our hospital or in our  
9 office any single day. I am personally amazed at  
10 the degree of puzzlement that we have about this  
11 reclassification. So, again, if that is out of  
12 line, you won't see me at another panel ever.

13 [Laughter]

14 MS. BROWN: I do have a question.  
15 Question number nine says for a device recommended  
16 for reclassification into Class II, should the  
17 recommended regulatory performance standard be in  
18 place before the reclassification takes effect.  
19 So, that is one of the questions that is here.

20 DR. WHALEN: Ms. Shulman?

21 MS. SHULMAN: Performance standard is  
22 recognized by rule-making; what we are talking  
23 about is a guidance document which is actually  
24 under question seven, under "other."

25 MS. BROWN: Oh, okay.

1 DR. CHOTI: Why not a performance standard  
2 rather than a guidance document? I know you don't  
3 want that.

4 MS. SHULMAN: It is through rule-making.  
5 It is more difficult to create. You certainly can  
6 vote for a performance standard instead, but it is  
7 not as easily changed for comment, and it can't  
8 evolve like a guidance document can.

9 DR. WITTEN: I think there is only one.  
10 We have one mandatory performance standard for FDA  
11 devices. That is for electrical stimulators.

12 DR. WHALEN: Dr. Dubler?

13 DR. DUBLER: I also have a funny feeling  
14 about this whole discussion, and the piece that I  
15 think is missing is I think we all acknowledge that  
16 industry has a conflict in arguing what should  
17 happen with the classification because, in fact,  
18 for the people who vaulted over the PMA, they are  
19 in pretty good shape and they can protect their  
20 turf. But I would like to argue that regulators  
21 also have a bit of a conflict of interest because,  
22 in fact, there is huge pressure not to regulate as  
23 much as we have before. Deregulation and smoothing  
24 things at the FDA is not an unknown discussion in  
25 Washington. So, I think that the FDA has its own

1 set of interests in this discussion.

2 And, I am sitting here thinking it really  
3 works and if it "ain't" broke don't fix it. So, I  
4 grant you that they really are safe and they do a  
5 really good job, and I think for me the question is  
6 how do we ensure that that remains the standard  
7 given this sort of what Dr. DeMets called quality  
8 slide--I am not quite sure what the term is. So,  
9 it may sound like it is kind of a silly discussion,  
10 but I think it has some interesting and hard  
11 elements to it.

12 DR. WHALEN: Starting with question number  
13 one, Ms. Shulman?

14 MS. SHULMAN: Question number one, is the  
15 device life-sustaining or life-supporting?

16 DR. WHALEN: Dr. DeMets?

17 DR. DEMETS: I honestly don't know how to  
18 answer that. It is certainly important. I guess  
19 it is, I don't know.

20 DR. WHALEN: You say yes? Dr. Chang?

21 DR. CHANG: Yes.

22 DR. WHALEN: Dr. Miller?

23 DR. MILLER: Yes.

24 DR. WHALEN: Dr. Newburger?

25 DR. NEWBURGER: Yes.

1 DR. WHALEN: Dr. Choti?  
2 DR. CHOTI: Yes.  
3 DR. WHALEN: Dr. Dubler?  
4 DR. DUBLER: Yes.  
5 DR. WHALEN: Dr. McCauley?  
6 DR. MCCAULEY: Yes.  
7 MS. SHULMAN: Okay, the first one is yes.  
8 Number two, is the device for a use which is of  
9 substantial importance in preventing impairment of  
10 human health?  
11 DR. WHALEN: Dr. Chang?  
12 DR. CHANG: Yes.  
13 DR. WHALEN: Dr. Miller?  
14 DR. MILLER: Yes.  
15 DR. WHALEN: Dr. Newburger?  
16 DR. NEWBURGER: Yes.  
17 DR. WHALEN: Dr. Choti?  
18 DR. CHOTI: Yes.  
19 DR. WHALEN: Dr. Dubler?  
20 DR. DUBLER: Yes.  
21 DR. WHALEN: Dr. McCauley?  
22 DR. MCCAULEY: Yes.  
23 DR. WHALEN: And Dr. DeMets?  
24 DR. DEMETS: Yes.  
25 MS. SHULMAN: Number three, does the

1 device present a potential unreasonable risk of  
2 illness or injury?

3 DR. WHALEN: Dr. Miller?

4 DR. MILLER: No.

5 DR. WHALEN: Dr. Newburger?

6 DR. NEWBURGER: No.

7 DR. WHALEN: Dr. Choti?

8 DR. CHOTI: No.

9 DR. WHALEN: Dr. Dubler?

10 DR. DUBLER: No.

11 DR. WHALEN: Dr. McCauley?

12 DR. MCCAULEY: No.

13 DR. WHALEN: Dr. DeMets?

14 DR. DEMETS: No.

15 DR. WHALEN: And Dr. Chang?

16 DR. CHANG: No.

17 MS. SHULMAN: The third one is no. Number  
18 four, did you answer yes to any of the above three  
19 questions? The answer is yes, and we go to  
20 question seven. Is there sufficient information to  
21 establish special controls to provide reasonable  
22 assurance of safety and effective? So, the first  
23 part of that question is can we establish special  
24 controls? If the answer is yes we will go to what  
25 the special controls will be.

1 DR. WHALEN: And there is the rub! Dr.  
2 Miller?  
3 DR. MILLER: Yes.  
4 DR. WHALEN: Dr. Newburger?  
5 DR. NEWBURGER: Yes, other.  
6 DR. WHALEN: Dr. Choti?  
7 DR. CHOTI: Yes.  
8 DR. WHALEN: Dr. Dubler?  
9 DR. DUBLER: Yes.  
10 DR. WHALEN: Dr. McCauley?  
11 DR. MCCAULEY: Yes.  
12 DR. WHALEN: Dr. DeMets?  
13 DR. DEMETS: Yes.  
14 DR. WHALEN: And Dr. Chang?  
15 DR. CHANG: Yes.  
16 MS. SHULMAN: The answer to that is yes,  
17 and it is recommended to be reclassified in Class  
18 II and now we will name the special controls that  
19 you feel will be appropriate. On the list guidance  
20 document is not listed; it is under "other".  
21 DR. WHALEN: Starting with Dr. Newburger?  
22 DR. NEWBURGER: I would include postmarket  
23 surveillance, performance standards--I would  
24 include everything.  
25 DR. WHALEN: Dr. McCauley?

1 DR. MCCAULEY: I think there is some  
2 confusion here. I think this question asked are  
3 there specific controls available? We know they  
4 can be developed but we don't have them actually  
5 right here at the present time.

6 DR. WHALEN: Let's retreat for a moment  
7 because I, personally, was staggered that that  
8 question went so well but with my prejudice about  
9 it I just let it slide. But we need to go back a  
10 step. There was confusion about the question and  
11 whether there are not special controls. So, we  
12 need to redo that question. Before we redo that  
13 question, is there any comment or question about  
14 the implications of it by any panel member? Dr.  
15 Dubler?

16 DR. DUBLER: Yes, I meant for it to stay  
17 as a Class III now, but we also lost this tabling  
18 motion which I thought short-circuited this vote.

19 DR. WHALEN: The motion to table can  
20 supersede, as I understand it. We run basically  
21 under parliamentary procedures. Before we go  
22 ahead, and I am just an outgoing chair and probably  
23 not quick enough, but is that correct?

24 DR. WITTEN: Yes.

25 DR. WHALEN: So, a motion to table can be

1 entertained at any time.

2 DR. DUBLER: I would make a motion to  
3 table.

4 DR. WHALEN: Is there a second for that  
5 motion? If we don't have a second, it dies.

6 DR. MCCAULEY: Can we discuss it?

7 DR. WHALEN: Not unless it is seconded.  
8 You can second it for discussion and vote it down.

9 DR. MILLER: I will second it.

10 DR. WHALEN: It has been made and  
11 seconded. Is there any discussion on the motion to  
12 table?

13 DR. DUBLER: Let me just say why I think  
14 it would be helpful. I don't think there is  
15 disagreement among the panel on the fact that these  
16 are very safe, and it would be a good thing if it  
17 was easier for new industries to enter the market,  
18 and my perspective--I won't speak for the panel; I  
19 will speak for me, my perspective is that I want to  
20 be certain that the quality measures are  
21 sufficiently precise to ensure that these remain as  
22 effective as aspirin or better than aspirin.

23 I think that process needs a little bit of  
24 support given all of the competing items on the  
25 agenda of the FDA. So, I would give it that

1 support by making this a matter where we would  
2 table it and ask for it to come back. My  
3 understanding from the discussion was that it would  
4 mean that it would come back, whereas nothing else  
5 we could do would make it come back, and have that  
6 opportunity for the FDA and industry to get its  
7 guidance together and try again.

8 DR. WHALEN: Dr. McCauley?

9 DR. MCCAULEY: Basically the way I see  
10 this is that I think it ought to remain a Class III  
11 device until an appropriate guidance document has  
12 been developed by FDA and industry. I do not feel  
13 it needs to come back to the panel for approval of  
14 that documentation as long as that documentation is  
15 adequate for the FDA with the help of industry; I  
16 don't think it needs to come back to the panel.  
17 Once that occurs, I think it should be classified  
18 as a II.

19 MS. SHULMAN: If I can clarify something,  
20 reclassification would be based on the special  
21 controls guidance document. So, it cannot be  
22 reclassified until a guidance document is in place.

23 DR. MCCAULEY: Exactly.

24 DR. MILLER: So, voting today--I am sorry.

25 DR. WHALEN: Further discussion of the

1 motion on the table? Dr. Miller?

2 DR. MILLER: Thank you. So, voting today  
3 to change to a Class II, that is exactly what Dr.  
4 McCauley says? If we say we vote to make it Class  
5 II, what happens is what Dr. McCauley described, it  
6 stays in Class III until the guidance document is  
7 created and approved by everybody, and then it gets  
8 shifted to Class II.

9 DR. WHALEN: That is right, but we would  
10 not necessarily have a voice in what the guidance  
11 document is.

12 DR. DUBLER: And, "approved by everybody"  
13 is the definition that I need. Approved by  
14 everybody would mean? I find myself arguing for  
15 industry, which is such a bizarre place for me to  
16 be in that I am wondering if I have done something  
17 wrong. But would that mean that industry would, in  
18 fact, agree that the production standards would  
19 remain sufficiently high to protect patients?

20 DR. WHALEN: It is implied. Dr. Witten?

21 DR. WITTEN: Well, I am a little confused  
22 because there are so many questions, but as far as  
23 the guidance document process, if we, with industry  
24 input, were to develop a guidance document, it goes  
25 on the web for comment and those include, of

1 course, and in general are primarily industry  
2 comments, then we evaluate those comments, whatever  
3 they are, and respond to them, then if we still  
4 thought it should be Class II with a guidance, we  
5 would come out with a final guidance document. We  
6 certainly try to reach harmony with our  
7 constituents, including industry and everyone else,  
8 but I would say "agree" may be too strong or too  
9 optimistic a word from time to time.

10 DR. DUBLER: That is important. Is it  
11 your experience, Dr. Witten, that when something  
12 moves from a III to a II there is pretty much  
13 consensus that what exists as a guidance in the  
14 future is sufficiently rigorous?

15 DR. WITTEN: That is a judgment call.  
16 There aren't such a huge number of products that  
17 get reclassified from Class III to Class II so that  
18 I can really answer generally. I would say there  
19 is a range of how much agreement there is about  
20 what should be in a guidance document. Sometimes  
21 it is quite clear to everyone certainly what should  
22 be in there and sometimes that is not the case.

23 DR. WHALEN: Further discussion on the  
24 motion on the table? Dr. DeMets?

25 DR. DEMETS: I don't want to prolong it

1 but I have a lot of confidence in the FDA staff,  
2 with input and feedback, that we would get a good  
3 document. But what troubles me is having this  
4 panel, or at least my vote to approve something I  
5 haven't seen. I can vote for a process but I have  
6 difficulty, and I have been backed into these  
7 corners before--I mean, would any IRB approve a  
8 protocol that was going to be written? The answer  
9 is, of course, no. Why do they insist on seeing  
10 it? They want to see the language. That is where  
11 I am stuck. I have confidence that this will come  
12 out all right, but I don't want the excuse to be  
13 that we voted for something we haven't seen.

14 DR. WHALEN: I just have to interject  
15 again that I find it ironic that we are worried  
16 that the government is not going to regulate this  
17 enough.

18 [Laughter]

19 DR. DEMETS: They might over-regulate it,  
20 for all I know.

21 DR. WHALEN: Further discussion on the  
22 motion on the table?

23 DR. MILLER: I guess the specter of  
24 putting something in a bleeding wound and have it  
25 not clot for 15 minutes or ever clot, that

1 terrifies me. These people have gotten my  
2 attention, that there is enough sophistication in  
3 the process that that is possible. So, that has  
4 shaken my certainty a little bit in these things.  
5 Maybe there is a lot more to making this effective  
6 device than I realized, and I agree with the  
7 comments about the guidance document and maybe we  
8 should see that before we move on.

9 DR. WHALEN: Seeing no further discussion,  
10 we will call the question just by a show of hands.  
11 Those who are in favor of tabling this action,  
12 please raise your hand.

13 [Show of hands]

14 DR. MCCAULEY: Do we have an alternative  
15 to that?

16 [Laughter]

17 DR. WHALEN: If you defeat the motion  
18 there are always alternative motions, but the  
19 motion we are voting on right now, which just  
20 carried by a majority of 4-3--those who are against  
21 tabling, please raise your hands.

22 Dr. Witten, your advisory committee has  
23 voted 4-3 to table this action. If I can take the  
24 prerogative of the chair to add to that, I believe  
25 it is because they would like to see sufficient

1 amplification of what a guidance document would be  
2 before taking any action for reclassifying the  
3 hemostatic agents.

4 DR. WITTEN: Thank you.

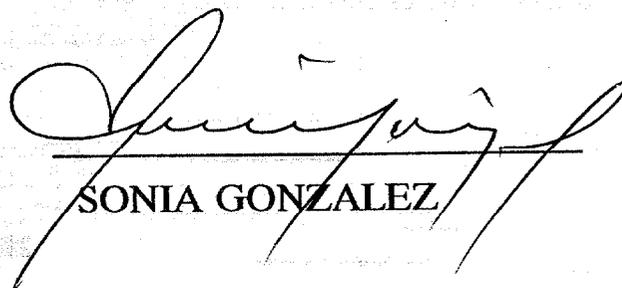
5 DR. WHALEN: That concludes our day's  
6 activities. I would like to thank everyone who  
7 presented to us, and especially the committee for  
8 their action. We are adjourned for the day.

9 [Whereupon, the proceedings were recessed  
10 at 5:45 p.m., to be resumed on Tuesday, July 9,  
11 2002 at 8:00 a.m.]

12

**C E R T I F I C A T E**

I, **SONIA GONZALEZ**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



SONIA GONZALEZ