1 over-the-counter, it seems like we may have put up
2 another barrier to its use that wasn't here before
3 the panel meeting.
4 DR. WHALEN: Thank you. I would like to
5 announce that the recommendation of the panel, with
6 six votes for the motion and one abstention, is
7 that the silicone elastomer for scar management
8 intended for use in the management of intact
9 skin--which I still won't get right but what you
10 see up on the screen, with hyperproliferative
11 scars, parentheses, keloid and hypertrophic scars,
12 be classified into Class I.
13 In so doing, I would like to thank the
14 panel and thank Dr. Arepalli and the industry reps
15 for what they have done for us. We have another
16 item of business but we will take a ten-minute
17 break and reconvene promptly at 3:25 to being that
18 process.
19 [Brief recess]
20 **Reclassification of Absorbable Hemostatic Agents**
21 **and Dressings**
22 DR. WHALEN: I would like to call this
23 meeting back to order. Could I first ask that the
24 voting panel members pass toward the center of the
25 table, toward me, their classification

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1 questionnaires on the last item of business so that
2 we can collect them for the FDA?
3 I would like to remind the public again
4 that while this portion of the meeting is open for
5 the public for their observation, public attendees
6 may not participate except at the specific request
7 of the panel.
8 We now will proceed to the open committee
9 discussion. We will begin the discussion on the
10 reclassification of absorbable hemostatic agents
11 and dressings with serial presentations from
12 industry, first by Dr. John D. Paulson, vice
13 president for quality assurance and regulatory
14 affairs, Johnson & Johnson Wound Management, a
15 Division of Ethicon, Inc., followed by Ms.
16 Ronnemoes Bobak, vice president for product
17 development, Ferrosan A/S, and then Ms. Judith E.
18 O'Grady, senior vice president, regulatory, quality
19 and clinical affairs, Integra LifeSciences
20 Corporation.
21 The FDA presentation and a reading of the
22 FDA questions will follow these presentations. We
23 will then have a general panel discussion of this
24 topic, followed by a more focused panel discussion
25 aimed at answering FDA's questions. Before we

1 complete the reclassification worksheet and
2 supplemental worksheet, we will have an open public
3 comment period. Then we will complete the
4 reclassification worksheet and supplemental
5 worksheet. The vote on these worksheets will
6 constitute the panel's recommendation to the FDA.
7 I would like to remind public observers at
8 this meeting that while this portion of the meeting
9 is open for public observation, again, public
10 attendees may not participate except at the
11 specific request of the panel. I probably should
12 seriously point out that even though I am from
13 Robert Wood Johnson Medical School in New
14 Brunswick, New Jersey, there is not a financial
15 interrelationship with Johnson & Johnson although,
16 God knows, my dean would love to have a stronger
17 one. We will begin with Dr. Paulson's
18 presentation.
19 **Industry Presentation**
20 DR. PAULSON: Dr. Whalen, Dr. Krause, Dr.
21 Witten and panel, thank you for the opportunity to
22 present here today.
23 There are several different types of
24 products in the category of absorbable hemostatic
25 agents. I am here today to present concerning

1 Surgicel, oxidized regenerated cellulose,
2 representing one of these product types.
3 I would like to talk to you about globally
4 available ORC products while noting that Surgicel
5 is currently the only available ORC product in the
6 United States. There was previously another
7 manufacturer making a similar product, using
8 essentially the same chemistry and manufacturing
9 process which we licensed jointly from the
10 third-party company. They have since stopped
11 making that product. But their safety record is
12 going to be discussed, I am sure, by Dr. Krause and
13 will reflect product made by the same manufacturing
14 process in essence.
15 I will talk to you briefly about the
16 manufacturing process; the mechanisms of
17 hemostasis, just very briefly; biocompatibility and
18 hemostasis data; and then provide a brief summary
19 of my conclusions. I will try to do that all in
20 less than fifteen minutes.
21 The Surgicel family of absorbable
22 hemostats includes three basic product types,
23 Surgicel, Surgicel Nu-Knit and Surgicel Fibrillar,
24 representing different physical forms of product
25 made with essentially the same process, although

1 representing different weaves and manufacturing
2 processes after the chemistry has taken place.
3 These products are used adjunctively in
4 surgical procedures for the control of capillary,
5 venous or small arterial bleeding and rapidly stop
6 the bleeding by acting as a matrix for the
7 formation of a clot, and some other mechanisms that
8 I will talk to you about a little bit later. The
9 product is often left behind in part of in whole
10 and is readily absorbed from the site of
11 implantation with minimal tissue reaction, which is
12 very important because it is frequently used in
13 cardiovascular procedures and frequently in
14 neurosurgical procedures where other methods of
15 hemostasis may not be suitable, for instance,
16 electrocautery.
17 There are other ORC products available in
18 the global market. This is Cellulostat. it is
19 available in Taiwan and China. You can see it
20 magnification at 12x having a slightly different
21 pattern of knit or weave. And, there is an ORC
22 product developed from Europe, by the name of
23 Curacel. So, I will talk a bit about those
24 products as well.
25 This is just to remind you that

1 regenerated cellulose products are more than just
2 an isolation of cellulose. They are derived from
3 wood pulp which contains about 50 percent cellulose
4 by weight, and also contains significant amounts of
5 lignin and other inter-fibrillar materials which
6 act as adhesives to kind of keep the physical
7 structure of the wood intact. There are
8 significant chemical processes in place here that
9 affect the qualities of the fabric which becomes
10 the raw material for the oxidation process. This
11 basically digests the cellulose and then
12 reconstitutes it prior to oxidation. The material
13 that we are talking about here is bright rayon, and
14 it is essentially pure cellulose.
15 This then goes into knitting and
16 purification processes and conditioning of the
17 fabric, controlled oxidation reactions which are
18 used to define chemistry and define processes,
19 involve displacement of solvents and reactants,
20 purification of the materials, dehydration and then
21 processing the material into its final product
22 forms, along with sterilization and QA testing and
23 release.
24 What I wanted to call your attention to in
25 all of this is really the complex nature of the

1 processing that is involved. This is not just an
2 isolation of cellulose as a chemical derivation,
3 and you can think of this as a biosynthetic
4 material rather than an isolated biological
5 material.
6 Cellulose is a polymer of glucose
7 basically, and oxidized regenerated cellulose in
8 its simplest form involves the oxidation at the
9 sixth position, changing it from an alcohol
10 function to a carboxylic acid function. There are
11 also other chemical byproducts, and I will call
12 your attention to the 2- and 3-ketone ORCs as well
13 as aldehydes, ketones, dialdehydes, and so on.
14 These can vary in ratios depending on the controls
15 and nature of oxidants in the oxidation process.
16 Again, we are talking about
17 cellulose-related materials. This is a reminder
18 that cellulose itself does not absorb. This is a
19 cotton suture that has been implanted for two
20 years. You can see a chronic inflammatory reaction
21 here and continued presence of the cellulose.
22 Cellulose is also well-known to surgeons from use
23 in gauze, and lint from gauze is well-known to
24 cause chronic inflammatory reactions and adhesions.
25 We don't want to end up with cellulose so

1 consistency of the process is important to achieve
2 a biocompatible and degradable material.
3 This is just a brief reminder of the
4 complex relationship between physiologic processes
5 involved in hemostasis, involving vasoconstriction,
6 platelet activation, coagulation activation,
7 conversion of fibrinogen to fibrin by thrombin. I
8 will mention briefly that Surgicel acts both in
9 terms of platelet activation and activation of
10 intrinsic and extrinsic pathways or coagulation
11 activation.
12 Surgicel at the wound site has multiple
13 mechanisms. Here it is applied to a vessel. There
14 is fluid absorption which results in a relative
15 hemoconcentration. There is hemoglobin oxidation
16 resulting in a gel formation or false clot which
17 helps achieve tamponade in conjunction with manual
18 compression.
19 You can see in the upper right-hand
20 depiction adherence of platelets to the fibrillar
21 structure of the material and ultimately clot
22 formation on the matrix of fabric.
23 I will use this swine spleen incision
24 picture to demonstrate some of the actual use of
25 the product. You can see here that in a model

1 which we used to measure hemostasis time, using a
2 controlled incision of 1.5 cm by 0.3 cm deep, that
3 you see a darkening of the blood which has to do
4 with its oxidation. You can see gel formation and
5 false clot formation, fluid absorption, and so on.
6 In this model we applied digital compression and
7 can measure time to hemostasis, as I mentioned
8 earlier. I will refer to some data later from this
9 model.
10 I am going to try to relate to you some of
11 the mechanisms of action that we talked about
12 earlier in hemostasis and some of the attributes of
13 Surgicel. I will also talk to you about how they
14 relate to controls which exist in the U.S.
15 Pharmacopeia.
16 In the first column you will see
17 mechanisms of action include tamponade due to
18 digital compression, fluid absorption, swelling and
19 gel formation. Then, at the chemical and biologic
20 level we talked earlier about protein adsorption,
21 platelet adherence, platelet aggregation and
22 platelet activation, and intrinsic and extrinsic
23 pathway activation. This relates to a variety of
24 physical and surface chemistry attributes of the
25 product that are shown in this panel. Then, if one

1 looks at USP specifications for oxidized
2 regenerated cellulose, you see that they are very
3 incomplete in addressing those items which we
4 identify as important to achieving effectiveness of
5 the product and in achieving hemostasis.
6 Similarly for biocompatibility, we have
7 highlighted just a few of the key areas of
8 biocompatibility that are important
9 here--cytotoxicity, acute inflammation,
10 biodegradation and absorption, immunogenicity and
11 neurotoxicity.
12 Surgicel properties include carboxyl
13 content and pH. Degradation, interestingly, does
14 not appear to be related to carboxylation of the
15 alcohol functions but, rather, the ketone formation
16 at C2 and C3, which is not controlled by USP
17 specifications or other recognized standards for
18 these products.
19 In terms of immunogenicity and
20 neurotoxicity, the exact determinants are not
21 clear, but it is clear that they depend on high
22 material purity and controlled chemical processes
23 and ingredients. Again, USP specifications appear
24 to be inadequate in addressing these essential
25 requirements of the product.

1 We have done some physical and chemical
2 analysis of the three product types that I showed
3 you earlier. Many of these are USP tests, for
4 instance, identification loss on drying, nitrogen
5 content and carboxyl content are USP tests. You
6 will see that Surgicel passes all of these, while
7 Curacel fails for carboxyl content; Cellulostat
8 fails on several accounts. In the right-hand
9 column you can see those USP specifications for
10 these parameters.
11 We have also assessed pH, which is
12 somewhat related to carboxyl content but
13 post-oxidation treatment can neutralize the pH and
14 add back other ions. You can see that Cellulostat
15 has a different pH, while Curacel appears to have
16 calcium added into the process.
17 Physical strength varies which, of course,
18 can affect clinical use. Water solubility varies
19 for these products and spectral identification
20 suggests that Cellulostat is not, in fact, ORC
21 despite its labeled claim to be so.
22 Time to hemostasis was measured in the
23 model that we showed you earlier. The top two bars
24 represent some historical data that we have for
25 Surgicel Nu-Knit and Surgicel. Then, due to

1 limited numbers of samples available for Curacel
2 and Cellulostat in the short time since this
3 meeting was announced, we have done some
4 head-to-head comparisons of Cellulostat and
5 Curacel, and you can see that with Surgicel the
6 mean time to hemostasis for those specific wounds
7 that we discussed earlier is approximately eight
8 minutes; for Curacel, approximately ten minutes;
9 and for Cellulostat, essentially none of them
10 achieved hemostasis in the 12 minutes that we
11 defined as the maximum time period for this model.
12 So, what do we conclude from all that?
13 Our summaries are that Surgicel Absorbable Hemostat
14 does, indeed, have a long history of safety and
15 effectiveness. I think Dr. Krause will speak to
16 you about that. Given the limited time for this
17 presentation, I haven't gone into it but it
18 certainly does have a commendable history.
19 There is complex chemistry and processing
20 required to create the unique product properties
21 here. There are multiple physiological
22 interactions required for safety and effectiveness.
23 Other ORC products are not equivalent, and USP
24 requirements do not address many critical product
25 attributes.

1 So, our conclusions are that the USP is
2 not adequate to control key product attributes, and
3 that we do not know of other standards for these
4 products which are established and accepted.
5 Finally, in the absence of recognized
6 standards, we believe that reclassification is not
7 appropriate. I would again refer back to the fact
8 that these products are often left as implantable
9 devices in critical portions of the circulatory
10 system and the central nervous system. So, I am
11 sure that as physicians and scientists you can
12 appreciate the great degree of control and
13 assurance of biocompatibility and effectiveness
14 that are needed there. Thank you.
15 DR. WHALEN: Questions for Dr. Paulson?
16 MS. BROWN: I have a question. If the FDA
17 developed a guidance document would you be in
18 support of a down-classification?
19 DR. PAULSON: I think if an adequate
20 guidance document can be created and is dictated in
21 the regulation, then that would be a reasonable
22 approach. However, at this time I am not aware of
23 what the contents of that would be so I would be
24 reluctant to say that that is the way to go in the
25 absence of a standard that we could ponder and

1 consider the adequacy of.

2 MS. BROWN: thank you.

3 DR. WHALEN: Other questions?

4 [N response]

5 Thank you. Next, we will hear from Ms.

6 Bobak.

7 MS. BOBAK: First, I would like to thank

8 you for giving me the opportunity to speak here,

9 and having the ability to have an impact during

10 this panel discussion on reclassification of

11 absorbable hemostatic agents and dressings.

12 My name is Lone Ronnemoes Bobak. I am

13 representing Ferrosan. Ferrosan is a Danish

14 medical device manufacturing company, and we have

15 given the distribution rights of our absorbable

16 gelatin sponge Surgifoam to Ethicon and they

17 distribute our absorbable gelatin sponges.

18 What I will be talking about is the

19 current regulatory status because it is different

20 in Europe and in U.S. I will talk about the

21 essential quality control elements which we have

22 implemented. I will talk about the usage of

23 Surgifoam in critical surgical procedures and give

24 my conclusion.

25 The current regulatory status in EU is

1 that it has a long product history of safety and
2 effectiveness. We have had the product on the
3 market for more than 40 years and, due to some
4 changes in regulation, it was dropped prior to '96
5 and then the CE regulation came and we got it
6 classified as CE Class III medical device in
7 December of 1996.
8 Right now there is discussion in EU about
9 reclassification borderline products into drugs,
10 meaning that products like ours might have an
11 impact and could become a drug again.
12 The current regulatory status in the
13 United States is the fact that Ferrosan, in March
14 '97, submitted an IDE, and over the next years we
15 performed extensive clinical trials on humans, and
16 they were multicenter trials. In 1999, based on
17 the outcome of these clinical trials, we submitted
18 the PMA to FDA, had the inspection in August of '99
19 and got the license to export products to the
20 United States in September of '99.
21 Since 1999 we have submitted an amendment
22 to this PMA several times. The new license has
23 been granted based upon clinical studies on humans
24 as well as clinical trials on animals and, of
25 course, by use of design controls and risk

1 management.

2 Ferrosan has achieved a commission also

3 for usage during neurological surgery. For

4 achieving that authorization, we got some

5 preclinical data as well as clinical trials and

6 filed for getting information for use in our

7 logical procedures. As you are, of course, aware

8 elevated sensitivity to toxic and infective agents

9 and the gelatin could be an infectious agent if not

10 treated right. About toxicity, I am also talking

11 about endotoxin testing which we are performing

12 both on raw materials, as well as the finished

13 products. During neurological surgery there is a

14 potential for physical damage and there are fewer

15 choices for adjunctive hemostasis.

16 The surgical product consists of gelatin,

17 water and nitrogen. Surgifoam is a very safe

18 product and we have had no MDRs in the years that

19 we have supplied product to the U.S. market. But

20 this is only caused by the additional quality

21 control measurements that we have had since the USP

22 standards that are right now in place don't fulfill

23 all the requirements that we feel must be in place.

24 When we are searching for raw materials,

25 and please recall that the gelatin is a very

1 complex biological raw material, we must make sure
2 that our pig skin gelatin is not deteriorated by
3 bovine originated gelatin or by alkaline based
4 gelatin. We have required that the animal
5 supplying the gelatin has been subjected to both
6 pre- and postmortem veterinary controls, and that
7 this is stated in the veterinary certificate
8 accompanying each batch of the gelatin. We have
9 required that the supplier certify that the gelatin
10 is an accordance to an EC standard as regards
11 manufacturing of these materials.
12 We are using a safe but also sensitive
13 method for sterilization of the finished product.
14 When I am talking about sensitive, it is dry
15 sterilization in comparison to sterilization using
16 formaldehyde. We are working on stringent hygienic
17 and very low microbial conditions during the
18 manufacturing of the sponges.
19 As we have had products on the European
20 market for more than 40 years, we feel it is safe,
21 and we felt safe about our products though we did
22 agree with the FDA on the list of requirements put
23 forward when we issued the IDE in 1997. We
24 performed extensive clinical trials in '99 and it
25 seems as if a lot has changed during these two

1 years.

2 We don't feel that the current standards

3 control all the critical elements for gelatin

4 hemostats. So, we don't feel, from a Ferrosan

5 point of view, that reclassification is appropriate

6 as long as there is no proper guidance and

7 controls. Thank you very much.

8 DR. WHALEN: Questions for Ms. Bobak? Dr.

9 Newburger?

10 DR. NEWBURGER: With all of the furor

11 about spongiform encephalopathy that seems to have

12 swept Europe, I assume with the herd and animal

13 controls that is looked at as well?

14 MS. BOBAK: Yes, definitely. But since

15 our gelatin is originated from pig skin, we don't

16 have the BSE impact on the products but, of course,

17 we must make sure that our gelatin has no contact

18 at all to bovine-originated gelatin, and the

19 guidance in Europe is to control that issue which

20 we, of course, follow very stringently.

21 DR. WHALEN: This product has been in

22 clinical use for how long?

23 MS. BOBAK: Forty-eight years.

24 DR. WHALEN: Certainly in my medical

25 school years it was nothing new. I remember seeing

1 it in the operating room and that was in the early
2 '70's. There is a multitude of manufacturers of
3 it?
4 MS. BOBAK: Yes and no. In the U.S. there
5 is manufacturing of a gelfoam product. In Europe
6 there is actually our manufacturer of a sponge,
7 Curacel. Then there are some in China and in India
8 which is sterilized and manufactured in strange
9 ways. So, I won't say many but there are some,
10 yes.
11 DR. WHALEN: And over the several decades
12 that it has been in existence, has there been any
13 scientific advance or manufacturing change that has
14 made a substantial increment in the effectiveness
15 that you perceive?
16 MS. BOBAK: We have changed our
17 manufacturing procedures several times. We have
18 had--how do you say that in English?--something
19 that changed the surface of the product. We had
20 sodium laurel sulphate in the product twenty years
21 ago. We changed that because we found out, doing
22 other precautions during our manufacturing process,
23 that it wasn't necessary to have that. Twenty-five
24 years ago we had formaldehyde as a sterilization
25 agent. We have omitted that completely. So, from

1 a Ferrosan point of view, we have definitely made
2 more stringent our manufacturing process a great
3 deal over the years.
4 DR. MILLER: So you, and I think Dr.
5 Paulson also before you, seem to be not in favor of
6 reclassifying this to a lower classification than
7 it is now. Is that what I am to understand?
8 MS. BOBAK: I would answer yes and no, if
9 I may. I can, of course, see something positive in
10 a declassification but as long as there is no
11 guidance document stating all the additional
12 quality control elements that must be in place, or
13 not having any risks to the consumer, then I am not
14 in favor of a declassification on the sponges, no.
15 DR. WHALEN: Dr. Choti?
16 DR. CHOTI: The comparisons between the
17 two products, they are both hemostatic agents but
18 prepared very differently and they are very
19 different products. Tell us a little bit about the
20 mechanism of action of the gelatin sponge versus
21 the cellulose product we have just heard about.
22 MS. BOBAK: I am sorry, I don't think I
23 would be the right person to answer that question.
24 MS. GORMAN: Hi. My name is Anne Gorman,
25 from Johnson & Johnson. Both products have very

1 similar mechanisms of action in that they act as
2 surfaces on which platelets can be bound, the
3 gelatin being more specific, Surgicel being less
4 specific. Gelatin has a specific binding site for
5 the platelets. With the Surgicel it is more of a
6 physical phenomenon and once platelets are
7 activated you have coagulation activation and clot
8 formation.
9 DR. WHALEN: Thank you, Ms. Bobak.
10 MS. BOBAK: Thank you.
11 DR. WHALEN: Now we will continue with Ms.
12 O'Grady's presentation.
13 MS. O'GRADY: Good afternoon. I am Judy
14 O'Grady, senior vice president of regulatory,
15 quality and clinical affairs for Integra
16 LifeSciences Corporation.
17 I would like to thank the Food and Drug
18 Administration and all the members of the General
19 and Plastic Surgery Devices Panel for allowing me
20 the time to speak at this public advisory committee
21 regarding the reclassification of transitional
22 Class III devices, the absorbable hemostatic agent
23 and dressing devices intended for hemostasis during
24 surgical procedures.
25 I will try to keep within the fifteen

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--Bbasic 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 ben 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 see 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 tat 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 apprpoved. 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 [illegible]

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 - - -

CERTIFICATE

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.

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