

1 clarification if I may for Dr. Witten. How common is
2 it that a sponsor would come without a sponsored -- a
3 company-sponsored trial, as opposed to independent
4 investigators?

5 DR. WITTEN: Well, certainly the most
6 common thing is for a sponsor to actually design and
7 conduct a trial, but we have had other products,
8 applications in which there is other ways in which the
9 information has been gathered.

10 The ones that I can think of off-hand
11 involve information that was gathered by investigators
12 and published in literature, and so we look at product
13 applications based on literature articles, for
14 example.

15 DR. FISH: Is this related to the
16 accelerated?

17 DR. WITTEN: No, there is a hierarchy of,
18 quote, valid scientific evidence for FDA, and it just
19 fits within the spectrum for devices, and this fits in
20 within the spectrum of what we would like at
21 potentially to support product approval.

22 DR. FISH: Thank you. I, too, would agree

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1 though that I would certainly like to see a follow-up
2 study, and in particular looking at issues of CD4
3 stratification, and might there be different
4 responses.

5 And/or different nodule formations in
6 people who are more immune-replete, versus those who
7 are more CD4 depleted, and then also this group that
8 we have already mentioned, or in the minority
9 population.n

10 CHAIRMAN CHOTI: Dr. Miller.

11 DR. MILLER: I agree with all these views
12 expressed. I think the company needs to work with the
13 FDA to ensure that the post-approval trials would be
14 very well designed, and answer a lot of the questions.

15 I think if this were for any other target
16 population that these things would be probably
17 required before we would even move ahead on the PMA,
18 but it is the strength of the value to the target
19 population that is really guiding us. So we need to
20 have post-approval studies.

21 CHAIRMAN CHOTI: Thank you. Dr. Leitch.

22 DR. LEITCH: I would agree that we do need

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1 to have longer term follow-up studies, and I think
2 that this is in consideration of the patient
3 population that we are considering this for, and as
4 Dr. Miller said, we are sort of making some exceptions
5 here.

6 But we also want to ensure the safety for
7 that population given all the medical problems that
8 they deal with, and that we won't give them another
9 one to deal with. So I do think that is also
10 important, and as you can probably tell from my other
11 comments, I am highly interested in studies that
12 address the mechanistic action for the response.

13 CHAIRMAN CHOTI: Thank you. Dr. Chang.

14 DR. CHANG: If the sponsor has originally
15 been able to plan a prospective study, I would have
16 loved to have seen a planned randomized study
17 comparing the sponsor's product with native fat
18 injection, and it could have been randomized according
19 to one side or the other for the nasolabial fold or
20 the cheek.

21 But be that as it may, my recommendation
22 for a post-marketing approval study would be to

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1 address the questions of again what happens over time,
2 and if a patient in this population acquires multiple
3 treatments, and then what happens to persons of color,
4 and to women who receive this product.

5 Just as a comment, minority may be --
6 actually the persons of color may soon be the majority
7 demographically in the country, and so these questions
8 have not been answered thus far with the data
9 presented.

10 CHAIRMAN CHOTI: Dr. Blumenstein, are you
11 going to recommend a post-approval randomized trial?

12 DR. BLUMENSTEIN: I am not going to add
13 anything to what has been said.

14 CHAIRMAN CHOTI: Dr. Witten, at least no
15 one said that they want MRI scans of the nodules every
16 three months. Do you think based on the -- and I am
17 not recommending that, but based on the panel's
18 discussions do you think we have adequately addressed
19 Question Number 3?

20 DR. WITTEN: Yes, thank you.

21 CHAIRMAN CHOTI: At this point, why don't
22 we go ahead and take a break for lunch, and I will

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1 resume the FDA questions. Why don't we meet promptly
2 at 1:30 to resume.

3 (Whereupon, at 12:28 p.m., a luncheon
4 recess was taken 1:31 p.m.)

5 DR. KRAUSE: Good afternoon, everybody.
6 It's time for us to start again.

7 I hope everybody had a good lunch. If
8 everybody could please grab their seats, I think we'll
9 go on with the FDA questions as soon as everybody's
10 situated.

11 Before I start, I just wanted to reiterate
12 what I said earlier. Anyone who felt like they were
13 passed over or didn't get a chance to speak at the
14 earlier open session, we're going to have another open
15 session. If anyone's feeling a little self-conscious
16 and does not wish to make their statement because
17 there are cameras in the room, they can give their
18 statement to Ayana Hill.

19 Ayana, can you stand up so people can see
20 who you are? You can give your statement to Ayana and
21 she will give it to me, and I will be glad to read it
22 into the record.

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1 So if everybody's situated, I think we'll
2 get started for the afternoon.

3 Dr. Choti, please

4 CHAIRMAN CHOTI: Thank you, Dr. Krause.

5 So we've responded to questions 1 through
6 3, that's correct. So we're on question 4.

7 DR. LERNER: Question 4: A large volume
8 of this device, up to 11 ccs per treatment is required
9 to achieve an optimal cosmetic effect and precise
10 placement of the material in the correct dermal plane,
11 deep dermis or subcuticular layer is important.
12 Please advise FDA whether a physician training program
13 is indicated for those wishing to use this device, and
14 if so what type of training would be appropriate.

15 DR. MUNK: Excuse me. I have a question
16 for FDA. Do these questions become part of the public
17 record? The questions themselves?

18 DR. KRAUSE: Yes, they already are.

19 CHAIRMAN CHOTI: And your comments?

20 DR. MUNK: Well, what I was hoping is that
21 we could edit one word and change "cosmetic" to
22 "corrective." Is that possible?

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1 DR. WITTEN: Well, it's certainly I think
2 appropriate for you to make the comment that you think
3 that, you know, cosmetics should be corrective. I
4 mean, these questions are up on the web and they're
5 part of the transcript of the meeting.

6 DR. MUNK: Okay.

7 DR. WITTEN: But any comments to the
8 questions themselves certainly I think would be of
9 value.

10 CHAIRMAN CHOTI: Why don't we start with
11 Dr. Chang.

12 DR. CHANG: To answer question four, I
13 believe the answer is yes that there should be a
14 physician training program on the proper application
15 of this product, proper use and application as well as
16 to achieve the optimal desired effect. And the type,
17 I believe, should be modeled after the type of
18 training that Dr. Engelhard received when he went
19 overseas to know how this product was being used
20 overseas. So before he started using this in the
21 United States there was a training process, however
22 long it took. It may not require a long time period

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1 as there has been some experience by clinicians for
2 tissue fillers. But I've heard from the presentation
3 that there is a difference. And so certainly there
4 should be a training process so that clinicians would
5 be able to do this correctly.

6 CHAIRMAN CHOTI: Dr. Blumenstein?

7 DR. BLUMENSTEIN: I don't have any comment
8 on this.

9 CHAIRMAN CHOTI: Dr. Newburger?

10 DR. NEWBURGER: I agree. Training has to
11 be done in a formal hands on setting.

12 CHAIRMAN CHOTI: Dr. Munk?

13 DR. MUNK: I agree. And, you know, my
14 understanding not being a dermatologist is that there
15 is substantial variation in different filler products,
16 whether there's injection at a single point or at
17 multiple points and deep to go and what pattern to
18 use. So, definitely, yes.

19 DR. BARTOO: I agree that training should
20 be done.

21 DR. DOYLE: I think it's important,
22 particularly since many of the physicians who may be

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1 later using it will not be dermatologists and will not
2 have the necessary skills in this type of injection.
3 So I think they should have it and it should be hands
4 on.

5 DR. DOYLE: Dr. Li.

6 DR. LI: Well, I'm in a quandary because
7 if I remember right, almost all the data was between 1
8 and 8 cc, so I'm not quite sure that I know what 11 cc
9 does. I'm not at all sure that we have an optimal
10 effect and we've talked nothing about placement. So
11 I'm left with a feeling that the physicians do need
12 training, although I'm very unclear as to what that
13 training would be given the absence of that
14 information.

15 CHAIRMAN CHOTI: Dr. Olding, can you give
16 us more details how you thin should be doing this or
17 should it be restricted and how should those
18 individuals be trained?

19 DR. OLDING: May I answer a different
20 question? I think that's what you're supposed to do
21 when you're uncomfortable with the question you've
22 been asked.

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1 First of all, I think I'm going to be in
2 the minority here in saying that I don't think you
3 need special ability to inject this product. I don't
4 think you have to have special training to inject this
5 project. It's not injected any different than in any
6 other product. But what makes it different is the
7 response to its being injected is different. It just
8 doesn't theoretically sit there. We have this
9 inflammatory response.

10 So, although I will inject in the same or
11 nearly the same location as I do other products, I
12 don't know what the response to all of this, what
13 really the mechanism of action is. So I think I'm
14 going to go ahead and agree with the rest of the panel
15 or what I suspect will be the rest of the panel that
16 you do need some hands on training with the product.
17 Not to learn how to inject the product, that it's any
18 different than any others, but rather to experience
19 firsthand the result of that injection.

20 CHAIRMAN CHOTI: Dr. Li?

21 DR. LI: Can I ask Dr. Olding a question?

22 Are there any other fillers that require

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1 you to premix the slurry or the suspension prior to
2 injection?

3 DR. OLDING: There are certainly products
4 that you have to refill or that you have to
5 reconstitute. The most commonly used one is Botox.
6 But of the fillers that are currently on the market,
7 this is really the only one that I'm aware of that
8 requires a reconstitution. Perhaps Dr. Newburger
9 might refute that, but I think it's the only one.

10 DR. NEWBURGER: Isn't Symmetra --

11 DR. OLDING: I don't use Symmetra, so I'm
12 not sure.

13 CHAIRMAN CHOTI: Dr. Penneys?

14 DR. PENNEYS: Yes, I would agree that
15 education is necessary, but I'm not sure about
16 training. I mean, this morning on the record we heard
17 from a physician that less is more, that you inject
18 and wait. Well, so that's education to me. In other
19 words, there has to be suitable education on how
20 people respond to it. And I'll defer to the people
21 who actually inject it in terms of what the people
22 need for learning how to inject it.

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1 CHAIRMAN CHOTI: Dr. Fish?

2 DR. FISH: I'm just wondering about the
3 practicality of a hands-on training program and, you
4 know, how many people actually have that experience to
5 actually do it. So that thought has come to mind.

6 I would think that probably plastic
7 surgeons and dermatologists who are doing this would
8 already know how to do it. So I'd have to defer to
9 the experts in that regard, whether those folks would
10 need additional special training. I think certainly
11 if someone were not doing this and were wanting to do
12 it outside of those subspecialty fields, would
13 certainly need some kind of hands-on training.

14 Someone else can comment in terms of the
15 training if it were needed for dermatologists or
16 plastic surgeons.

17 CHAIRMAN CHOTI: Yes, Dr. Newburger?

18 DR. NEWBURGER: My comment is that the
19 current approved fillers all you fill either to
20 complete correction or overcorrection depending on the
21 substance. This is different and it seems to keep on
22 developing a response, so I think there has to be

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1 simply from that point of view a difference in terms
2 of injection technique. Because if you just take
3 people who are used to injecting for corrective or
4 cosmetic uses and have them inject this, you're going
5 to end up with more prominent lumps where there,
6 perhaps, defects -- yes, depressions.

7 DR. FISH: Yes. I understand. Thank you.

8 So there's two kinds of trainings then.
9 Kind of an education, kind of letting people know
10 versus a hands-on kind of training; is that feasible?

11 DR. NEWBURGER: Right now there is from
12 the last approved filler Restylane, they do have a
13 training program that is both by CD-ROM as well as
14 hands-on training. And that seems to be going fairly
15 well in the community. And it's not insurmountable.
16 That was also done for collagen way back when it was
17 approved several decades ago.

18 DR. OLDING: Just a question, though.
19 That, as I recall, is not a requirement to have a
20 hands-on training for Restylane. There is no
21 requirement that you have a hands-on. We did not do
22 that at that panel, I do not believe.

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1 CHAIRMAN CHOTI: And although we've heard
2 anecdotally that there's a certain technique not to
3 fill, overfill and so forth, I don't think we've seen
4 any data regarding whether technique makes a
5 difference that overfilling will result in a more
6 prominent -- and so forth. It's pretty hard to say.

7 Dr. Miller?

8 DR. MILLER: I think if this is identical
9 in use to other fillers, then probably training is not
10 necessary. If there are nuances in using this that
11 are different, then I think the clinician who uses it
12 needs to be instructed about that.

13 CHAIRMAN CHOTI: Hands-on? Videotape?
14 What are some specifics?

15 DR. MILLER: Well, I think that you know,
16 ideally hands-on. I mean it maybe require nothing
17 more than the rep whose serving that clinician just
18 being there to talk to him as he does his first one or
19 something. I mean, i'm not sure.

20 But, you know, supposedly this is a very
21 specific indication for people with a very specific
22 program. And I don't know what the numbers will be,

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1 but if the clinician wants to begin to care for these
2 people, I think that some training and how
3 specifically to care for this particular problem is
4 indicated to have instruction.

5 CHAIRMAN CHOTI: Dr. Leitch?

6 DR. LEITCH: I think as Dr. Miller was
7 saying, you know there's the issue of doing a
8 procedure in a population that other medical issues.
9 And so you don't want it done by somebody who is
10 oblivious to those other issues that these patients
11 may have or at a spa or whatever. You want it done by
12 someone who is attentive to the issues of that patient
13 as a whole. And so since it's being approved for that
14 particular population, then I think there should be
15 training materials that reflect that population as
16 well as the issues we've already discussed about, you
17 know, that you don't quite fill the defect because it
18 was have this later effect and how that might be
19 different from what people have typically done with
20 injections.

21 Again, the idea of whether everybody would
22 have hands-on training, you know sometimes that can be

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1 technically difficult to accomplish. But there should
2 be some training that is available and
3 enthusiastically supported by the company in order to
4 be certain that it is applied properly.

5 CHAIRMAN CHOTI: Mr. Witten, I think a
6 little bit of mixed feelings here, mixed views, but I
7 think the consensus is that some kind of specialized
8 training would be felt to be indicated. How the
9 specifics of that are somewhat unclear with some mixed
10 opinions.

11 Does that adequately address some of your
12 concerns regarding question four?

13 DR. WITTEN: Yes. Thank you.

14 CHAIRMAN CHOTI: Is that all for the
15 questions? Yes.

16 We can have a little bit of general
17 discussion. Dr. Blumenstein?

18 DR. BLUMENSTEIN: I'd like to ask Dr.
19 Witten some questions.

20 If this is not approved, can patients
21 still get access to it?

22 DR. WITTEN: Well, in general if a product

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1 isn't commercially available, there are mechanisms for
2 it to be available to them through studies and
3 different study designs. So that would --

4 DR. BLUMENSTEIN: You mean if they agree
5 to participate in a future study, then they would --

6 DR. WITTEN: No. They could get it as
7 part of a study of some nature. I mean, there's
8 different kinds of studies, as we've heard. There's
9 sponsor investigator studies, you know. Studies
10 supported by the sponsor. There's you know different
11 study designs depending on what stage of product
12 development a sponsor is in. So there's continued
13 access. But there's specific requirements for each of
14 those access mechanisms.

15 DR. BLUMENSTEIN: And can you explain to
16 me what compassionate use really means and how broadly
17 can that be applied, that sort of thing?

18 DR. WITTEN: Yes. Well, compassionate use
19 is -- we encourage there to be a study, for patients
20 to be enrolled if a product is not available as part
21 of a study. So in general for compassionate use, it's
22 if there's a study ongoing and then there is a patient

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1 who shows up who is in part of that specific study
2 protocol, then we may make an exception for them under
3 compassionate use. So it's not really meant to be a
4 widespread distribution mechanism. It's meant to be a
5 couple of patients here and there type of thing.

6 DR. BLUMENSTEIN: Okay.

7 DR. WITTEN: Does that answer?

8 DR. BLUMENSTEIN: Yes, that answers my
9 question.

10 Now my next question is if this is
11 approved, then could you describe to us mechanisms
12 that we as a committee could discuss or modify the
13 indication or whatever things are there to minimize
14 offlabel use or at a minimum, make it a problem for
15 those who wish to make it, to use it offlabel?

16 DR. WITTEN: I think beyond expressing the
17 concern, which we've heard very clearly today, I can't
18 think of any specific regulatory actions that you can
19 suggest or that you have as part of your discussion to
20 suggest. I mean, you could comment on labeling,
21 specific labeling that you think ought to be -- you
22 know, information that should be in the label about

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1 the product. But in terms of suggesting a mechanism
2 for it, you know, not to be available -- once a
3 product is on the market, it's really pretty much
4 practice of medicine how it's used. But there is --

5 DR. BLUMENSTEIN: But if we put things in
6 the label that indicate specific concerns and so forth
7 like that, does that the effect of limiting offlabel
8 use?

9 DR. WITTEN: I can't say what effect it
10 has on practice. It doesn't have a regulatory effect.

11 I mean there is one mechanism which, I
12 don't know whether -- there is one mechanism which we
13 have never used since I've been here. So I can't
14 really tell you exactly --

15 DR. BLUMENSTEIN: Oh, good. I want to hear
16 about this.

17 DR. WITTEN: Where you can make something
18 a restricted device. And I must admit since we
19 haven't done that ever, I can't tell you exactly what
20 that would entail. But, you know, you can express the
21 concern.

22 CHAIRMAN CHOTI: Dr. Newburger?

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1 DR. NEWBURGER: Thalidomide is available
2 to patients who have very clearly defined and
3 documented diagnoses. And if a patient fills out and
4 their physician fills out that documentation, then the
5 patient can purchase that drug.

6 Is there perhaps a similar mechanism, or
7 if that's not the one that you were obliquely
8 referring to, is it possible that something like that
9 can be established?

10 DR. WITTEN: As far as I know, there is
11 nothing like that that could be established for
12 devices. I'm not aware of anything and it's not
13 something that since I've been here that we've done.

14 You know, if you make that recommendation,
15 we could certainly look into it. Cut isn't something
16 where I could tell you this is the regulatory path we
17 would follow.

18 CHAIRMAN CHOTI: Yes.

19 DR. BLUMENSTEIN: There's Accutane. It
20 seems like that that has some kinds of restrictions
21 and might be a model, is that --

22 DR. WITTEN: Well, that's a drug.

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1 DR. BLUMENSTEIN: A drug, yes.

2 DR. WITTEN: Both of what you're citing
3 are drugs. And so they may have additional regulatory
4 authority that we don't have. So I can just say that
5 you can make the recommendation about what you think
6 we ought to try to achieve and then if, you know, we
7 can go back and evaluate that assessment and decide
8 whether we want to do that and what the mechanism
9 would be.

10 In the time that I've been at FDA, I'm not
11 aware of anything like that being done for any
12 devices.

13 Do you have anything? no.

14 CHAIRMAN CHOTI: Dr. Witten, just along
15 those lines, short of in the final recommendations of
16 the panel, if there are some panel members concerns
17 regarding offlabel use, how is that, in what context,
18 short of just seeing the transcripts of the panel's
19 discussion is that transmitted in the recommendations
20 from the panel? Is there some way to do that in the
21 conditions or in some other --

22 DR. WITTEN: Well, you know, again we

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1 certainly take every part of the discussion into
2 account when we complete our review. So we've
3 certainly heard the message about the panel's concerns
4 about offlabel use already in the discussion.

5 You know, it is something that if the
6 panel wanted to suggest as a condition that we look
7 into this possibility, you could add it as one of your
8 recommended conditions. And as I've already said, I'm
9 not sure exactly what that would translate to in terms
10 of regulatory action. But you could make that
11 recommendation.

12 In addition, I think we've heard it very
13 clearly already in the discussion to date. You
14 certainly are free to make that recommendation
15 additionally when you go to the vote with the
16 conditions. And I think that's the panel choice.

17 CHAIRMAN CHOTI: Yes, Dr. Monk?

18 DR. MUNK: May we ask the clinicians
19 present to comment on the training, especially the
20 idea that physicians who are HIV specialists but not
21 necessarily dermatologically trained maybe using this
22 product?

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1 CHAIRMAN CHOTI: Which clinicians?

2 DR. MUNK: The ones who conducted the
3 studies.

4 CHAIRMAN CHOTI: Yes. Which specific one
5 would you like to hear from?

6 DR. MUNK: All three of them in the front
7 row.

8 CHAIRMAN CHOTI: Please, go ahead and
9 address your specific question.

10 DR. MUNK: Okay. Dr. Engelhard, Dr. Conant
11 and Dr. Humble, what's your perspective? My impression
12 is that all three of you have experience with using
13 various filler products. When you think about this
14 product if it were to be approved, if it were to be
15 used by a more general population of HIV treating
16 physicians, what's your perspective on whether or not
17 training would be required and what type of training?

18 CHAIRMAN CHOTI: Could you please use the
19 microphone?

20 DR. ENGELHARD: I agree that this product
21 is no more difficult to inject, per se, than say
22 collagens or Restylane, but again the difference being

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1 that you do treat to an under treatment point and then
2 wait is the message that has to be conveyed.

3 I think a non-dermatologic physician or
4 someone that's not used to injecting intradermal or
5 subcutaneous injections anyway needs to be trained
6 whether they're going to be giving Restylane, collagen
7 or New-Fill or Sculptra. I don't think that is
8 particularly product dependent.

9 What is product dependent is the fact that
10 you under treat in areas with this product and wait.

11 So I don't know if that answers your
12 question, but I think a physician that is not using
13 dermatologic procedures should be trained in any of
14 these soft tissue correction techniques. Is Sculptra
15 going to be significantly different training wise?
16 Only in the under treatment area.

17 DR. MUNK: Thank you.

18 CHAIRMAN CHOTI: Dr. Conant?

19 DR. CONANT: You said guys that aren't
20 dermatologists, but unfortunately I'm a dermatologist,
21 too.

22 But I think quite honestly, you can train

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1 people with a CD-ROM. I'm not even sure you need
2 hands-on.

3 I went to the Netherlands and studied with
4 Danny Vieggaar, not so much because I thought I needed
5 the training. I mean I had read about under treating
6 and where to put. I wanted some proof that if I got
7 sued, that I had gone to the proper extent. And I
8 think a lot of physicians are not going to need
9 regulations from the FDA. If it's simply labeled, if
10 you don't know what you're doing be careful with this
11 stuff, that's enough. Because there are other
12 mechanisms that control physician behavior, including
13 liability.

14 CHAIRMAN CHOTI: Dr. Mest?

15 DR. MEST: I agree that hands-on physician
16 training probably isn't necessary as long as the
17 message of -- there's no much water that you put in
18 this and then that's reabsorbed; you actually have
19 this fill and then it goes down. You have to manage
20 the patient's expectations that they've lost their
21 correction because it is over a period of time. And
22 that's when you reassess and retreat. But that can

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1 easily be, I think, disseminated by probably the reps.

2 CHAIRMAN CHOTI: Yes, Dr. Witten?

3 DR. WITTEN: Yes. I wonder if I can add to
4 my answer to two prior questions.

5 And the first is for Dr. Monk. Perhaps my
6 answer wasn't complete. And, you know, we have heard
7 the concern about what this is to be used for and how
8 it is to be characterized. And I think you certainly
9 could feel free to make a comment on the indication
10 statement when it gets to the discussion of this
11 product and approvability. When you're talking about
12 public record, that probably is what's the most
13 important to I think many people, would be my guess,
14 is the indication and how that's worded. So that
15 would be a place to make your comments if you wanted.

16 And then the second regarding offlabel
17 use. I'll just say the panel could ask the sponsor
18 what they intend to do about the issue of offlabel
19 use. So that might be a question you want to ask the
20 sponsor.

21 CHAIRMAN CHOTI: Why don't we go ahead and
22 ask the sponsor now that very question. As good a

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1 time as any.

2 Who wants to field that question? Dr.
3 Levy?

4 DR. LEVY: Well, I think that relates to
5 the whole arena of training that was brought up today.

6 And the focus of our support program if the product
7 is eventually approved will hinge around training and
8 assuring that the appropriate injectors; it was
9 mentioned today most likely dermatologists, plastic
10 surgeons who have experience with injectable materials
11 so they're technically proficient. And we would
12 expect as well that there'll be a number of HIV
13 specialists who will be interested in providing this
14 kind of care to their patients. And we want to be
15 able to support them in appropriate use of this
16 product.

17 Right now we're in the midst of working
18 through the appropriate training program which would
19 include many of the things that were brought up today
20 with emphasis on very specific materials that
21 highlight technique. And we're planning to provide a
22 video CD format because I think that the technical

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1 aspects have been brought up from a lot of the
2 clinicians as well as the panels. And that needs to
3 be conveyed in a format that physicians have available
4 to them over time so they can continue to refer to it.

5 We also will have available to the
6 physicians who will needs it, and perhaps those are
7 physicians who are less acquainted with the technical
8 aspects of the product, workshop formats, regional
9 meetings so that they can see the product and
10 experience it closer and know more firsthand how to
11 use the product, as well as having support in terms of
12 the availability of peer-to-peer consultations.

13 So we'll do that to try to focus the
14 appropriate support directed to the use that's been
15 approved.

16 CHAIRMAN CHOTI: Although that addresses,
17 perhaps the training question. How will you address
18 the panel's concern regarding offlabel use?

19 DR. LEVY: Yes. Again, the information
20 that we've brought forward to the panel today deals
21 with the indication at hand, which is in correction of
22 the defects of facial lipoatrophy in HIV effected

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1 patients. And part of the training effort will be
2 directed toward education of the physician population
3 in the appropriate use of the product in the
4 appropriate patients.

5 CHAIRMAN CHOTI: Dr. Blumenstein?

6 DR. BLUMENSTEIN: Do you have any plans to
7 study the use for cosmetic purposes in other than HIV
8 patients?

9 DR. FORBES-McKEAN: Currently we do have
10 an open IDE that we are working on with the FDA and
11 are currently finalizing the plans for a protocol that
12 will look at the cosmetic use in a well controlled
13 comparative trial for that indication.

14 CHAIRMAN CHOTI: Yes?

15 DR. FISH: Do you have the data now from a
16 lot of the European usage, as we understand that it
17 seems to be quite extensive for non-HIV infected
18 individuals or for cosmetic purposes?

19 DR. FORBES-McKEAN: As Dr. Levy pointed
20 out this morning, we do have post-marketing experience
21 base don the European use of this trial which, you're
22 correct, has been in more than the HIV population has

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1 been in the cosmetic use of the product. However, to
2 get the required valid scientific evidence for safety
3 and efficacy in that population and for that use,
4 we're going to complete a comparative study as is
5 required by FDA for approval in the U.S.

6 CHAIRMAN CHOTI: Just a reminder panel,
7 that we really are focusing on the intended use based
8 on this PMA, but I think it just does transmit to the
9 FDA the concern about what may be a large population
10 of patients treated offlabel.

11 Yes, Dr. Newburger?

12 DR. NEWBURGER: I'm sorry. Back to the
13 attempt to control the conditions for which this
14 device is used. I'm still not clear how you're going
15 to control that.

16 You know, with the other fillers we see
17 all manner healthcare providers injecting them. We
18 certainly have nurse practitioners, we have
19 podiatrists in our community injecting Restylane and
20 collagen. What kind of mechanism would you think
21 would be effective in helping the healthcare provider
22 to use it for this indication?

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1 DR. FORBES-McKEAN: As Dr. Witten noted,
2 and with those other products that you noted as well,
3 all companies receive an approved label for their
4 product. And the intent is that label will reflect
5 the intended use for that product both in the
6 indication as well as in the clinical section of that
7 label we have proposed the intended use for this
8 product, as do other product. And that approved
9 labeling is what the product then is intended for its
10 use and it's what the company is bound to promote the
11 product according to that approved label. And that is
12 what we will intend to do.

13 CHAIRMAN CHOTI: Yes. Last few question.
14 Dr. Monk?

15 DR. MUNK: Do you have any experience with
16 reduction of overcorrection?

17 DR. FORBES-McKEAN: Sorry. Could you
18 repeat the question again?

19 DR. MUNK: Do you have any experience with
20 reductions of overcorrection?

21 DR. FORBES-McKEAN: For that question, I
22 would have to address that to the clinicians that have

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1 been injecting the product and ask if one of the
2 clinicians we have here has any experience, they can
3 comment on that, please. Dr. Danny Vieggaar

4 DR. VIEGGAAR: Again, my name is Danny
5 Vieggaar.

6 When I started to use the product 4? years
7 ago with some other dermatologists plus experience
8 from other countries, we were at that moment not
9 completely aware about the right technique. We had
10 advice, of course, but it was the beginning.

11 We had some overcorrections in the early
12 days and it seemed to vary amongst colleagues who had
13 several hundreds of patients between 2 and 6 percent.

14 Now for us at that time to avoid future
15 overcorrections. By discussing our experience and
16 extending our experience and fine tuning the
17 technique, we were able to diminish those
18 overcorrections to under 1 percent varying from 0.3 to
19 0.6 percent.

20 Now to follow up on those overcorrections
21 I've been doing in some of the patients gave me the
22 impression that the overcorrections, like already the

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1 discussed nodules, appear within the first year and
2 then stay stable for let's say a time of 2 years. And
3 in this time there is not really any signs of activity
4 or clinical complication. And what I observe now,
5 which is beyond 3 years in some overcorrections is
6 that without interfering there is a spontaneous
7 regression going on of these overcorrections.

8 Other management of overcorrections, of
9 course, have been tried in the way that
10 overcorrections with other products also have been
11 addressed, like intralesional injections. But after a
12 period of 3 years there does seem to be spontaneous
13 regression.

14 CHAIRMAN CHOTI: Dr. Bartoo?

15 DR. BARTOO: I'd like to find out if the
16 sponsor has any plans or protocols for further studies
17 related to this intended use?

18 DR. LEVY: Well, as we heard today from Dr.
19 Engelhard and Dr. Mest, they have ongoing protocols
20 which are still following patients for an extended
21 period for which additional data will be gained. And
22 as I understand from Dr. Mest as a follow on to the

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1 IDE protocol that was addressed this morning, there
2 will be a retreatment protocol.

3 At this time we do not have an additional
4 study that we have submitted to the FDA for review.

5 CHAIRMAN CHOTI: Thank you. If there are
6 no further questions, why don't we go on to the second
7 open public comment session.

8 As we stated earlier, all persons
9 addressing the panel speak clearly into the
10 microphone, again as the transcriptionist are
11 dependent on this for documentation.

12 Both Food and Drug Administration and the
13 public believe in a transparent process of information
14 gathering and decision making. To ensure transparency
15 at the open public hearing session of this Advisory
16 Committee meeting, the FDA believes it is important to
17 understand the context of an individual's
18 presentation. For this reason, FDA encourages you, the
19 open public hearing speaker at the beginning of your
20 written or oral statement to advise the Committee of
21 ny financial relationship that you may have with the
22 sponsor, its product and if known, its direct

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1 competitors. For example, if this financial
2 information may include the sponsor's payment to your
3 travel, lodging or other expenses in connection with
4 your attendance to this meeting.

5 Likewise, the FDA encourage you at the
6 beginning of your statement to advise the Committee if
7 you do not have any financial relationships.

8 If you choose not to address this issue of
9 financial relationships at the beginning of your
10 statement, it will not preclude you from speaking.

11 Why don't we begin again with those
12 individuals that are scheduled. The first listed is
13 Dr. Saylan.

14 DR. SAYLAN: My name is Saylan. I'm from
15 Germany. I'm a general surgeon. I inject the facial
16 fillers a lot.

17 I'm sorry. I have no financial interests.
18 Nobody paid my trip to Washington. I came yesterday
19 from Germany, Dusseldorf, for a meeting which is
20 starting tomorrow. I am the invited chair of the
21 meeting.

22 And I have been injecting in the past

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1 years the New-Fill or Sculptra several times. And I
2 had some concerns about the material.

3 I was here six weeks ago at the
4 dermatologic meeting. I presented this presentation, I
5 said why don't you present it to the FDA. I send my
6 papers. Thank you very much that you give the
7 possibility to talk here.

8 The material as the Sculptra is called
9 here, it is a poly lactic acid, natrium-carmeliose and
10 mannitol. They are all sugar products. I hope that
11 this morning here the discussion here about the
12 product itself, there was no concerns, but I do have
13 some. I want to share them with you. And these are
14 all sugar products. And as we know from the basic
15 science and microbiology, where you use them to breed
16 microbes in agar plates, which is also possible for
17 the HIV patients with not an intact immune system to
18 help infections. This is also true for the non-HIV
19 patients. But I advise the panel to limit the use of
20 this material only for the HIV patients with intact
21 immunologic system.

22 I had talked to Dr. Michael Cole at the

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1 Georgetown University. He also said to me it will be
2 not advisable to use PLA and the mannitol sugar as a
3 skin filler for HIV patients since they could be
4 regularly utilized as carbon sources by bacteria.
5 For example, mannitol is regularly by Staphylococcus
6 or those bacteria that is commonly found in the skin.

7 And I got it written here. I can give it
8 to the panel, the original piece.

9 And as I started injecting it in 1999, I
10 comment in this paper, I also original piece here in
11 German, I have it here. It can cause like all --
12 fillers. It can cause bleeding, hematomas,
13 infections, abscesses, damage to nerves. And it causes
14 an infection of the veins of the occur. You will see
15 some vasculitis, okay. But I haven't seen this
16 complications in the description to other fillers,
17 like the abscess or like the necrosis, or the nerval
18 damage.

19 And it come from the manufacturer, which
20 I heard several times here today, should be injected
21 subdermally, not deeper. And then my colleagues just
22 a few minutes ago, it should be injected

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1 subcutaneously, which is logic if you want to augment
2 the cheek bones of a patient, you have to inject a lot
3 of material there, at least 11 cubic centimeter, which
4 is more sugar, more additional infection and it may
5 cause some trouble. And in my prescriptions I have
6 from the German company it says don't inject more --
7 all 7 centimeters, it's same side. Okay. This is
8 another thing.

9 And it says if there is any kind of dermal
10 infection don't apply any new fill. This is what I
11 got written here, the original pieces. And this is my
12 infections up to 14 days. This is not an HIV patient,
13 I must tell you, but it happens by healthy patients.
14 It will also happen by the HIV patients.

15 This is the scars left after the incision.
16 And this is another thing which I have a discussion
17 with the company. The company blames me -- I've got
18 it also written here -- that I had injected Botox to
19 the glabella of the patient and for that reason the
20 New-Fill is infected here. I don't agree with this,
21 but the company wants to tell me like. And I just want
22 to present it here.

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1 These are some directions. I have given
2 antibiotic and they answer to antibiotics, which means
3 it is a bacteriologic effect. And this is in my
4 opinion, I don't know, I'm not a microbiologist, it
5 comes from the sugar in the material.

6 And another things is the granulomas.
7 This is a powder here to m ix it with the water,
8 saline or you can mix it with local anesthesia. At
9 the beginning to compensate 3 milliliters, now they
10 say 6, where some of you say 8 or 10. I don't know.
11 But I cannot mix it well. Powders stay. And they
12 cause foreign body reactions and they end up result
13 with such granulomas. You take them surgically out.
14 It is not a problem by HIV patients? I don't believe
15 that. It will be also problem there.

16 And this -- I bought a machine, a shaking
17 machine that shakes the solution for hours, for a day.

18 It's supposed to melt the powder. It doesn't
19 function every time. Some powder particulates stay
20 and they cause the infections.

21 CHAIRMAN CHOTI: Why don't you summarize
22 please, for us?

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1 DR. SAYLAN: Okay. I'll finish.

2 I've got some HIV patients. I had not
3 problem. These are infections I had with the things
4 and this is the -- it's my statistics here. I got
5 five severe infections, 12 case of hardening, 3 cases
6 of allergic reactions.

7 I believe it is -- it should be allowed to
8 inject, but only to the patients with intact
9 immunologic system.

10 Okay. Thank you very much.

11 CHAIRMAN CHOTI: Thank you, Dr. Saylan.

12 Are there any questions from the panel to
13 Dr. Saylan? Yes, Dr. Li?

14 DR. LI: Maybe not to Dr. Saylan, but
15 perhaps a sponsor comment. Is the New-Fill used in
16 Europe exactly the same as the ones that were used in
17 the clinical trials here? I mean like exactly the
18 same, not just generically?

19 DR. LEVY: Yes.

20 DR. LI: They were?

21 DR. SAYLAN: It was the same I've seen,
22 the same product. Same sugar in it, same mannitol and

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1 poly lactic acid.

2 DR. LI: Now it's going to a little finer
3 cut. So same molecular weight, same crystallinity,
4 same everything?

5 DR. LEVY: Yes.

6 DR. LI: Okay.

7 CHAIRMAN CHOTI: Sorry. Dr. Olding, a
8 question?

9 DR. OLDING: Dr. Saylan, I have a question
10 over here. Dr. Olding.

11 It is surprising for us sitting on this
12 panel to see the number, I don't know how many this
13 represents; there's no denominator to the numerator of
14 X number of infections that you've shown us. But I'm
15 surprised to see them because we haven't seen it in
16 the other studies that we've discussed.

17 DR. SAYLAN: Yes.

18 DR. OLDING: And also I believe there's a
19 reporting system in Europe, much the same as there is
20 here, for adverse effects. And I don't have that data
21 in front of me, but I believe in those adverse effects
22 lists from 1993 to 2003 there were only two reported

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1 infections.

2 Now, that tells me either they're not
3 being reported -- and in fact because you've presented
4 more than two, you're not reporting them.

5 DR. SAYLAN: That's the point. I just
6 told Dr. Krause today, I got a meeting, doctors says I
7 two cases of the New-Fill injections. I go where,
8 which patients? They don't say anything. They don't
9 give me any information.

10 I was going to come here and show you more
11 statistics, but I couldn't go -- the doctors
12 cooperate. They all keep quiet. They don't want to
13 talk about -- some of the patients you have seen. You
14 have seen that infection is already healed. It came
15 from other doctors to me. I call the doctor, how much
16 you injected, what you have done --

17 DR. OLDING: Sir, I'm sorry. I got the
18 impression when you gave this talk that it was your
19 patients. Now you're telling us that it's not? It's
20 somebody else's patients?

21 DR. SAYLAN: Two of them were other
22 doctors.

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1 DR. OLDING: Okay. And we don't know if
2 they're physicians or nonphysicians.

3 DR. SAYLAN: I think that they were
4 physicians.

5 DR. OLDING: Okay.

6 DR. SAYLAN: I treated them, yes.

7 DR. OLDING: Okay. So, again, it's
8 surprising when they're in the national statistics
9 from Europe, there were only two infections reported
10 and you've seen more than two. And, you know, one
11 would think that since you are very interested in this
12 sort of thing that you might report those so that we
13 would have data, because we're obviously using them.
14 That's just a comment.

15 And secondly, at least in the United
16 States most injectables are at least at the beginning
17 in the realm of the plastic surgeon, the
18 dermatologists who is experienced. I just wonder. We
19 were talking bout experience here. I wonder how you
20 gained your own personal experience for injection?

21 DR. SAYLAN: Before I tell you about it, I
22 want to tell you something else. In Germany where I

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1 come from, we've got a wonderful system which includes
2 everything. Since we've got the European community,
3 they all come from other countries. From Portugal,
4 from Spain, from Holland from other countries to us,
5 which we have no control about this material anymore.

6 You see, before the German authorities approved all
7 the filler themselves. Now we cannot do it. We
8 cannot do it because they come from Belize or from
9 other countries.

10 My trouble is that I know that many
11 doctors, they got infection with the facial fillers,
12 not only with New-Fill, others. And there's a big --
13 I don't know -- about the companies in Germany that
14 they bring this -- such material without any tests,
15 without any clinical tests or microbiologist tests
16 like in -- you talk to a microbiologist about it. And
17 we need an organization like you have here in Germany.

18 It's not that good in good in Germany like you have
19 it here.

20 CHAIRMAN CHOTI: Okay. Thank you, Dr.
21 Saylan.

22 Our next public speaker listed is Dr.

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1 Frechette.

2 DR. FRECHETTE: My name is Gervais
3 Frechette. I was -- I didn't have my travel sponsored
4 by Dermik and my lodges, but I have no personal
5 interest would with the company. Sorry about this.

6 So I'm an HIV specialist working in New
7 York City. I have been working with people with HIV
8 for 17 years and for the last 6 years, I would say
9 that lipoatrophy --

10 CHAIRMAN CHOTI: would you please speak up
11 a little bit?

12 DR. FRECHETTE: I'm sorry. Lipoatrophy,
13 which is the larger syndrome where facial
14 lipodystrophy is one of the problems, has been one of
15 our major concern.

16 I went, Dr. Engelhard, to get trained in
17 France with Dr. Lagienne with several workshop in the
18 year 2000/2001. And I was going to present five
19 patients of mine who have had different treatment or
20 possibility of treatment with mostly plastic surgeon.

21 I don't know if we're going to be able to get them.
22 I definitely have not seen any rate of infection like

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1 the gentleman before me has presented that. And I've
2 injected several hundred patients in the year
3 2001/2002.

4 So hopefully you will be able to see the
5 pictures. I apologize for this.

6 The first picture is a patient who saw a
7 plastic surgeon in New York City who was telling him
8 that, you know, if you have like -- I mean, if you
9 could provide \$24,000 I will give back your face to
10 you. This patient was extremely fit and had like no
11 fat where it could be like liposucked and reinjected
12 in his face. With six sessions you see the
13 difference, and I apologize for not having the proper
14 pictures. I am a physician, I am not a professional
15 photographer. But you can easily see that with six
16 sessions this patients has regained a lot of his --
17 what I would call -- would I would say normal
18 appearance even in the temples on the left side as
19 well. And that was like six sessions.

20 This patient came back. He was -- we did
21 the six sessions, the last session was in the mid
22 2002. And he came back from a retouch in 2003.

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1 He did not report any adverse events.

2 Second patient is a Haitian patient. I
3 apologize again for the poor quality of the pictures.

4 But you'll see better on the second pictures that he
5 has facial lipoatrophy on both sides. And a lot of
6 the scar from his acne when he was a teenager.

7 With again six sessions with this patient
8 we were able to: (1) correct the facial lipoatrophy.

9 You see that very well on the top pictures on the
10 left side compared to the right side and on the left
11 side. And you even correction of the scar from the
12 acne.

13 The consistency, the texture of the skin
14 is very, very nice with this patient.

15 I spoke to all these patients in the last
16 days and everybody's very happy.

17 This patient, a plastic surgeon said let's
18 cut some of your muscles, it will help you to
19 masticate. And we see the result on the left side.
20 And almost more than a year later I saw him, and did
21 about 7 treatment of New-Fill -- I'm sorry, Sculptra
22 and you see the result.

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1 The plastic surgeon kept saying to the
2 patient you will have -- I mean, these scar that you
3 see on the top left and the lower left will disappear,
4 but they were never disappearing. And, again, I spoke
5 with this patient. He is from the midwest. Is very
6 happy with his result with no retouch. And we're
7 talking about two years now.

8 This patient has seen another plastic
9 surgeon in the south where he has two implant go like
10 asymmetrical, not only just like -- one is like lower
11 than the other one, but the right one on the right
12 side actually you don't really see right now, was like
13 sticking out a little more on his right side. So my
14 concern was that I didn't want to give him a more
15 like fat face since the patient was really fit.

16 You see the correction after six
17 treatments of this patient. He did come back for a
18 touch-up. You see that I was unable to cover the right
19 side implant on this patient, but the left side was
20 like totally covering. The patient is still very
21 happy. Again, mid 2002.

22 The fifth patient, a patient who was

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1 receiving collagen treatment about \$1,000 every like
2 two months and a half and was unhappy with the result.

3 After six sessions you have the result on the right
4 side. Patient was very happy. Did come back for a
5 touch-up because he wanted to have like more perky
6 cheeks.

7 So not only you see the correction of the
8 fat pad or the cheek, but you see also the correction
9 of the temples on both side. And, again, no infection
10 or like adverse that the patient reported.

11 Thank you.

12 CHAIRMAN CHOTI: May I ask you, were you
13 participating in a trial or how did you get access to
14 the New-Fill?

15 DR. FRECHETTE: With the buyer's club in
16 2001/2002.

17 CHAIRMAN CHOTI: Thank you.

18 DR. FRECHETTE: Thank you.

19 CHAIRMAN CHOTI: Our next speaker is Diane
20 Zuckerman. Is she here?

21 MS. FOLLOWS: Good afternoon.

22 Most of you probably recognize that I am

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1 not Dr. Diane Zuckerman. My name is Jill Follows, and
2 I speak on behalf of the National Center for Policy
3 Research for Women and Families, of which Dr.
4 Zuckerman is our President.

5 Dr. Choti, Dr. Krause, members of the
6 panel, I have no conflict with either the sponsor or
7 its competitors even outside of my capacity as the
8 senior health policy fellow with this national center,
9 I also serve as a judge pro tem in the Philadelphia
10 County Court of Common Pleas and I am an acting
11 practicing attorney in Philadelphia. And I have a
12 master's in nursing.

13 The center has great respect for the work
14 of this panel and for the Food and Drug
15 Administration. And we concur in large part with the
16 expressed and reasoned opinions of this esteemed panel
17 up until this point today.

18 We additionally, are very sympathetic to
19 the desire of people with AIDS to look as healthy as
20 possible; facial fat loss can mark a person as having
21 AIDS and therefore, certainly has implications for
22 that individual's mental health and could help target

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1 that person for discriminatory behaviors. Having
2 given this preliminary statement, the center now
3 raises two particular concerns.

4 First, our center is committed to the
5 fundamental scientific principle that clinical trials
6 evaluating the safety of medical products should
7 reflect the diversity of the population that will use
8 the medical product.

9 We are supported in this position by the
10 expressed policy of the U.S. Department of Health and
11 Human Services, which is to promote the availability
12 of standard racial and ethnic data. That goal should
13 apply to all medical products, including Sculptra.
14 When there is reason to believe that variation among
15 racial or ethnic groups may influence the safety or
16 effectiveness of a medical device, then the
17 manufacturer should include all relevant racial or
18 ethnic groups in its studies.

19 The record will clearly show this panel's
20 concern over the lack of pertinent data on women and
21 minority groups, and even children query whether it is
22 timely and reasonable to pierce the veil of this

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1 sponsor's regulatory strategy and look below the
2 surface for scientific evidence that addresses the
3 concerns of the obvious offlabel uses for this device
4 among varying populations that are not studied.

5 The lack of data on women and minorities
6 has consistently been raised before this panel. The
7 National Center for Policy Research respectfully asks
8 when will this panel make it clear that data on people
9 of color and of all gender is expected for FDA
10 approval?

11 By taking such a position, this panel
12 would be in good company with former FDA Commissioner
13 Jane Henney who said it is only through participation
14 of many populations that will ultimately receive a new
15 product that we can ensure that the medical products
16 we approve are appropriate, safe and effective for all
17 Americans and not just a narrow cut of our country's
18 population.

19 In the Center's view, FDA approval should
20 require adequate research on human subjects that are
21 representative of the target population intended to be
22 treated by the medical product. The only exception

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1 should be when the manufacturer presents compelling
2 scientific evidence for the exclusion of a racial or
3 ethnic population based on legitimate study concerns
4 and agrees to label the product as contraindicated for
5 that population.

6 Our second concern at the National Center
7 mirrors that of this panel. The potential for, indeed,
8 imminent likelihood of offlabel use of this product.
9 We encourage you to make recommendations about dealing
10 with conditions of offlabel use. The Center's view is
11 not constrained by the FDA's comment that forecloses
12 you from considering offlabel use in deciding on this
13 particular PMA.

14 The Center is greatly concerned about
15 offlabel use of this product and at a minimum requests
16 your consideration of a black box warning specifying
17 the lack of long term safety data on health risks to
18 patients who are not HIV positive, as well as the lack
19 of scientific data on the risks of this product on
20 women, minorities and children.

21 Thank you for your attention.

22 CHAIRMAN CHOTI: Thank you.

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1 That concludes the scheduled speakers for
2 the open public comment session. Is there anyone else
3 in the audience that requests that would like to
4 address the panel? If so, please approach the podium.

5 If not, then again I would like to thank
6 all of you for taking time out of your schedules in
7 order to testify to this panel.

8 All right. Why don't we take a 15 minute
9 break and then we will proceed after. Thank you.

10 (Whereupon, at 2:34 p.m. a recess until
11 2:51 p.m.)

12 DR. KRAUSE: Find your chair. We don't
13 have far to go, so if everybody could find their
14 chair, we could start to get to the end.

15 Okay. I think we're just about to go here.

16 And I'd like to turn the meeting back over to Dr.
17 Choti

18 CHAIRMAN CHOTI: Thank you, Dr. Krause.

19 Before we proceed with a vote, are there
20 any further comments from anyone from the FDA? Dr.
21 Witten?

22 DR. WITTEN: No. No further comments from

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1 FDA. Thank you.

2 CHAIRMAN CHOTI: Is there any further
3 comment or summary from the Dermik Laboratories?

4 DR. FORBES-McKEAN: On behalf of Dermik,
5 I'd like to thank the members of the Advisory Panel
6 and the members of the FDA for their constructive
7 discussion and comments today.

8 We are looking forward to further
9 collaboration with the Agency to make this important
10 treatment available to people with human
11 immunodeficiency virus.

12 Lastly, Dermik would also like to extend a
13 special thanks to the patients themselves that had the
14 courage today to provide their personal experiences
15 with this debilitating condition.

16 Thank you.

17 CHAIRMAN CHOTI: Thank you.

18 Now we can proceed to the voting part.

19 Dr. Krause, will you read the voting
20 instructions to the panel at this time?

21 DR. KRAUSE: Okay. I'm going to read the
22 voting instructions. Please listen carefully.

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1 The Medical Device Amendments to the
2 Federal Food Drug and Cosmetic Act as amended by the
3 Safe Medical Devices Act of 1990 allows the Food and
4 Drug Administration to obtain a recommendation from
5 an expert advisory panel on designed medical device
6 pre-market approval applications or PMA that are filed
7 with the Agency. The PMA must stand on its own merits
8 and your recommendation must be supported by safety
9 and effectiveness data in the application or by
10 applicable publicly available information.

11 Safety is defined in the Act as reasonable
12 assurance based on valid scientific evidence that the
13 probable benefits to health under the conditions on
14 the intended use outweigh any probable risks.

15 Effectiveness is defined as reasonable
16 assurance that in a significant portion of the
17 population the use of the device for its intended use
18 and conditions of use when labeled will provide
19 clinically significant results.

20 Your recommendations options for the vote
21 are as follows:

22 Approval, if there are no conditions

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1 attached.

2 Second choice: Approvable with
3 conditions. The panel may recommend that the PMA be
4 found approvable subject to specified conditions such
5 as a physician or a patient education, labeling
6 changes or a further analysis of the existing data.
7 Prior to voting, all of the conditions should be
8 discussed by the panel.

9 The third choice is not approvable. The
10 panel may recommend that the PMA is not approvable if
11 the data do not provide a reasonable assurance that
12 the device is safe or if a reasonable assurance has
13 not been given that the device is effective under the
14 conditions of use prescribed, recommended or suggested
15 in the proposed labeling.

16 Following the voting the Chair will ask
17 each panel member to present a brief statement
18 outlining the reasons for their vote.

19 CHAIRMAN CHOTI: Thank you.

20 Is there a motion from the panel? Dr.
21 Newburger?

22 DR. NEWBURGER: I move that the device be

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1 voted as approvable with conditions.

2 CHAIRMAN CHOTI: Is there a second? Dr.
3 Olding?

4 DR. OLDING: Second.

5 CHAIRMAN CHOTI: Motion has been made for
6 approvable with conditions. So, therefore, no vote at
7 this time but we will then proceed with defining
8 conditions.

9 Do I have a motion for a first -- or a
10 condition? Dr. Chang?

11 DR. CHANG: One of the conditions is that
12 a study be undertaken so that the use of this product
13 in persons of color and in women be pursued, a minimum
14 of 2 years as this PMA is brought forth today, ideally
15 for at least 5 years.

16 CHAIRMAN CHOTI: So the motion is for a
17 post-approval study with some of the points you
18 mentioned. Is there a second to that motion?

19 DR. NEWBURGER: I second it.

20 CHAIRMAN CHOTI: Dr. Newburger second.

21 Why don't we open this condition for
22 discussion. Dr. Blumenstein?

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1 DR. BLUMENSTEIN: I think we had a
2 discussion earlier today about all of the features of
3 the study that we would like to see. So maybe we
4 could ask the FDA to just cut and paste those things
5 into this proposal?

6 CHAIRMAN CHOTI: Well, why don't you start
7 by giving some specifics regarding the general design
8 and then perhaps, what data elements we can then
9 summarize which we think are important?

10 DR. BLUMENSTEIN: We hall went around and
11 there were so many of them. Yes.

12 CHAIRMAN CHOTI: Well, there was anything
13 from a randomized trial to a long term follow up in
14 the broader patient population to both histologic and
15 clinical end points. So how do you see -- what would
16 you recommend as a post-approval trial as part of the
17 condition?

18 DR. BLUMENSTEIN: Let me think about the
19 exact structure of the trial. I mean, I think others
20 can make their favorite comments about addressing
21 different populations and so forth. I'll come back to
22 this.

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1 CHAIRMAN CHOTI: Well, I wrote a few
2 things we can talk about that were mentioned. Women
3 and minorities, looking at adverse events, some
4 questions regarding mechanistic action although that
5 data elements, that was a little bit hard to define.
6 Some mentioned variable duration of follow up. Again,
7 weight, number of touch-ups, antiviral treatment,
8 multiple injections, CD4 stratification. These were
9 some of the things mentioned at our earlier
10 discussions.

11 Can we crystalize that a little bit more?

12 Dr. Fish?

13 DR. FISH: I think ideally it would be
14 nice to have a randomized trial. And I liked the
15 design of the Chelsea-Westminster trial in terms of
16 the delayed treatment group and an immediate treatment
17 group as an internal strategy as opposed to, you know,
18 comparing it to some other product which might be much
19 more challenging. And I think the issues were that --
20 that my concerns were looking at the durability and
21 the duration of the effect, the adverse events that
22 you elucidated, long term potential side effects and

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1 analyses by CD4 strata was their different responses
2 based on low CD4s versus those with higher CD4s under
3 200, maybe 200 to 500, above 500; something like that.

4 And those, I think, were the important
5 points. And then an attempt to stratification of
6 demographics to include the groups that were left out
7 here in terms of women and minorities and potentially
8 even children, although I know that it's trickier.

9 CHAIRMAN CHOTI: Dr. Witten, may I ask you
10 if a post-approval study such as this is recommended,
11 how does one follow up the results of such a trial?
12 Who is that reported to? Is that something that the
13 panel needs to see back again or --

14 DR. WITTEN: If a post-approval study is
15 recommended and then agreed to between FDA and the
16 sponsor, the sponsor will work with FDA to design the
17 study to achieve the objective that we decide on. And
18 the study ultimately would get reported in a label.

19 So ultimately it doesn't come back to the
20 panel. It could if we had some specific questions
21 about how to interpret the results. But in general,
22 those get added to the label as extra information for

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1 the clinicians who may use the product.

2 CHAIRMAN CHOTI: Thank you.

3 Yes, Dr. Penneys?

4 DR. PENNEYS: I think a small study needs
5 to be included that addresses the histologic changes
6 that occur following injection over time. And it
7 doesn't have to be a big thing. It could be an area,
8 a non-cosmetic area that's 2 centimeters by 2
9 centimeters and injected at times zero and 3 mm punch
10 biopsies taken, for example, quarterly over a period
11 of 2 years maybe, or every 6 months. And then I would
12 be interested in seeing that in the target populations
13 that's the subject of this PMA versus a similar
14 identical study done in immunocompetent individuals
15 who are going to be used in the other study that is
16 being planned for cosmetic purposes.

17 And then all sorts of things can be done
18 with the histologic material once it's available.

19 DR. NEWBURGER: Excuse me. And I agree
20 with Penneys' suggestion. And that could also be done
21 in another area effected by lipoatrophy such as an
22 extremity which is not going to be cosmetically

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1 evident, but you would think that many of the similar
2 local environmental issues are operant there.

3 CHAIRMAN CHOTI: Any other discussion? Dr.
4 Li?

5 DR. LI: I think if you're going to do a
6 histology, I think I would put in some assessment of
7 the actual amount of PLA that's left in at those
8 different time periods, seeing as how there's some
9 discrepancy over the rate of degradation between the
10 in vitro and the in vivo data. I haven't seen
11 anything that actually tells me how long that material
12 is actually still around.

13 CHAIRMAN CHOTI: Is anybody thinking
14 about, perhaps, recommending a post-approval
15 randomized trial perhaps compared to another agent?
16 Dr. Blumenstein?

17 DR. BLUMENSTEIN: Yes. I'm -- of course.
18 I think that would be the ideal. In thinking about
19 it, though, I wonder whether we wouldn't get the same
20 kind of information from the trial they're planning
21 for strictly cosmetic use. So I'm a little reluctant
22 to be very firm on that. I think that I would rather

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1 leave it more open to address the issues and leave the
2 structure of the trial, the specific structure of the
3 trial more open.

4 CHAIRMAN CHOTI: Any further discussion on
5 this motion for this first condition?

6 The first condition motion is to recommend
7 a post-approval study, the specific of which,
8 obviously, we're not going to outline but there are
9 defined general areas regarding longer term side
10 effects, adverse effects, a broader population, some
11 stratification regarding the groups of patient,
12 histologic changes, addressing women and minorities
13 and perhaps other sites and multiple or repeat
14 injections.

15 Show of hands for approval of this first
16 condition. Those in favor? Let's record. Nine in
17 favor. And those opposed? Zero.

18 So the first condition was approved.

19 Is there a motion for a second condition?

20 Yes, Dr. Blumenstein?

21 DR. BLUMENSTEIN: Based on concern about
22 offlabel use, I would put a condition that the

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1 training program include a module explaining to the
2 student the consequences of offlabel use with respect
3 to liabilities and a potential for lawsuits, etcetera.

4 CHAIRMAN CHOTI: Let me just rephrase that
5 as a motion to recommend a training program. Any
6 seconds for that motion?

7 Yes, Dr. Newburger seconds.

8 This condition is open for discussion.

9 DR. PENNEYS: Can I ask a question. I'm
10 not sure how training connects to liability, but if
11 it's in the package insert, if there's all sorts of
12 negatives about we're not to use it in the package
13 insert, that will certainly control part of offlabel
14 usage. Because that for sure can be used as a denial
15 for a malpractice coverage in a difficult situation.
16 Is that what you're talking about?

17 DR. BLUMENSTEIN: Well, i was going to get
18 there, too.

19 DR. PENNEYS: Okay.

20 DR. BLUMENSTEIN: I just think it would be
21 a good idea for there to be something in the training
22 program.

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1 CHAIRMAN CHOTI: So the issue about
2 concerns with offlabel perhaps could be addressed in
3 the labeling, but you're bringing up the possibility
4 of bringing it up somehow in the training program?

5 The suggestion was if somehow that if the
6 training program could include indications or risks of
7 offlabel use. I think is that a fair way to specify?

8 DR. KRAUSE: Just thinking about it, I
9 would go even further and make sure that the training
10 program includes a very careful review of the data
11 collected so far and its limitations, in particular
12 its limitations with respect to uses and other -- or
13 the lack of data for the possible approval here.

14 DR. BLUMENSTEIN: Can I just get a
15 clarification? I'm writing this down.

16 And I know that we were -- you know,
17 everybody here at the table were discussing earlier a
18 training program. So do you want to make a motion for
19 a training program that includes not only training for
20 the device, but to include these other factors.

21 DR. KRAUSE: Yes.

22 DR. BLUMENSTEIN: We're talking one

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1 training program as --

2 DR. KRAUSE: Yes, we're talking about one
3 training program, one component of which would be a
4 module having to do with the potential for legal
5 ramifications for offlabel use. I think there are
6 other issues that we discussed with respect to the
7 training program, such as hands-on versus CD versus
8 all that other stuff. I'm not addressing those things
9 at this time.

10 CHAIRMAN CHOTI: But your motion is this
11 idea about offlabel, some education to be incorporated
12 within one training program?

13 DR. KRAUSE: Yes. Just this one part of
14 the training program, yes.

15 CHAIRMAN CHOTI: One part of it. Any
16 other discussion on a training program in general?
17 Dr. Miller, you think hands-on should be the way we
18 should try to craft it?

19 DR. MILLER: I think ideally hands-on, at
20 least with a rep present in first injection,
21 especially for people who don't have previous training
22 in other injectables.

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1 So some way to assure that the person
2 using this is qualified to use injectable tissue
3 fillers.

4 CHAIRMAN CHOTI: Any other discussion.
5 Dr. Olding?

6 DR. OLDING: It's difficult for me because
7 what I want is to make sure that people who have the
8 problem and that it go for its intended use only. I
9 don't know how strongly I want to feel about doing
10 these things based on how restrictive we can be in the
11 final analyses.

12 Somewhere along the line I want to be as
13 restrictive as possible in the use of this devise. I
14 don't think that restricting it to a hands-on session
15 is particularly necessarily, as I've stated before,
16 but I think it has to be limited to people who are
17 comfortable doing it and who have had experience with
18 injectables before; and I don't know how to do that.
19 I wouldn't want to be too restrictive.

20 So I would vote against us having a hands-
21 on session for the same reason that we voted against
22 it another panel, the Restylane panel.

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1 DR. KRAUSE: Can I just clarify what Dr.
2 Miller said? He said hands-on training for
3 individuals with no previous experience with tissue
4 filler.

5 DR. OLDING: Who is going to monitor that?
6 I think that any logical respectable physician would
7 certainly not inject a product that they had not
8 injected before without the rep being there at the
9 very least, no matter what the product was.

10 CHAIRMAN CHOTI: The hands-on may focus
11 more on technique, I would think, than indications.
12 Although I may be wrong. Maybe that would some enforce
13 indications.

14 Comments, Dr. Newburger?

15 DR. NEWBURGER: My comment really would
16 relate to the another condition that I'd like to --

17 CHAIRMAN CHOTI: Yes?

18 DR. MILLER: Isn't it possible to have the
19 person ordering this material have to check off a box
20 or something saying that I have experience with
21 injectables or whatever? Some way to get an
22 indication to the company before they ship it to this

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1 person that that person needs to have the rep come by
2 and show them how to do it? Because I'm impressed.
3 Because the long last nature of this and some of the
4 nuisances of injecting it and things like that, I mean
5 I'm impressed enough with it. And I don't do a lot of
6 injections, so I may have a greater discomfort level
7 than my colleague here who does a lot of injections.
8 It's a little more of a mystic to me about doing the
9 injections than maybe the average plastic surgeon.

10 So I would feel better if there was
11 someway to be sure that there was some control over
12 who does this so that it just -- you know, the nurse
13 in the HIV clinic can't just pick up the phone and
14 order a bunch of this and start injecting it and learn
15 how to do it in the first 50 patients, and then start
16 getting good results. I mean, that's what I would
17 like to avoid.

18 CHAIRMAN CHOTI: Any other discussion
19 regarding training?

20 If not, then the motion is that of
21 incorporating as the second condition a training
22 program for the use of this device and the nature of

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1 which needs to be defined a little bit more clearly,
2 but the theme is that it's incorporated a combination
3 of improved or quality and technique as well as
4 clarifying indications.

5 Can we have a vote? A show of hands for
6 those in favor of this second condition as described.

7 Those in favor? And those opposed?

8 Let the record show an unanimous decision
9 in favor of the second condition.

10 Do we have a motion for a third condition?

11 Dr. Newburger?

12 DR. NEWBURGER: Thank you, Dr. Choti.

13 We're being asked to approve this device
14 on a compassionate basis. Not on a scientific basis
15 really, but on its empirical performance. And as
16 such, I would like to take whatever steps are
17 necessary to limit its use to those who require it on
18 a compassionate basis. I don't know if the best way
19 to do that would be to have a physician registration
20 program such as is being anticipated now for Accutane,
21 which is above and beyond the SMART program which was
22 initiated by the manufacturer, the original

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1 manufacturer or whether it would be to provide
2 documentation in the records that those for whom it is
3 being used have presence of virus, CD4 counts that
4 have been compromised in some way. I don't know what
5 that mechanism is. But I would like to take stringent
6 measures at this time until we have more information
7 about its activity; all the other things that we
8 normally require to approve such an injectable device
9 where this would be used offlabel.

10 CHAIRMAN CHOTI: Can you summarize that in
11 a sentence?

12 DR. NEWBURGER: I'd like to limit in the
13 employment of this device for those who have HIV
14 associated lipoatrophy. I would like to do that either
15 by documentation that the subject has HIV induced
16 lipoatrophy or by registration of the physician who
17 gets the device shipped.

18 CHAIRMAN CHOTI: Okay. So the motion is as
19 stated to limit this device to HIV by some form of
20 documentation or registration. Do I have a second for
21 this motion? Dr. Olding seconds it.

22 This condition is open for discussion.

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1 Dr. Penneys?

2 DR. PENNEYS: Dr. Newburger, I'm just
3 curious, what does registration of the physician do?
4 In other words, suppose they order it and they use it
5 anywhere they want? Is there any penalty for that in
6 this type -- in other words, I can understand limiting
7 it to HIV positivity. That absolutely limits it
8 pretty much to this group. But what does physician
9 registration really do?

10 DR. NEWBURGER: Physician registration
11 could -- physicians who would be registered would be
12 those, really who you could be sure have read the
13 package insert. Because most physicians don't read
14 package inserts of devices they use or medications
15 even that they prescribe. And sometimes you have to
16 get someone's attention by with a 2x4 when they won't
17 listen to your words.

18 So it would just be a way to triple
19 underline the use of this device and put the physician
20 really on notice.

21 DR. PENNEYS: But they still, because they
22 have a license to practice medicine, can take this

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1 material and use it cosmetically, for example, or for
2 something else?

3 DR. NEWBURGER: Indeed. My preference
4 would be the documentation of HIV associated
5 lipoatrophy.

6 DR. OLDING: Is it possible for us to make
7 that recommendation as two separate or just as a
8 documentation of HIV? It would be my preference that
9 we do the former rather than the latter.

10 DR. FISH: Yes, I would agree. I think I
11 would potentially keep them a separate issue and just
12 have the indication or the recommendation for the
13 indication to be restricted to those who are HIV
14 positive, period. And the documentation of that being
15 in the hands of the physician.

16 DR. NEWBURGER: I would agree with that.

17 CHAIRMAN CHOTI: So we're going to
18 reformulate this motion, this description as to limit
19 this device to HIV by documentation.

20 DR. FISH: Of HIV positive sero status.

21 CHAIRMAN CHOTI: And we have a second for
22 the motion. So now this condition is open for

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1 discussion now as rephrased.

2 Yes, Dr. Li?

3 DR. LI: Perhaps this is a question for
4 Dr. Witten. I'm completely in agree with Dr.
5 Newburger's wishes.

6 How is this different from perhaps putting
7 an exclusion in the labeling, like we can exclude
8 patients that are not HIV positive? Which would be
9 the most effective way to do that?

10 DR. WITTEN: Well, I think what I'm
11 hearing the recommendation is that -- at least what it
12 sounds like is that it not actually provided unless
13 there is documentation that the patient is HIV
14 positive. I mean, I'm responding to what I'm hearing
15 the panel recommend.

16 DR. LI: Okay. But that's kind of a
17 practical suggestion or that -- that is the question?

18 DR. WITTEN: That's a very good question.
19 And as I said earlier, it's not something that we've
20 ever done that I'm aware of or at least since I've
21 been there in my division I'm not aware of that. And
22 so we will do with this panel's recommendation for

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1 this product, as we do anytime we have a panel
2 recommendation, is take the recommendation back and
3 evaluate it as we complete or review and see whether
4 there is something that we need to explore that would
5 accomplish the goal incorporated into this
6 recommendation from the panel. If this is actually a
7 condition that you all vote and agree on.

8 CHAIRMAN CHOTI: But, Dr. Witten, this may
9 limit the ability to vote for this approval with
10 condition if we don't know whether this condition can
11 actually be met. Is there a way we can find out a
12 little bit more detail about a restricted condition
13 that would actually restrict its use?

14 DR. WITTEN: Well, when you vote if you
15 vote, you're voting with recommendations. You know,
16 with recommendations for conditions. So that's your
17 vote. I mean, that's the same with any recommendation
18 for conditions that a panel makes.

19 You know, the panel makes recommendations
20 and we don't follow all of them.

21 CHAIRMAN CHOTI: Right.

22 DR. WITTEN: But the panel's made its

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1 recommendation based on their best advice to us about
2 what they thin would lead to safe and effective use of
3 the product. So we're just asking you to make your
4 recommendation about what you think would lead to safe
5 and effective use of the product. And if that
6 incorporates this recommendation, you make this
7 recommendation and you make your vote accordingly.

8 CHAIRMAN CHOTI: But it sounds like the
9 panel needs to know that this condition may not be
10 possible to be met, it sounds like. We don't know
11 enough about it.

12 Yes, Dr. Monk?

13 DR. MUNK: Yes. I'm wondering if perhaps
14 an effective way to do this would be in the labeling
15 as a contraindication that the product should not be
16 used in any patient without evidence of HIV infection?

17 CHAIRMAN CHOTI: Dr. Newburger?

18 DR. NEWBURGER: That still has an issue as
19 is the physician going to comply with the insert. As
20 I mentioned before, Thalidomide is a medication which
21 is available for certain specified conditions that the
22 treating physician has to document to the manufacturer

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1 before the manufacturer will allow the pharmacy to
2 sell it. Now, once a patient fulfills those
3 conditions, they can certainly gain access to it very
4 easily. Myeloid dysplasia is one condition. And
5 these people get a month's supply at a time, and they
6 go through this documentation every single month they
7 get the medication.

8 And I don't see that this would be
9 onerous. After at least the first few treatments, it
10 wouldn't be on a monthly basis, you know, for a couple
11 of years. So I'm wondering if that would give us
12 closer control.

13 DR. MUNK: My thinking, too, is that if is
14 a contraindication, that it's clearly a liability
15 exposure for a physician who uses in a patient without
16 HIV infection. And perhaps FDA can work on the best
17 way to implement this. I don't know.

18 CHAIRMAN CHOTI: Although that may be more
19 in a labeling condition.

20 And then the other issue is the definition
21 of contraindication without hard data supporting its
22 contraindication as opposed to -- yes. So anyway we

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1 can discuss that if that's proposed as a separate
2 condition.

3 Yes, Dr. Leitch?

4 DR. LEITCH: Well, the idea of reporting
5 to someone that the patient is HIV positive in order
6 to get the product, that may be unacceptable to the
7 patients and maybe somebody should speak to that who
8 is a patient. But I would think there would be some
9 reluctance on the part of physicians to reveal that
10 information, you know, all these HIPAA issues that
11 have come up these days. So I think particularly that
12 type of information to be released to a company might
13 be distasteful both to physicians and to patients.

14 CHAIRMAN CHOTI: Well, it sounds like
15 we've modified this condition not to a registry, per
16 se, a registration but not --

17 DR. LEITCH: No, not registering the
18 physician, but you said one way would be like with the
19 Thalidomide, confirming to the company that the
20 patient is HIV positive.

21 CHAIRMAN CHOTI: But this is really
22 restricted to HIV patients. It's just like antiviral.

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1 It's a therapy that we're recommending restricted to
2 HIV patients with lipodystrophy.

3 Dr. Fish?

4 DR. FISH: Yes. I think a parallel could
5 be using zidovudine, using AZT in someone who doesn't
6 have HIV. I mean, it would be malpractice, it
7 wouldn't be done or if it was done, you know, it just
8 wouldn't happen. So I think that the labeling if we
9 just restrict it, I agree with you that we don't need
10 a patient registration sent into the company. I'm not
11 advocating for that. But just documentation the
12 physician needs to know that they are treating HIV
13 associated lipodystrophy.

14 CHAIRMAN CHOTI: Two separate things,
15 though. It is not a labeling issue, this is a
16 recommendation that it has -- if possible, a
17 restricted use.

18 Yes. Dr. Blumenstein?

19 DR. BLUMENSTEIN: Well, I think there's
20 lots of levels of restriction on this. One is that you
21 identify the specific patient to the company before
22 their product is released. The other is that the

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1 physician who wants to use the product or the health
2 care provider, I suppose I should say it that way,
3 would just, in the order that there would be a pledge
4 that it is being ordered for a patient to take that's
5 HIV positive, in which case you're not revealing the--
6 I think the FDA has to be the one to work this out.
7 And I believe that they have some analogies. The
8 Accutane. What was it you said? Thalidomide and so
9 forth. So I think that this is a problem we have to
10 let the FDA figure out the details. But I don't
11 believe -- I think if the spirit of your
12 recommendation is to have something more than just
13 words in the label, and I think that's -- I definitely
14 go along with that.

15 CHAIRMAN CHOTI: Any other comments?

16 So the condition as specified is condition
17 3, which is to limit the use of this device in a
18 restricted fashion to patients with HIV and
19 lipodystrophy.

20 This is now up for a vote. Those in favor
21 of such a condition raise your hand? It looks like
22 it's unanimous. So let the record show that it's a

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1 unanimous vote in favor of this condition.

2 A motion for an additional condition? Dr.
3 Li?

4 DR. LI: This must be the first
5 application for something for a device where the
6 material specifications are still being worked out
7 before they get to the panel. So I think the product
8 specifications have to be specific and in place.
9 Specially going over the information they provided, I
10 believe that the primary specification should be based
11 on the final objected project, although the starting
12 material and process are important, I think the most
13 important thing is the characteristics of the final
14 injected product. This includes molecular weight,
15 crystallinity.

16 We're injecting small particles. It's a
17 little peculiar to me, i spend the rest of my life
18 trying to keep small particles out of the human body
19 and now I'm here sitting on a panel, presumably to
20 approve injecting particles into the body. But we
21 don't really have a good idea of the particle size
22 distribution of these. And we do know that that is a

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1 very important factor in cell response.

2 We've conflicting data on resorption rate.

3 And near as I could tell, no in vivo resorption rate
4 for this rate.

5 And the thing I'm perhaps most bothered
6 about, we don't seem to have any positive or negative
7 controls on this. You know, we don't really know how
8 much is too much. We don't know how fast is too fast.

9 And the other variables superimposed upon that.

10 So I think the product specifications have
11 to be worked out and they have to be worked out in the
12 absence of, I think I've said this before, in the
13 absence of a mechanism I think the product
14 specifications have to be in a very narrow band
15 limited to their actual experience. Because we have
16 very little scientific data. This whole application,
17 it's all based on experience. So I think the product
18 specifications must be -- and they may be doing this
19 already, be limited very specifically to things they
20 have already direct experience with.

21 CHAIRMAN CHOTI: So you're not a post-
22 approval trial to look at some of these questions,

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1 but--

2 DR. LI: Well, I think when we talked
3 about -- I meant, anyway, when we talked about the
4 post-approval studies are things like the actual
5 concentration of the lactic acid remaining at
6 different time periods be assessed and the histology I
7 think which was raised. So I think those would be my
8 material characteristic that I would like in the post-
9 market study.

10 But I guess what I'm raising here is I'd
11 like to put in this -- the approvable has to be, in my
12 mind, a specification sheet of what this material
13 actually is at the time it's injected, which we don't
14 have in front of us right now.

15 CHAIRMAN CHOTI: Okay. So the motion is
16 for product specification. Is there a second to that
17 motion? Dr. Pennys second.

18 This condition is open for discussion.
19 Any other comments?

20 So this information would be identified if
21 not currently available, then through additional
22 animal studies or other studies, is that your

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1 suggestion?

2 DR. LI: Well, the only thing I could see
3 where you'd want to do an animal study would be if you
4 wanted to do some in vivo resorption rate. But if
5 you're going to histology on patients, I would propose
6 that would be a better source rather than get into an
7 animal study. So I could get it however you could get
8 it. If it's already done, that's great. But if they
9 don't have the information to do these specifications,
10 they should get it.

11 CHAIRMAN CHOTI: Any further discussion on
12 that condition? Dr. Chang?

13 DR. CHANG: I'm presuming that there is a
14 standard of good manufacturing practices so that any
15 product that has been on the market has to have some
16 range and consistency. That's what I'm presuming that
17 it is even for this PMA, that there has been some
18 consistency in the product that's being used for the
19 clinical studies.

20 And so the question to Dr. Li is do you
21 want that tightened up so that they know specifically
22 what is in this vial that's being injected? Is that

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1 what you're --

2 DR. LI: Well, what I saw -- and again you
3 could me if I missed it in the volumes of data that
4 was supplied, was what I saw was a lot of
5 characteristics of what was used, but no list of what
6 the product should be. In other words, if they said
7 for instance the molecular weight was 40 to 60,000
8 after milling and in gamma irradiation. Well, if they
9 get a 30,000 is that acceptable, or if they get a
10 70,000 is that acceptable? That information is
11 nowhere in there.

12 In other words, they told us reasonably
13 well what they're using, they just didn't provide us
14 any limits of what that window is.

15 DR. CHANG: So you want a tighter limit?

16 DR. LI: Well, I want limits, period. I
17 didn't see any. Okay.

18 CHAIRMAN CHOTI: Any further discussion?

19 So this motion number 4 is up for a vote,
20 that is of providing more specifics regarding product
21 specification.

22 Those in favor raise your hand. I think

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1 it's unanimous, is that right? Yes. So for the
2 record it's unanimous to approve that specification or
3 that condition.

4 Is there a motion for an additional
5 condition? Yes, Dr. Mock?

6 DR. MUNK: I'd like to propose that the
7 Committee consider some wording changes in the
8 labeling.

9 CHAIRMAN CHOTI: So a condition regarding
10 specifications within labeling. Is there a second?
11 Dr. Fish seconds.

12 This is open for discussion. Yes, Dr.
13 Olding?

14 DR. OLDING: Are we going to go through
15 them individually as part of this now?

16 DR. FISH: I have some specific ones to
17 propose.

18 DR. OLDING: Okay.

19 CHAIRMAN CHOTI: Yes. So the motion is
20 really to define some aspects, specific aspects
21 regarding labeling.

22 DR. FISH: And these are all in the first

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1 two pages of the labeling. The first under intended
2 use and indications, it currently reads "Intended to
3 correct shape and contour deficiencies resulting from
4 facial fat loss, lipoatrophy in people with human
5 immunodeficiency virus." I would propose changing
6 that to facial fat loss, lipoatrophy caused by human
7 immunodeficiency virus infection or its treatment, the
8 reason being the possibility that some reimbursement
9 programs may balk at the fact that we've got HIV and
10 we've got lipoatrophy but we have no statement
11 connecting them causally.

12 CHAIRMAN CHOTI: Yes, Dr. Olding?

13 DR. OLDING: If I could just make a
14 friendly maybe amendment to that. Because I feel so
15 strongly about the use in this population, I would say
16 Sculptra is only intended.

17 CHAIRMAN CHOTI: And particularly if that
18 third condition, that is the restricted use, becomes
19 difficult then I think it makes sense if we're
20 concerned about it to emphasize it again as strongly
21 as possible in the labeling, if that's what the
22 feeling is.

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1 DR. MUNK: I don't know if you want to go
2 to the other comments?

3 CHAIRMAN CHOTI: Yes, why don't you.

4 DR. MUNK: Under the warnings, I would
5 like to see a stronger statement about overcorrection.
6 It currently simply says that it should be avoided,
7 but the information we heard is that overcorrections
8 may persist for two or more years.

9 CHAIRMAN CHOTI: Okay.

10 DR. MUNK: On the second page there is a
11 statement that the safety of Sculptra for use during
12 pregnancy or in infants and children has not been
13 studied. And I think there ought to be a parallel
14 statement about populations other than caucasian adult
15 males. I mean, I don't know how you would word it
16 exactly. There has been some study, but insufficient
17 study to reach conclusions about safety.

18 CHAIRMAN CHOTI: We can also specify that
19 that be highlighted in a black box or emphasized
20 within the label as well.

21 DR. MUNK: I'm not making that suggestion.

22 CHAIRMAN CHOTI: Okay.

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1 DR. MUNK: And then the last one I have is
2 under adverse events, the "nodules" appears several
3 times. And I would defer to my esteemed colleagues who
4 know more about dermatology than I do and suggest a
5 change in wording to something that is consistent with
6 dermatologic practice.

7 CHAIRMAN CHOTI: Any other discussion on
8 labeling recommendations?

9 DR. OLDING: I have some other
10 recommendations also in the warnings?

11 CHAIRMAN CHOTI: Dr. Olding?

12 DR. OLDING: Should I do that now or--

13 CHAIRMAN CHOTI: Yes.

14 DR. OLDING: I would say in the warnings,
15 you know 52 percent of these patient have nodule
16 formation whether it's palpable or visible, they have
17 nodule formation. So I would like to include that in
18 the warnings. It brings it more to the forefront
19 rather than just putting in with a whole bunch of
20 other things. And I would suggest that in the
21 warnings we write "Nodular formation occurs in 52
22 percent of the patients and extreme caution must be

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1 exercised in the per-orbital and peri-oral areas."
2 Perhaps taking out from the overcorrection should be
3 avoided change, just removing that peri-orbital and
4 peri-oral area and moving it up to the separate out.

5 And I would also suggest that in the
6 precautions to be consistent with what we're
7 recommended for the training program that we add to
8 the -- it should be only used by health care providers
9 with expertise in the correction of valan defects and
10 after completing the required training program, or
11 something to that effect, and familiarizing themselves
12 with the product and its complete package insert.

13 CHAIRMAN CHOTI: Since we're going to vote
14 on these as a group, the recommendations that were
15 brought up, are there any discussion regarding any
16 specific points that were mentioned, agree or
17 disagree?

18 DR. MILLER: Can I make one more
19 recommendation? Can I make more?

20 CHAIRMAN CHOTI: Yes, please, Dr. Miller.

21 DR. MILLER: In the warnings, just again
22 to emphasize the fact that this is not to be use din

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1 non-HIV patients, maybe we could say something like
2 the performance of this device in immunocompetent
3 individuals is uncertain and unproven and may be
4 hazardous to your health, or something like that.
5 Something to emphasize that this is not to be used in
6 that population because it really has not been
7 demonstrated satisfactorily that the -- the risk
8 profile has not been demonstrated satisfactorily.

9 CHAIRMAN CHOTI: Not to be used in non-HIV
10 patients.

11 DR. MILLER: And we keep saying it over
12 and over, I know. I mean, if a person reads this and
13 sees in over and over again, then I mean every little
14 reenforcement of that may be one fewer episode where a
15 person gets this who doesn't fit this criteria.

16 DR. OLDING: Yes, Dr. Bartoo?

17 DR. BARTOO: I have another recommendation
18 under the precautions. There's a section on no
19 studies of interactions with other drugs. Perhaps a
20 statement that there have been no studies of long term
21 safety or efficacy.

22 CHAIRMAN CHOTI: Any other discussion

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1 regarding labeling changes or specifications,
2 recommendations?

3 So the fifth condition is that of the
4 recommendations of changes in the labeling as
5 specified in the transcripts. I'm not going to go
6 over all of them. This is as a group of labeling
7 changes, this is now up for a vote.

8 Those in favor of these labeling changes,
9 raise your hand. Let the record read that it is
10 unanimous in favor of that condition.

11 Any other motions for additional
12 conditions? It looks like we have a total of five
13 conditions.

14 Just to summarize them briefly, the first
15 condition is that of a post-approval study with
16 various issues that we're concerned about. The second
17 is that of a training program. The third condition is
18 to define restricted use to HIV patients only with
19 lipodystrophy. The fourth condition is product
20 specification regarding providing more information
21 about the specifics of the product. And the fifth
22 condition about labeling recommendations.

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1 So now this PMA is -- we are to vote on
2 whether approvable. So this has been moved and
3 seconded for the pre-market approval application for
4 Sculptra from Dermik Laboratories to recommend
5 approvable with conditions. Those in favor, raise
6 your hand.

7 Let the record show that it's unanimous
8 for approval with conditions.

9 At this point, I'd like to just briefly go
10 through and -- why don't we briefly go through the
11 group and just a summary statement regarding why you
12 voted as you did. Why don't we start with Dr. Li?

13 DR. LI: Well, I have to say I voted for
14 approval, interestingly enough, more with my heart
15 than my head. I'm moved by the general need by this
16 specific patient population. I was moved by the
17 personal presentations of those who have benefitted
18 from the device. And I was also convinced of the
19 efficacy by the physicians that made the
20 presentations.

21 But what we seem to have here from my view
22 on a scientific side is a really large anecdote. And

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1 as I tell my students, data is not the plural of
2 anecdote.

3 The science really just isn't there. It
4 seems to work, but we don't really know why. And the
5 scary part there is we just really don't know what the
6 boundaries of this are; you know if you put in a
7 little too much, if you change your particle size, if
8 this really works there'll be competitors that will
9 use PGA, PGA-PLA blends and there's basically no basic
10 understanding for this device although it seems to
11 work in this patient population that they've studied.

12 I'm really bothered by we can't even
13 answer the question is this material dependent or not.

14 You know, we don't even know that much about it. So
15 the fundamentals are really virtually absent in why
16 this works the way it does.

17 So this is a vote from my heart and not
18 from my head.

19 CHAIRMAN CHOTI: Dr. Olding?

20 DR. OLDING: I won't spent a lot talking.

21 I'll just tell you that I am not comfortable with the
22 science involved. I believe that a great deal more

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1 work needs to be done by the company on that science,
2 and I think that, hopefully, the conditions we've
3 placed on the approval of this product and the
4 limitation to the people who it is intended for have
5 at least done those things.

6 And I would echo the fact that one must
7 vote from one's heart to approve this today. And I
8 will be happy to see it on the market for the patients
9 for its intended use.

10 CHAIRMAN CHOTI: Dr. Penneys?

11 DR. PENNEYS: Well, I certainly with that.

12 I keep having images of a Trojan Horse in my mind,
13 but I hope I'm wrong. In the end, there's real pain
14 and there's real improvement in the real time, and I
15 think in this case I'll take the real gain and the
16 real time and hope that we can work out these
17 unknowables going forward.

18 CHAIRMAN CHOTI: Dr. Fish?

19 DR. FISH: My approval vote is based
20 largely on the urgency of the need. Clearly that has
21 been demonstrated by those of you who have taken the
22 time to come today, and that is much appreciated.

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1 I think that I, too, am bothered by the
2 really hard scientific data that we really like when
3 we're going for approval and it puts you in somewhat
4 of an uncomfortable situation when we're making a
5 recommendation based on somewhat empiric information.

6 Our basic tenant is do no harm, and we don't want to
7 be back in five or ten years seeing pictures and
8 people very, very unhappy with treatment outcomes. And
9 so I think that's the intent of the conditions.

10 CHAIRMAN CHOTI: Dr. Miller?

11 DR. MILLER: Yes, I agree with the
12 sentiments that have been expressed. And it's really
13 the desire to see something done for these people
14 suffering with this problem that motivates me to vote
15 for it. But I would so much prefer to have a lot of
16 these questions resolved before we ever had to vote to
17 release this. And I will be extremely disappointed if
18 in the future we see that this has been sort of a back
19 door way of getting a product available whose real
20 intention is for basically to handle the hundreds of
21 thousands of people who want tissue fillers rather
22 than the thousands of people who have HIV and

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1 lipoatrophy. So I hope the sponsor will take the
2 conditions very seriously and do all they can to
3 handle this in a responsible manner.

4 DR. OLDING: Dr. Leitch?

5 DR. LEITCH: Well, my approval also is
6 highly based on the desire to help the patients and
7 listen to what they have told us today, and also the
8 data that was presented by the physicians where the
9 satisfaction seems to be very high from the patients.
10 And notably, we did not hear from the patients a
11 strong objection to approval of this product.

12 I, like the others on the panel, feel
13 strongly that the manufacturer should take to heart
14 what we've talked about in terms of what the
15 requirements would have been in order to approve this
16 for other uses. We have not been presented any data
17 that would approve it for uses outside of this
18 population. And I think we've given some hints and
19 clues about what would be required in order to do
20 that. So, I hope those recommendations will be
21 heeded.

22 CHAIRMAN CHOTI: Thank you.

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1 Dr. Chang?

2 DR. CHANG: For myself, this is primarily
3 a compassionate vote. And also with the expectation
4 of future today and a true earnestness on the part of
5 the sponsor to provide the information that has been
6 lacking for this presentation.

7 CHAIRMAN CHOTI: Dr. Blumenstein?

8 DR. BLUMENSTEIN: I think what we've been
9 given here is a whiff of efficacy data and a whiff of
10 safety data. And my vote is mainly based on the
11 perception of compassion needed for the patients to
12 which this is directed.

13 The rest of my considerations are all
14 based on scaring the sponsor. Without the
15 registration condition, I don't think I could have
16 voted for this; that is the necessity to somehow or
17 another indicate that the product is to be used in
18 HIV patients.

19 I also feel that our discussions here have
20 relayed to the sponsor the necessity for rigor about
21 any future study for cosmetic use and the need to have
22 those studies really well and to have the data that's

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1 missing from here, both product data, safety data,
2 etcetera.

3 And finally, I feel like that what our
4 discussions here have done has given some lawyers who
5 are paying attention to some bullets. And I hope that
6 everybody's paying attention to that and so that any
7 offlabel use would be conditional on knowing that
8 those lawyers have some bullets.

9 CHAIRMAN CHOTI: Dr. Newburger?

10 DR. NEWBURGER: I'm in accord with my
11 colleagues. I voted for approval because of the very
12 pressing need for a long lasting filler for this
13 terribly disfiguring condition, which is not trivial,
14 it's not simple rejuvenation or filling in wrinkles.
15 But it really relates to the fact that an individual
16 puts to the public and impacts tremendously sense of
17 self and ability to function in the world.

18 It certainly wasn't a yes vote on the
19 basis of scientific data, which is virtually absent.
20 We've been asked to suspend our criteria that we
21 normally use for other cosmetic type fillers. We have
22 made other companies really jump through hoops.

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1 I'm kind of surprised that Dermik had this
2 substance for just about two years, and we don't have
3 any further data in terms of what it does, there
4 hasn't been anything implanted. This isn't the
5 company that I know of that has an extraordinary
6 reputation in terms of their scientific studies. So I
7 hope, along with my panel members, that this is just a
8 temporary stopgap measure to make this product
9 available and that the due diligence and rigor with
10 which previous studies from this company have been
11 conducted, we will be able to read about in short
12 order.

13 CHAIRMAN CHOTI: And comments from our
14 non-voting but very instrumental members of the panel,
15 Dr. Monk, comments?

16 DR. MUNK: I'm just very pleased with the
17 Committee's decision and I think that the critical
18 needs of patients with HIV facial lipoatrophy will be
19 served by this decision and this product.

20 CHAIRMAN CHOTI: Thank you.

21 Dr. Bartoo?

22 DR. BARTOO: From an industry

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1 representative point of view, I have to echo the rest
2 of the panel's sentiment that the data that has been
3 provided here is well below par of what's industry
4 standard in terms of what kind of data people would
5 present in their PMA. I can only hope that the
6 motivation for submitting this type of data is to get
7 it approved quickly for this group of patients who
8 have the urgent need. And I think that's a good
9 reason to come forward. But I think it would behoove
10 the sponsor to really do due diligence in their post-
11 approval studies.

12 CHAIRMAN CHOTI: Dr. Doyle?

13 DR. DOYLE: I think the Committee has used
14 the old fashioned benefit and ratio of risk to benefit
15 well today. I think until such time as the patient
16 with AIDS does not base subtle but certainly real
17 discrimination and that this is a condition that is
18 just, to me, it looks as clearly as though you had
19 painted on somebody's forehead the word "AIDS," that
20 is a definite need that we did do for a compassionate
21 vote, whether the science is there or not. The non-
22 science was compelling to me in this issue.

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1 CHAIRMAN CHOTI: Dr. Witten and members of
2 the FDA, I think the panel has spoken, fortunately
3 unanimately this time. And so I think our message is
4 pretty clear.

5 Did that fulfil the requirements you asked
6 of us?

7 DR. WITTEN: Yes.

8 I'd like to thank the panel for their
9 participation in our process today. Thank you.

10 CHAIRMAN CHOTI: Thank you very much.

11 And now this meeting is adjourned.

12 (Whereupon, at 3:50 p.m. the meeting was
13 adjourned.)

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