

1 there.

2 The differences in trend for difference  
3 did not persist, however, for patients with location,  
4 ulcer location, on toes, patients with multiple  
5 ulcers, or patients with Charcot's disease. Again,  
6 though, these subgroups are very small.

7 Specifically, though, for Charcot's  
8 disease, it is notable, as the sponsor has reviewed,  
9 that for patients treated with control, whether or not  
10 they had Charcot's disease, the incidence of closure  
11 was similar and the median time to closure was  
12 similar; whereas, in the Apligraf-treated group, the  
13 patients without Charcot's disease had a higher  
14 incidence of healing than those treated with control;  
15 whereas, those who had Charcot's disease had a much  
16 lower incidence of healing compared to control as well  
17 as compared to the non-Charcot disease cohort when  
18 treated with Apligraf. The numbers here are small.

19 From the perspective of safety, laboratory  
20 assessments, vital signs, and immunologic evaluations  
21 showed no remarkable values.

22 Adverse events can be looked at in various

1 ways. Specifically, in this study, the adverse events  
2 were looked at from the perspective of study site and  
3 non-study site and well as later from the perspective  
4 of study limb and non-study limb.

5 From the perspective of study site versus  
6 non-study sites, there is some variability for wound  
7 infection and cellulitis and osteomyelitis between the  
8 groups, sometimes in one direction, sometimes in the  
9 other.

10 The non-study site, however, may have been  
11 either on the study extremity with any proximity to  
12 this study ulcer or it may have been on the non-study  
13 extremity. So, for this reason, it's reasonable to  
14 look at the incidence of infection from the  
15 perspective of the study limb versus the non-study  
16 limb.

17 These numbers are here from a previous  
18 slide and for your reference. And this represents the  
19 first incidence of any infection on the study limb.  
20 And, as the sponsor has reviewed, this included  
21 incidences of wound infection, cellulitis,  
22 osteomyelitis, gangrene, and abscess, any first

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1 infection.

2           What you see here is with the increasing  
3 application of Apligraf, there is an increasing  
4 incidence of wound infection per that subgroup again.  
5 However, also there were more patients healed total.

6           When you sum all of these infections per  
7 cohort or randomized cohort, you find that the  
8 incidence of any infections on the study limb were  
9 quite comparable. And the incidence of amputation was  
10 not increased with device use.

11           Ulcer recurrence. Ulcer recurrence can be  
12 viewed as to whether ulcer recurrence occurred before  
13 four weeks or after four weeks of closure. The  
14 American Diabetes Association refers to ulcer  
15 recurrence as being ulcers which recur at less than  
16 four weeks. And in this case, looking at the  
17 incidence of recurrence per subgroup, you see that the  
18 incidence is almost always consistently about 40  
19 percent.

20           However, of these patients, nearly all of  
21 them closed, 100 percent here, 100 percent with 2  
22 applications, 100 percent with 3 applications, and

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1 nearly all also with 5 applications, given a sum of  
2 the closure of these recurrences of 86 percent. In  
3 comparison, the closure for control patients with  
4 recurrence at less than or equal to 4 weeks of  
5 treatment was 60 percent.

6 When you look at the cohort of patients  
7 who reopen after four weeks of treatment, you see that  
8 this cohort was quite small. And it was quite small  
9 in both the Apligraf-randomized group and the control  
10 randomized group. And based on the number of patients  
11 who closed here, you see that the incidence of  
12 reclosure is also quite similar.

13 In summary, Apligraf-treated patients had  
14 53 percent of patients requiring 5 applications in a  
15 tenth for closure. The incidence of 100 percent wound  
16 closure increased with the number of Apligraf  
17 applications. The median time to 100 percent wound  
18 closure increased with the number of Apligraf  
19 applications also.

20 The Apligraf compared to control-treated  
21 patients had an increased incidence of wound closure  
22 overall and a decreased median time to wound closure

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1 overall. The difference in trend for difference did  
2 not persist in certain subgroups, but these were very  
3 small subgroups.

4 From the perspective of safety, infection  
5 rate increased with the number of applications.  
6 However, again, overall, the incidence of infection  
7 with the Apligraf and control-treated patients was  
8 comparable. Ulcer recurrence as well as lab, vital  
9 sign profiles in the Apligraf and control-treated  
10 groups were comparable and no neurologic responses  
11 were evidence to Apligraf in this study.

12 And, with this thought, I'd like to  
13 introduce Ms. Phyllis Silverman, our biostatistician  
14 who will go over the statistical perspective in the  
15 study.

16 MS. SILVERMAN: Good afternoon. I'm  
17 Phyllis Silverman, the statistical reviewer for this  
18 PMA.

19 You are already familiar with the  
20 sponsor's safety and effectiveness results. My  
21 comments will focus on issues related to the validity  
22 of the sponsor's study design and data analysis.

1 Randomization. As you are all aware, 27  
2 patients randomized to Apligraf and 42 patients  
3 randomized to the control for subsequent screening  
4 failures and not treated. I examined these patients  
5 with respect to demographics, wound characteristics,  
6 and diabetes type to ensure that there was no bias in  
7 the exclusion of these cases.

8 Many of these patients were excluded  
9 because their ulcer closed more than 30 percent during  
10 the waiting time between randomization and treatment,  
11 which was one week. The patients who were excluded  
12 had ulcers that were smaller on average than the  
13 treated population but were otherwise comparable.

14 Ideally, the sponsor should have screened  
15 first and then randomized at the initiation of  
16 treatment. However, I don't think that there was a  
17 measurable bias from exclusion of these subjects  
18 because their exclusion was based on one or more of  
19 the inclusion criteria, which wasn't evident at the  
20 time of randomization.

21 Further, the remaining cohorts of 112  
22 Apligraf and 96 controls were very comparable with

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1 respect to demographics and wound characteristics.

2 Sample size. The sponsor's study was  
3 designed to detect a 20 percent difference in healing  
4 rates with 80 percent power. This required a minimum  
5 sample size of 93 per group, which was verified at the  
6 IDE stage.

7 The sponsor exceeded this by treating 112  
8 Apligraf and 96 controls, which increased the  
9 statistical power to 84 percent. Therefore, I am  
10 comfortable that the overall sample size was adequate  
11 in the study.

12 Poolability across centers. This clinical  
13 study was conducted at 24 centers, with most centers  
14 having only a few patients. In fact, 19 of 24 centers  
15 had less than or equal to 5 patients per treatment  
16 group. And 7 out of 24 had less than or equal to 2.

17 Thus, pooling cannot be justified on a  
18 statistical basis. And we can only assume that there  
19 were no differences in patient population or the  
20 administration of the protocol across the various  
21 centers.

22 The sponsor created seven, quote, "pooled

1 centers" using the same algorithm as from their  
2 original PMA. An analysis of the pooled centers  
3 showed that there was no treatment by center  
4 interaction.

5 That is, Apligraf was numerically superior  
6 for incidence of wound closure by 12 weeks at each  
7 pooled center. In fact, Apligraf was numerically  
8 superior at 18 of the 24 individual centers. The six  
9 centers where the control did better had very small  
10 numbers. I do not see any indication that the data  
11 cannot be pooled across centers for the analysis.

12 Protocol violations. Twelve Apligraf and  
13 nine control patients were treated, even though they  
14 were considered protocol violations. Of these, seven  
15 Apligraf and two control were violations for ulcer  
16 area, which is known to be associated with healing.  
17 Six of these area violations for Apligraf were ulcers  
18 below the lower bound of one square centimeter, as  
19 opposed to only one for the control group.

20 In order to determine if there was a bias  
21 in favor of Apligraf from the inclusion of several  
22 easy-to-heal ulcers in theory, I recalculated the

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1 primary endpoint excluding the protocol violations for  
2 area. As you can see, the results were still  
3 statistically significant, even with the exclusion of  
4 the ulcer area violations.

5 Discontinued patients. Twenty-two  
6 patients per treatment arm were discontinued at some  
7 time prior to six months. Both the Apligraf and  
8 control patients each had 17 patients discontinued at  
9 or before 12 weeks and 5 patients discontinued after  
10 12 weeks. Almost all of the patients discontinued at  
11 or before 12 weeks were unhealed. After 12 weeks, the  
12 numbers are very small.

13 Given the equal discontinuation rate  
14 between the 2 arms and the fact that most discontinued  
15 patients at or prior to 12 weeks were unhealed and,  
16 therefore, counted as failures, I do not think there  
17 is any appreciable bias from the discontinued  
18 patients.

19 Further, all of these discontinued  
20 patients would be included in the Kaplan-Meier  
21 analyses for the length of time that they were  
22 followed.

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1 Last observation carried forward. The  
2 sponsor's use of last observation carried forward does  
3 not affect the primary endpoint of percent healed at  
4 or any time before 12 weeks or the time to first  
5 closure analysis with one exception, which I will  
6 mention shortly.

7 What it does affect is the by-visit  
8 analysis because wound status at missed visits is then  
9 presumed and not verified. The use of last  
10 observation carried forward was mainly as a  
11 fill-in-the-blank for patients who missed visits and  
12 generally was not used for the 12-week visit.

13 Only three healed patients, 2 Apligraf and  
14 one control, had a last observation carried forward to  
15 week 12. And two of these were from week 11.

16 The exception where the primary endpoint  
17 would be affected is if any of the 14 Apligraf and 16  
18 control patients who were both unhealed and  
19 discontinued prior to 12 weeks actually healed after  
20 they were discontinued and did so before week 12.  
21 Their healing would not have been noted, and they  
22 would have been counted as a failure, instead of a

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1 success.

2 Because the number of patients, if any,  
3 healing between discontinuation and 12 weeks would be  
4 very small and because there were nearly equal numbers  
5 of unhealed dropouts in each group, I think any bias  
6 from the use of last observation carried forward would  
7 be minimal. Further, last observation carried forward  
8 was only one of three ways the data were analyzed, all  
9 with the same conclusion.

10 Co-variable and subgroup analyses. The  
11 sponsor provided an extensive co-variable and subgroup  
12 analysis using the log-ranked test and Cox regression.  
13 Two variables of particular interest were  
14 non-progressive Charcot's foot and ulcer location.  
15 The next slide shows the subgroup analysis of the  
16 Charcot's patients.

17 Although there was no statistically  
18 significant difference in healing between Apligraf and  
19 control, the healing rate for Apligraf was less than  
20 half that of the control, which is 17.6 percent versus  
21 36.4 percent.

22 The study was not powered to pick up

1 differences based on these small sample sizes.  
2 However, in light of these results, you will be asked  
3 to comment on the clinical use of Apligraf on patients  
4 with Charcot's foot.

5 As for ulcer location, Apligraf was  
6 statistically superior when the ulcer was on the  
7 metatarsal head and numerically superior for the  
8 mid-foot, but there were virtually equal percentages  
9 for the toes.

10 I must reemphasize that the study was not  
11 powered to pick up statistical differences in these  
12 subgroups. However, based on what these data suggest,  
13 you will be asked to discuss the role of ulcer  
14 location on Apligraf performance.

15 The sponsor has met their primary  
16 endpoints with accountability at 12 weeks of at least  
17 84 percent in each group. The data were analyzed  
18 several different ways; that is, based on all treated,  
19 only on those present at a visit, and with last  
20 observation carried forward. In each of these  
21 analyses, Apligraf was consistently statistically  
22 superior to the control for the total population.

1           Although there was variability in success  
2 rates across the pooled centers, Apligraf patients  
3 fared better than their respective controls at every  
4 pooled center.

5           The fact that the study was not masked is  
6 my only concern. I cannot evaluate exactly how  
7 objective determination of wound closure was and  
8 whether the unmasking could have induced a bias in  
9 favor of Apligraf. Perhaps you as a panel can  
10 consider this issue.

11           Thank you.

12           CHAIRMAN WHALEN: Thank you.

13           Are there any questions from any of the  
14 panel to FDA about their presentation? Dr. McCauley?

15           DR. McCAULEY: The question I have  
16 actually relates to disability of your product with  
17 the use of topical antimicrobial agents. Since this  
18 is frequently an applied therapy in patients with  
19 diabetic foot ulcer, how does Apligraf stand up to --

20           CHAIRMAN WHALEN: Is this a question for  
21 FDA?

22           DR. McCAULEY: This is a question to the

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1 sponsor.

2 CHAIRMAN WHALEN: Okay. We'll get to that  
3 in a little bit. FDA has just finished their  
4 presentation. We just want to ask them any questions  
5 we may have. We're going to have the lead reviewers.  
6 And then we'll go into the general question session.

7 DR. McCAULEY: Sorry.

8 CHAIRMAN WHALEN: No questions of FDA?

9 (No response.)

10 CHAIRMAN WHALEN: Very well. We'll begin  
11 our panel discussion with panel lead reviewers. The  
12 two lead reviewers that we have are clinically Dr.  
13 Boykin and statistics Dr. DeMets. We begin with Dr.  
14 Boykin.

15 DR. BOYKIN: Thank you, Tom.

16 The analysis I believe that I'd like to  
17 discuss is based on the strengths and weaknesses of  
18 the study that we have gone over this afternoon.

19 The strength I believe has to be looked at  
20 as the product technology. Apligraf is an incredible  
21 device, which is certainly <sup>\*\*</sup>going to broaden our  
22 application for wound healing in very complex areas

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1 like no other product before it. Its design is quite  
2 ingenious.

3 And the results that we have seen thus far  
4 are quite appealing. On the other hand, the  
5 weaknesses of the study, as we have gone over, show us  
6 that perhaps the surveillance of infection could have  
7 been improved. Even the role of prior podiatric  
8 surgical procedures I believe was not adequately  
9 documented in order for us to understand how these  
10 might have played as factors in terms of the control  
11 group versus the Apligraf group as well.

12 And, as I have already mentioned, I have  
13 some significant concerns about the study design and  
14 whether or not we really have comparable groups to  
15 evaluate it.

16 The issue of this design is not specific  
17 to this study because it does not look at a comparison  
18 of this device to an autograft, but I do believe that  
19 as we go back to the consensus statement from the  
20 American Diabetes Association, we'll note that as they  
21 address the question of how should new treatments be  
22 evaluated, that they state the clinical trial should

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1 also include an evaluation of cost and also the  
2 effective treatment on a patient's quality of life.

3 I don't really believe that given the  
4 information that we have at this point that it is  
5 possible to escape the argument that there may be  
6 reason for us to compare this device to an autograft.  
7 And certainly in that same regard, the clinical cost  
8 of application and the criteria that are established  
9 for its use in clinical practice I think might be more  
10 realistically defined.

11 This is, as I said, a very valuable  
12 product. We certainly don't want its use to be  
13 abused. There has been considerable cost in its  
14 development, which will be transferred to the general  
15 public. In that same regard, we should try to protect  
16 that interest as much as we possibly can.

17 I want to congratulate the sponsors on  
18 their product. And we'll move ahead with the next  
19 statistical review.

20 CHAIRMAN WHALEN: Thank you.

21 Dr. DeMets? \*\*

22 DR. DEMETS: I have listed here some

1 issues that I just wanted to briefly touch on. I  
2 won't touch on all of them, because some of them have  
3 been done quite adequately already, but let me put up  
4 the second transparency. I want to talk about the  
5 basic design and point out a few issues which have  
6 been alluded to.

7 As the sponsor has already talked about,  
8 an ideal design would have been perhaps the one I  
9 suggested at the top, where you screen patients, you  
10 randomize, they either get treatment or you control,  
11 and somewhere downstream you do an evaluation.

12 Now, the reason this design is sort of the  
13 standard, one of the gold standards, is that at this  
14 point in time, you have comparability of your patient  
15 populations if the sample size is large enough, and it  
16 is particularly important to note that you get  
17 comparability on the things you measure, but probably  
18 more importantly on the things that you can't measure,  
19 don't know how to measure at this point in time. So  
20 you base your analysis from that point on on this  
21 issue of comparability.

22 Now -- you can scoot that up a bit, David.

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1 The design that was used was to randomize at this  
2 point, and right here you have comparability, in the  
3 sense that you have randomized. Now you begin to  
4 screen, and as a matter of fact there are screening  
5 failures, about, I think, something like 19 percent on  
6 treatment and 30 percent on control.

7 Once you begin to peel off patients, you  
8 essentially take the risk of losing comparability. In  
9 fact, you have in some sense unrandomized your  
10 standard. I wouldn't -- I would say this study should  
11 not be defined as a randomized study, because of the  
12 way this design was applied.

13 Now, I asked the question earlier about  
14 comparability, and it's true that on the baseline  
15 demographics and some risk factors, there looks like  
16 comparability, but not finding differences doesn't  
17 mean that there are no differences. You have started  
18 taking that risk. I haven't read enough to know what  
19 the logistical problems were that they went to this  
20 design. There were obviously some. But I think the  
21 risk of using this design is that you have a potential  
22 at least, perhaps serious potential for bias in the

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1 comparison, especially when there is a difference in  
2 the rates of the screening failures.

3 Well, why do -- and as statisticians, most  
4 statisticians hang on to randomization as the one  
5 point of reference, so we have kind of lost that. Let  
6 me take two quick examples to show why I think that is  
7 true. Next slide, David.

8 This is a study, it's a different disease  
9 area. I apologize, I don't have good examples that  
10 are relevant to this study. But just to illustrate  
11 the point, this is a trial in heart attack patients  
12 using a beta blocker, and if you were to reclassify  
13 the patients according to whether they were eligible  
14 or not, you get differences in rates, whether you have  
15 them in treatment group or on a control arm. In fact,  
16 you get bigger differences on the placebo arm.

17 The important point is, you can't make  
18 those differences go away by any amount of covariate  
19 adjustment. The mathematical modeling just doesn't  
20 rescue this phenomenon. So that even though we have  
21 done some covariate modeling in this study, I don't  
22 think it necessarily rules out that there aren't some

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1 inherent differences in those two populations, the  
2 ones we can't put our finger on but still exist.

3 So this is looking at eligibility -- next  
4 slide, David. If you look at how patients did,  
5 whether they complied, did the full course, withdrew,  
6 whatever, this is another example which I happen to  
7 have with me. It's a breast cancer study, post-  
8 diagnosis to post-mastectomy, and what is plotted here  
9 is the percent of the amount of drugs that while they  
10 were in the study. This is patients that were more  
11 than 85 percent, 65 to 85, and less than 65, and it is  
12 the probability of disease-free survival.

13 Well, you can see that the good compliers  
14 here do better than the poor compliers, but the  
15 problem with this slide is the placebo arm. This is  
16 the control arm, and again, no amount of mathematical  
17 modeling can make this go away.

18 So I don't think we can find total  
19 comfort, some comfort but not total comfort, in the  
20 fact that we don't see differences and we have done  
21 covariate analysis to try to do some adjustments.

22 Okay, so. I think this issue of

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1 comparability, the design that was used, is an  
2 important, and I am not, quite frankly, as comforted  
3 as others that we have established comparability.  
4 Next transparency.

5           So now this issue of unbiased evaluation.  
6 I, too, worry about that. As we all know, our goal in  
7 trials is to minimize bias. One principle is to  
8 randomize. Well, I have argued or tried to argue that  
9 we perhaps have violated that a bit. The second is to  
10 do sort of a masked or blinded evaluation in our  
11 studies where we can. We do masked evaluations in two  
12 ways. Sometimes we double blind the trial, but we  
13 can't do that here for obvious reasons. In those  
14 cases, we sometimes move to a third party.

15           Well, that was sort of done here, and I  
16 must say I don't understand all of the details well  
17 enough to know, but I have a feeling that there was  
18 some potential for bias in the way those were  
19 assessed. I'd be happy here further comments on that,  
20 but that is a concern I have, and certainly my  
21 colleague at the FDA shared that concern, so I worry  
22 about this issue of masking. Next transparency.

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1 I -- this has to do with the issue of  
2 pooling. I am not, I guess, a great fan or champion  
3 of fussing too much about poolability across centers.  
4 This is again that same trial, that beta blocker heart  
5 attack trial, and this is the odds ratio, or the  
6 hazard ratio rather. This is the overall, which was  
7 a reduction by about 20 percent in the hazard ratio  
8 for the use of beta blockers, and what's plotted here  
9 is the hazard ratio and the confidence interval for  
10 all the different 32 centers, and you can see that,  
11 even though the overall was a reduction, a significant  
12 reduction, a p-value of -- quite significant, across  
13 centers you have scatter. Most of them are to the  
14 left.

15 My point is that, if you start looking at  
16 poolability across centers, and centers are small, as  
17 all centers usually are, that you should expect  
18 scatter by chance alone. It is not surprising, and  
19 you shouldn't get upset with this study. It's a very  
20 small study, and it had a very wide confidence  
21 interval.

22 So we start asking about poolability, I

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1 think the key thing is that you randomize within  
2 centers and then pool them, and if they scatter you  
3 should not be surprised nor upset. If you start  
4 fooling around and putting things together, I'm not  
5 sure what you're really accomplishing. I know that  
6 that has been an issue with regulatory agencies here  
7 and around the world, but I am not terribly  
8 sympathetic to that exercise.

9 I would say the same thing, by the way, to  
10 go on about subgroups. If you look at subgroups in a  
11 study this size, the sheer smallness of this study is  
12 -- once you move to subgroups, I think you should put  
13 your p-value in your pocket and forget about them, and  
14 what you want to look at -- you can imagine this is A,  
15 not A, B, not B, imagine these are subgroups up here.  
16 Well, again, with a small study of this size, you  
17 should expect subgroup results to be wandering around  
18 just as well as they do by center.

19 What you want to look at is doing what I  
20 call the squint test. Squint at that picture and say,  
21 in general, are things consistent to the left side?  
22 If that's true, that's about as far as you can push a

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1 study of this size.

2 So I am not I guess sympathetic with  
3 pushing the issue of centers too much or subgroups too  
4 much. The squint test for a study of this size is  
5 about as much as the study can handle. They are  
6 designed to answer a single question, and you hope you  
7 have got enough power to do that. The trial was  
8 designed well to answer their primary question, with  
9 the caveat of unrandomizing by the screening effect.

10 Go back to that first transparency, David.  
11 I think I have covered all the points I want to touch  
12 on very quickly. The other final thing is that there  
13 is a certain amount of consistency within these  
14 subgroups, even though they are small, and a certain  
15 amount of consistency across outcomes, and I think  
16 that's supportive in a positive sense.

17 I think I have touched on all of the  
18 issues that have come up. I didn't go over last  
19 observation carried forward, but I support the  
20 comments we made earlier, so I won't cover that.  
21 That's it.

22 CHAIRMAN WHALEN: Thank you, Dr. DeMets.

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1 This is indeed now a time that any panel member can  
2 make comment or ask questions of either FDA, sponsor,  
3 or our lead presenters, and so with that in mind, I  
4 would ask Dr. McCauley if he would like to ask that  
5 question now of the sponsor, it would be appropriate.

6 DR. MCCAULEY: I just have a couple of  
7 questions for the sponsor. The first relates to  
8 topical antimicrobial agents and whether the construct  
9 actually stands up structurally to that. There has  
10 been some data to suggest that other similar type  
11 products may not work well under conditions of topical  
12 antimicrobial agents.

13 DR. SABOLINSKI: The instruction is  
14 provided in the protocol, and the only information I  
15 have is according to the approved label, where we show  
16 a listing of those agents that are not able to be  
17 used. I am actually just looking in order to read  
18 this.

19 CHAIRMAN WHALEN: Perhaps you can have  
20 your second question while that's being investigated.

21 DR. MCCAULEY: Well, my second question  
22 relates to what is it that you think that the Apligraf

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1 truly is doing. There are multiple applications that  
2 are applied on 90 percent of the patients in the study  
3 arm, and certainly in patients that have wounds with  
4 significant bacterial counts, one of the ways you can  
5 actually prepare that wound for accelerated secondary  
6 closure or for primary closure with a graft is by  
7 using an allograft to decrease bacterial counts.

8 DR. SABOLINSKI: I think that the use of  
9 an allograft at least -- now, here is -- there are  
10 preclinical studies where bacteria are seeded on a  
11 wound bed, and shown to, with application of the  
12 product, to decrease over time. That, in fact, is  
13 something that was shown in a model. We don't have  
14 information in quantitative bacteriology in patients.

15 I'm sorry. I wanted -- I was handed the  
16 information on topical agents, and I'll read that, if  
17 I could.

18 "Do not use cytotoxic agents, including  
19 Dakin's solution, mafenide acetate, Scarlet Red  
20 Dressing, Tincoban, zinc sulfate, povidine-iodine  
21 solution, or chlorhexidine with Apligraf. In vitro  
22 and in vivo histology studies, exposure to these

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1 agents degraded Apligraf. Device exposure to mafenide  
2 acetate, Polymixin, Nystat, or Dakin's solution also  
3 reduce Apligraf cell viability."

4 If it's not on this list, then things --  
5 the one instruction is to say, "Do not use these." If  
6 anything in our study was used topically, it was  
7 captured, so I guess the answer to the question is  
8 that things that are not excluded were permitted in  
9 the protocol, and then recorded.

10 I'm sorry, Dr. McCauley, the second  
11 question you had regarding the graft, how is it that  
12 you think Apligraf is working? Okay.

13 The data presented in our clinical trials  
14 really don't allow us to directly answer that. I  
15 mean, our study is how many wounds are there, how many  
16 you close, and what is the frequency and time of  
17 closure. There is -- we can speculate on how the  
18 product may be working, and -- is there a slide that  
19 just, whether it's a histology of the product, or even  
20 just a schematic, the components of the Apligraf, it  
21 may be a mechanical barrier. The keratinocytes, when  
22 supplied, are viable. In vitro assays of the product

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1 in its five day shelf life show that cytokines are  
2 released, matrix proteins are made.

3 The thing is that we don't have the data  
4 to show this in a clinical trial. We don't know  
5 mechanism of action. Speculating, I think we see a  
6 range. For instance, the ten patients who received  
7 one, received one because the product ended up with  
8 achieving closure with one. The 59 patients that  
9 received five, received weekly applications over the  
10 first four weeks because the product had not  
11 established and completely covered the wound, or there  
12 was -- there is a range, and I don't think we know.

13 I think the only thing our data allows us  
14 to conclude is that, first venous ulcer and then in  
15 this study diabetic ulcer, that more wounds are  
16 closing over the periods of time shown. This is just  
17 the slide that says, what's the potential. Dr. Boykin  
18 referred to this as well. The keratinocytes and  
19 fibroblasts are living when supplied. The lifespan of  
20 the product on a patient is not known, and the only  
21 data that I have is -- and we have discussed this with  
22 FDA, is two of ten patients over four weeks in venous

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1 ulcer, and those two patients did not have DNA  
2 appreciated by PCR at eight weeks.

3 Matrix proteins. We haven't assayed for  
4 human collagen as opposed to bovine collagen in  
5 patients, and multiple mechanisms are possible, but  
6 there is a true difference from a skin graft, and I  
7 think Dr. Falanga addressed it. This doesn't seem to  
8 behave like an allograft which isn't rejected only.  
9 I mean, it seems to behave as something other than a  
10 routine skin graft.

11 DR. FALANGA: I agree with those comments.  
12 One thing that seems to occur consistently enough to  
13 observe clinically is the stimulation of the edge of  
14 the wound. If you apply this product say three  
15 centimeters from the wound, you can stimulate that  
16 previously dormant wound to flatten, for the  
17 epithelium to start migrating.

18 This is something that has been observed  
19 with keratinocyte sheets, back even 15 to 20 years  
20 ago, and this is something that is observed with this,  
21 so that at least part of the stimulation is to somehow  
22 either lay out, maybe lay down -- this is, again,

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1 speculative, but we have been asked to comment -- lay  
2 down some matrix material, so maybe the keratinocytes  
3 from the edges of the wound are able to migrate, or  
4 somehow some signals are generated that will stimulate  
5 those cells to migrate.

6 It's a very exciting thing to try to  
7 figure out these mechanisms. I'm afraid that right  
8 now, we are still not sure as to which one might be  
9 predominant.

10 CHAIRMAN WHALEN: Any other panel members  
11 have comments to make about the entire matter, or  
12 questions of either FDA or sponsor?

13 DR. CHANG: Just a practical question.  
14 How is this product secured to the wound bed, and do  
15 you know the percentage of debridements that needed to  
16 be carried out in the OR? Was an anesthetic used, if  
17 it was sutures that secured this to the wound?

18 DR. SABOLINSKI: First, in this study  
19 suturing was not performed. The product was held in  
20 place with, basically by the pressure dressings. In  
21 other clinical trials, for instance in a burn study  
22 under the IDE, stapling was done to secure the

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1 product. In a trial treating patients with removal of  
2 lesions of any sort, running sutures or basting  
3 sutures were used, but this trial -- the venous study  
4 used just the pressure dressings as well.

5 DR. CHANG: And no debridements in the OR?

6 DR. SABOLINSKI: The entire study was run  
7 on an outpatient basis, and to the best of my  
8 knowledge, no patients were followed in the hospital,  
9 or debridements carried out in the OR.

10 CHAIRMAN WHALEN: Yes, sir.

11 DR. REGER: Could you clarify for me why  
12 such a large difference between the number of devices  
13 and the number of grafts sold or applied in Canada  
14 versus the United States. I have, if I understand  
15 correctly from one of the slides earlier, there were  
16 10,000 versus 300 or 400.

17 DR. SABOLINSKI: I'll do the best I can  
18 with this, and it's a question that, if any of our  
19 partners at Novartis would like to comment on, I would  
20 welcome them, but I believe that the answer lies with  
21 the health care system and coverage of medical costs  
22 in Canada. In fact, again, I'm not familiar with the

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1 government policies, but I believe that the device is  
2 precluded from use if a patient decides to pay on  
3 their own, that physician would not be permitted to  
4 get government money. Again, somebody could correct  
5 me with that, but it's a matter of the coverage  
6 policies.

7 CHAIRMAN WHALEN: Ms. Maher.

8 MS. MAHER: I just want to comment briefly  
9 on Dr. Boykin's comments when he reviewed it, and that  
10 is his dislike or his comments about the clinical  
11 study design. In fact, as Dr. Witten said earlier,  
12 when you are developing medical devices, you are  
13 supposed to compare it against current standard of  
14 care, and we as a panel are supposed to be evaluating  
15 the safety and efficacy of the device against the  
16 current standard of care. While I think everybody in  
17 this room would agree that cost effectiveness is an  
18 important aspect to be looking at, that's not what  
19 this panel is supposed to be reviewing right now, so  
20 I just wanted to remind everybody of that.

21 CHAIRMAN WHALEN: Dr. McCauley.

22 DR. MCCAULEY: I have one final question.

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1 Do you think your -- at least on your labeling of this  
2 product, are you suggesting by the design of the study  
3 that Apligraf is only used for patients that have  
4 previously undergone conventional therapy that have  
5 failed, or would you apply this to every patient with  
6 an ulcer that fits within the criteria of the study?

7 DR. SABOLINSKI: I think that I would  
8 comment on that and use the sponsor's experience from  
9 our venous leg ulcer trial, and the subsequent --  
10 after the advisory panel for venous leg ulcer, we then  
11 sit with FDA, and FDA and sponsor works out the label.  
12 In that case, we were instructed to put as an  
13 indication for use the study population that was  
14 defined in the protocol, and anything that is in the  
15 protocol, and in this case, use of one week of  
16 conventional care is in the protocol, it would be a  
17 decision that FDA would make ultimately.

18 CHAIRMAN WHALEN: All right. Thank you.  
19 We'll proceed to the FDA questions for the panel, if  
20 they could please be projected, and we'll attempt to  
21 answer those.

22 Just as the first question is about to be

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1 read, it is one that deals with Charcot's disease, and  
2 since Dr. Chang has orthopedics in her appointment  
3 list, we'll begin the discussion with her once we have  
4 gone over the question.

5 DR. DURFOR: Very good. The first  
6 question reminds you of the observations that were  
7 observed with patients with Charcot's disease, as well  
8 as the comments that were in the PMA about hypothesis  
9 as to why the product performed as it did, and so what  
10 we asked the panel to do is to draw upon their  
11 experience and the data in the PMA to discuss the  
12 clinical use of the device on patients with Charcot  
13 foot disease.

14 CHAIRMAN WHALEN: Dr. Chang.

15 DR. CHANG: In the Charcot foot disease,  
16 there is an obvious prominence, and so no matter what  
17 kind of padding, protective device, and attempt to  
18 avoid shear, I believe that this is a very difficult  
19 mechanical aberration in the foot anatomy that would  
20 inhibit successful use of almost any product, and so  
21 I believe that using the device would not be very  
22 successful for those patients, and instead for the

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1 patient with a Charcot deformity, a referral to an  
2 orthopedic colleague or podiatrist, or the orthopedic  
3 surgeon would be in order in order to address this  
4 anatomical defect that would really predispose a  
5 patient to difficulty in closure or recurrence of the  
6 ulcer.

7 CHAIRMAN WHALEN: Dr. Reger.

8 DR. REGER: I think this condition  
9 represents a very different mechanical environment  
10 from the general other environments that testing was  
11 done. I think this issue should be studied  
12 independent of the rest of the problem.

13 CHAIRMAN WHALEN: Dr. Boykin.

14 DR. BOYKIN: I agree with the last two  
15 comments, and feel that perhaps even though the  
16 subsets are very small here, that it appears from this  
17 study that the device does not appear to be as  
18 effective as the standard to which it was compared.

19 CHAIRMAN WHALEN: Dr. Galandiuk.

20 DR. GALANDIUK: I agree with the comments  
21 made by Dr. DeMets earlier. I think the numbers are  
22 too small, really, to make a meaningful conclusion.

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1 CHAIRMAN WHALEN: Dr. DeMets, I'm sure you  
2 agree with Dr. Galandiuk.

3 DR. DEMETS: Always. I think that there  
4 may be clinical reasons to pursue this, but I don't  
5 want us to get too stuck on those numbers, because it  
6 could be 5 out of 17 and 6 out of 22 just as easily  
7 with a direction of the wind blowing, so I think if  
8 there are clinical reasons, do it, but don't base it  
9 on those numbers.

10 CHAIRMAN WHALEN: Dr. McCauley.

11 DR. MCCAULEY: I agree. I think the  
12 numbers are too small to draw any type of conclusion,  
13 but I do think it warrants further study.

14 CHAIRMAN WHALEN: Ms. Maher.

15 MS. MAHER: I have nothing further to add.

16 CHAIRMAN WHALEN: Ms. Brinkman.

17 MS. BRINKMAN: I agree. I think it is  
18 speculative for this small of a group.

19 CHAIRMAN WHALEN: Dr. Witten, as regards  
20 the population with Charcot's foot disease, the  
21 statistical argument has been well heard and  
22 articulated that these are very small numbers. This

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1 is indeed a difficult and different population, and  
2 probably should require some further study. Does that  
3 satisfy FDA?

4 DR. WITTEN: Thank you.

5 CHAIRMAN WHALEN: Question number 2.

6 DR. DURFOR: Question number 2 reminds the  
7 panel of the incidence of wound closure as a function  
8 of ulcer location, and asks the panel to discuss the  
9 impact of ulcer location on device performance.

10 CHAIRMAN WHALEN: Thank you, and we'll  
11 begin the discussion with Dr. Reger.

12 DR. REGER: If I remember the notes here  
13 correctly, I think the same thing applies here in my  
14 thinking, that the weight bearing conditions must be  
15 considered when various parts of the foot are covered  
16 by the graft, and that was not presented here.

17 CHAIRMAN WHALEN: Dr. Boykin.

18 DR. BOYKIN: Going back to Dr. DeMets, I  
19 believe that -- I don't believe we can really make a  
20 statement about the greater degree of significance  
21 from the sample size.

22 CHAIRMAN WHALEN: Dr. Galandiuk.

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1 DR. GALANDIUK: Echoing my comments  
2 earlier, unless there is information about the number  
3 of patients who underwent metatarsal head  
4 decompression earlier, I really don't think you say  
5 that statement.

6 CHAIRMAN WHALEN: Dr. DeMets.

7 DR. DEMETS: A don't really have anything  
8 to add to what I have said before.

9 CHAIRMAN WHALEN: Dr. McCauley.

10 DR. MCCAULEY: I don't have any additional  
11 comments. I think the numbers are relatively small to  
12 really make a statement.

13 CHAIRMAN WHALEN: Ms. Maher.

14 MS. MAHER: Nothing further to add.

15 CHAIRMAN WHALEN: Ms. Brinkman.

16 MS. BRINKMAN: Nothing further to add.

17 CHAIRMAN WHALEN: Dr. Chang.

18 DR. CHANG: Same comments as Dr. McCauley.

19 CHAIRMAN WHALEN: Dr. Witten, as regards  
20 the different geographic locale on the foot, the  
21 consensus of the panel is, first of all that the  
22 numbers may be too small, and this may be a

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1 distinction without a difference.

2 The salient point that I think should be  
3 resurrected that Dr. Galandiuk first brought up, and  
4 that is that we don't know about prior podiatric  
5 procedures that may have some influence, and that  
6 might bear at least some further elucidation without  
7 being restrictive upon our eventual action. Does that  
8 satisfy FDA?

9 DR. WITTEN: Yes.

10 CHAIRMAN WHALEN: Question number 3.

11 DR. DURFOR: Question number 3 asks the  
12 panel to discuss whether the safety data provided in  
13 the PMA supplement provide a reasonable assurance that  
14 the device is safe for its intended use.

15 CHAIRMAN WHALEN: Thank you, and we start  
16 with Dr. Boykin.

17 DR. BOYKIN: Yes, I think we can say that,  
18 despite shortcomings in some isolated areas, that the  
19 device is safe.

20 CHAIRMAN WHALEN: Dr. Galandiuk.

21 DR. GALANDIUK: I agree.

22 CHAIRMAN WHALEN: Dr. DeMets.

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1 DR. DEMETS: I agree.

2 CHAIRMAN WHALEN: Dr. McCauley.

3 DR. MCCAULEY: I agree.

4 CHAIRMAN WHALEN: Ms. Maher.

5 MS. MAHER: I agree.

6 CHAIRMAN WHALEN: Ms. Brinkman.

7 MS. BRINKMAN: Agree.

8 CHAIRMAN WHALEN: Dr. Chang.

9 DR. CHANG: The data shows the device is  
10 safe.

11 CHAIRMAN WHALEN: Dr. Reger.

12 DR. REGER: I agree.

13 CHAIRMAN WHALEN: Dr. Witten, we have that  
14 almost unique, wonderfully rare, unqualified yes. The  
15 final question.

16 DR. DURFOR: Question 4 asks the panel to  
17 discuss whether the use of the device in its intended  
18 use, when accompanied by appropriate labeling, will  
19 provide a clinically significant result in a  
20 significant portion of the target population.

21 CHAIRMAN WHALEN: Thank you. Dr.  
22 Galandiuk.

1 DR. GALANDIUK: Again, sorry to come back  
2 to my same old reservation, but surgeons at my  
3 institution literally use metatarsal head  
4 decompression as one of their main ways to get  
5 metatarsal ulcers to heal, and I think without data to  
6 that effect, since the majority of these ulcers were  
7 metatarsal ulcers, I really don't think I can conclude  
8 efficacy.

9 CHAIRMAN WHALEN: Dr. DeMets.

10 DR. DEMETS: Well, my reservations have  
11 been already stated, I think, in terms of the  
12 comparability as well as the bias and the assessment.  
13 Where I struggled with this for a while, and I guess  
14 where I come down to, is that I believe, with the  
15 exception of the qualifications of my colleague here,  
16 who I always, almost always agree with, I think it is  
17 probably effective, but I wouldn't want to argue how  
18 effective, given the biases, because I think this is  
19 a small study, relatively speaking, and therefore to  
20 make too much of what the size of the effect is, I  
21 think, would be pushing it. It would take quite a bit  
22 to undo and reverse everything that is in there, so I

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1 believe that there is a reasonable chance that this is  
2 effective, but I wouldn't want to argue how effective.

3 CHAIRMAN WHALEN: Thank you. Dr.  
4 McCauley.

5 DR. MCCAULEY: I agree. I think that  
6 there are some biases and shortcomings with the study,  
7 but I think with appropriate labeling, you can target  
8 a patient population where this product may be  
9 beneficial.

10 CHAIRMAN WHALEN: Ms. Maher.

11 MS. MAHER: Nothing further to add.

12 CHAIRMAN WHALEN: Ms. Brinkman.

13 MS. BRINKMAN: Overall I think it is  
14 effective for the population that it is intended for.

15 CHAIRMAN WHALEN: Dr. Chang.

16 DR. CHANG: I believe the product is  
17 effective.

18 CHAIRMAN WHALEN: Dr. Reger.

19 DR. REGER: I agree with Dr. McCauley's  
20 comments.

21 CHAIRMAN WHALEN: Dr. Boykin.

22 DR. BOYKIN: I believe that there is

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1 effectiveness demonstrated.

2 CHAIRMAN WHALEN: Dr. Witten, the  
3 preponderance of opinion on the panel is that it is,  
4 indeed, effective. There is some question of degree,  
5 and the reservation about prior podiatric procedures  
6 remains. Does that satisfy FDA?

7 DR. WITTEN: Yes.

8 CHAIRMAN WHALEN: Thank you. That  
9 completes the questions of the FDA, and so we will  
10 proceed into the second open public hearing session of  
11 this afternoon. If there is going to be anybody who  
12 wishes to speak to us, I will then make some remarks  
13 about what they would need to do. If there is anyone  
14 from the public who wishes to address the panel, would  
15 you please indicate by standing at this point in time?

16 Very well. Since there are no requests to  
17 speak, we will proceed to the final summations,  
18 beginning with FDA and then going to sponsor.

19 DR. DURFOR: Again, the FDA thanks the  
20 panel for its time that it has spent, both in  
21 reviewing the information and discussing the  
22 information today.

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1 CHAIRMAN WHALEN: Thank you, sir. If  
2 there is any further comment from the applicant,  
3 Organogenesis, you do have up to ten minutes if you  
4 wish to make any further comments.

5 DR. SABOLINSKI: We have no further  
6 comments, thank you.

7 CHAIRMAN WHALEN: I won't ask twice.  
8 Thank you. With all respect to one of Dr. Krause's  
9 most frequent comments in my ear, we are getting ready  
10 to vote, and I will need to ask you to clear that  
11 table, please. I wouldn't say that it is an  
12 idiosyncrasy of his, but it is a frequent complaint.

13 Prior to our voting, Dr. Krause will read  
14 the voting instructions for the panel.

15 DR. KRAUSE: I must say I get great glee  
16 from chasing people away from that table.

17 The medical device amendments to the  
18 Federal Food, Drug, and Cosmetic Act, as amended by  
19 the Safe Medical Devices Act of 1990, allows the Food  
20 and Drug Administration to obtain a recommendation  
21 from an expert advisory panel on designated medical  
22 device pre-market approval applications that are filed

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1 with the agency.

2 The PMA must stand on its own merits, and  
3 your recommendation must be supported by safety and  
4 effectiveness data in the application, or by  
5 applicable publicly available information. Safety is  
6 defined in the Act as reasonable assurance, based on  
7 valid scientific evidence, that the probable benefits  
8 to health under the conditions on intended use  
9 outweigh any probable risks.

10 Effectiveness is defined as reasonable  
11 assurance that, in a significant portion of the  
12 population, the use of the device for its intended  
13 uses and conditions of use, when properly labeled,  
14 will provide clinically significant results.

15 Your recommendation options for the vote  
16 are as follows. The first option is approval, if  
17 there no conditions attached. The second option is  
18 approval with conditions. The panel may recommend  
19 that the PMA be found approvable subject to specified  
20 conditions, such as physician or patient education,  
21 labeling changes, or a further analysis of existing  
22 data.

1 Prior to voting, all of the conditions  
2 should be discussed by the panel. The third option is  
3 not approvable. The panel may recommend that the PMA  
4 is not approvable if the data do not provide a  
5 reasonable assurance that the device is safe, or if a  
6 reasonable assurance has not been given that the  
7 device is effective under the conditions of use  
8 prescribed, recommended, or suggested in the proposed  
9 labeling.

10 Following the voting, the Chair will ask  
11 each panel member to present a brief statement  
12 outlining the reasons for their vote. Thank you.

13 CHAIRMAN WHALEN: Thank you, Dr. Krause.  
14 The Chair will now entertain a motion on the matter.

15 Dr. Boykin.

16 DR. BOYKIN: Mr. Chairman, I would like to  
17 make a motion. I would like to move that the PMA for  
18 Apligraf be approvable with conditions.

19 CHAIRMAN WHALEN: Is there a second to  
20 that motion? It has been moved and seconded. The  
21 Chair will now entertain an amendment motion for a  
22 condition upon that approval.

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1 Dr. Boykin.

2 DR. BOYKIN: I would like to suggest that  
3 our amendment direct the issue of applicability of the  
4 device in the overall treatment of the diabetic ulcer  
5 patient, and that the labeling describe the use of  
6 this product, of this particular product, rather, as  
7 one which should be sought after the failure of  
8 standard therapy in the diabetic ulcer patient.

9 CHAIRMAN WHALEN: Is there a second to  
10 that amendment? Moved and seconded.

11 DR. CHANG: To clarify, would you say  
12 failure after what period of time, or prefer to leave  
13 it ambiguous?

14 DR. BOYKIN: This might not be the best  
15 place to go through all of that. I would defer to Dr.  
16 Witten's group with some counsel to come up with those  
17 guidelines.

18 CHAIRMAN WHALEN: So you would prefer to  
19 leave it indefinite as an amendment.

20 DR. BOYKIN: As an amendment, yes. It  
21 will be structured, but I don't think -- we could be  
22 here all night discussing that.

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1                   CHAIRMAN WHALEN: So the first condition  
2 or amendment has been moved and seconded, in the  
3 applicability in the overall therapy of the diabetic  
4 patient, that labeling contain some phraseology that  
5 this treatment be considered after failure of standard  
6 therapy. Any discussion of that amendment. Seeing  
7 none, all those in favor of that amendment, please  
8 signify by raising your hands.

9                   That is unanimous among the voting  
10 members, and it passes as a condition. Is there any  
11 further amendment for condition of approval? Dr.  
12 DeMets.

13                   DR. DEMETS: I don't know if this is a  
14 motion, but somehow caution should be placed in what  
15 kind of estimates of effectiveness one puts into the  
16 label. That's something you could work out, I guess,  
17 but I think I have enough worries about this that I  
18 would want to have some caution in that labeling about  
19 size of effect.

20                   CHAIRMAN WHALEN: So, if I may, then, we  
21 would want, as a condition of this approval, to  
22 suggest to FDA that there be a significant examination

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1 of how efficacy is portrayed in the labeling of this  
2 product.

3 DR. DEMETS: Something of that nature, I  
4 would move.

5 CHAIRMAN WHALEN: Is there a second for  
6 that motion? There is a second. That is open for  
7 discussion. To the microphone, please.

8 DR. REGER: Does the efficacy would  
9 include the mechanical conditions of the region of  
10 application?

11 CHAIRMAN WHALEN: While it could, I would  
12 suggest that we might want to do that as a separate  
13 condition, if you feel that's appropriate.

14 DR. REGER: I don't feel that strongly,  
15 but I'd like to know how this addressed at one time.

16 CHAIRMAN WHALEN: For the condition at  
17 hand, in terms of recommendation to FDA that there be  
18 significant examination of how efficacy is portrayed  
19 in the labeling, is there further discussion? All  
20 those in favor of that condition, then, please signify  
21 by raising your hands. Those in favor of that, if you  
22 would keep raising your hands, please.

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1 Dr. McCauley, Dr. Reger, Dr. Boykin, Dr.  
2 Galandiuk, and Dr. DeMets. Those opposed? Dr. Chang  
3 abstains. That motion carries.

4 Is there further amendment of condition.  
5 Dr. Reger, do you wish any amendment or discussion  
6 about your concerns about mechanics and weight  
7 bearing.

8 DR. REGER: Not at this time. I think it  
9 is too complex an issue to address at this particular  
10 conjuncture.

11 CHAIRMAN WHALEN: That's fine. Of course,  
12 we are proceeding toward the final vote shortly. Very  
13 good. Dr. Boykin.

14 DR. BOYKIN: I think it would valuable for  
15 us, at least since I have kind of made myself clear on  
16 how I stand about this device and what I think it  
17 might represent, that at least the labeling indicate  
18 that studies of Apligraf, when used for the treatment  
19 of the neuropathic diabetic ulcer, have not been  
20 compared against the human autograft as a means of  
21 alternative therapy.

22 In other words, I just want the user to

1 understand that this device has not been compared  
2 against a human autograft, and that they shouldn't  
3 confuse this when it is purchased.

4 CHAIRMAN WHALEN: Does that motion receive  
5 a second? It has been seconded. The motion, then, is  
6 for an amendment that the labeling contain phraseology  
7 which demonstrates that the use of Apligraf in  
8 neuropathic ulcer treatment has not been compared with  
9 standard skin grafting. That is open for discussion.  
10 Dr. Galandiuk.

11 DR. GALANDIUK: I would even modify that  
12 so that you say it has not been compared to anything  
13 but standard saline dressings.

14 CHAIRMAN WHALEN: Would you accept that as  
15 editorial? It has not been compared to anything but  
16 standard saline dressings, and not to skin grafting.  
17 Will that be --

18 DR. BOYKIN: Well, I'd like to  
19 specifically include the term "human autograft" or  
20 "human skin grafts."

21 CHAIRMAN WHALEN: "And not to human skin  
22 grafts."

1 DR. BOYKIN: Yes.

2 CHAIRMAN WHALEN: Is there any further  
3 discussion upon that amendment? Seeing none, all  
4 those in favor of that condition, please signify by  
5 raising and keeping your hands up.

6 That is unanimous. Is there any further  
7 amendment with further conditions? Seeing none, we  
8 return to the parent motion, which is that the pre-  
9 market approval application for Apligraf, from  
10 Organogenesis, be recommended as approvable with the  
11 conditions we have just voted upon. Is there any  
12 further discussion of that parent motion? Seeing  
13 none, would all those in favor please signify by  
14 raising your hands and keeping them raised?

15 That is unanimous. The recommendation of  
16 the panel is that the pre-market approval application  
17 for Apligraf from Organogenesis be recommended as  
18 approvable with conditions. I would ask that we go  
19 around the panel and briefly mention the reasons that  
20 we voted as we did, beginning with Dr. DeMets.

21 DR. DEMETS: I think there are many  
22 strengths to the study, but there are some serious

1 flaws, and my reservations about the size of the  
2 effect, I think, is the only way I could vote in favor  
3 of this, because of the design and the bias in the  
4 evaluation, and so on.

5 CHAIRMAN WHALEN: Dr. McCauley.

6 DR. MCCAULEY: I agree with Dr. DeMets's  
7 comments. I would also like to say that I think the  
8 study is designed to look at recalcitrant ulcers,  
9 ulcers which are recalcitrant to standard therapy, and  
10 I think that's a major issue.

11 CHAIRMAN WHALEN: Dr. Chang.

12 DR. CHANG: Despite the flaws mentioned in  
13 the design of the study overall, I felt that safety  
14 and efficacy was demonstrated. I did not bring this  
15 up as an amendment, but given the data, small as the  
16 sample was, a precaution or warnings -- I'll leave up  
17 to the FDA to discuss about whether Charcot's joint is  
18 an indication, or a contraindication, or a relative  
19 contraindication, and would leave that open for the  
20 FDA to do, but I just didn't feel that was appropriate  
21 to make that a formal amendment, so overall I voted  
22 yes to -- for the approval of the product.

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1 CHAIRMAN WHALEN: Dr. Reger.

2 DR. REGER: I think the investigators have  
3 presented very convincing evidence for the graft to  
4 work well in a non-weight bearing mechanical  
5 environment. I think, however, its application to an  
6 area where mechanical forces are acting upon the newly  
7 healed wound need to be investigated more closely and  
8 further.

9 CHAIRMAN WHALEN: Dr. Boykin.

10 DR. BOYKIN: I believe that given the  
11 clinical study that we have before us, it appears that  
12 this product is quite novel, safe, and effective. My  
13 concern, as with all new technology, is that the  
14 clinicians who are involved in its use not simply  
15 resign from their own curiosity about alternative  
16 methods, and that they continue to be encouraged to  
17 seek cost effective means of treating these problems.  
18 This was not part of our task today, but it certainly  
19 should be kept in mind.

20 CHAIRMAN WHALEN: Dr. Galandiuk.

21 DR. GALANDIUK: I think the device is  
22 definitely safe, and I think it is probably effective,

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1 with the same reservations I had earlier.

2 CHAIRMAN WHALEN: Thank you. I would like  
3 to thank all the panel members, and now, having  
4 completed our business, this 57<sup>th</sup> meeting of the  
5 General and Plastic Surgery Devices Panel is  
6 adjourned.

7 (Whereupon, the proceedings in the above-  
8 entitled matter were concluded at 4:51 p.m.)  
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                                  57th Meeting - Afternoon Session

Before:                       DHHS/FDA

Date:                         May 8, 2000

Place:                        Gaithersburg, MD

represents the full and complete proceedings of the  
aforementioned matter, as reported and reduced to  
typewriting.

  
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