Appendix B

APPENDIX B

Excerpt from the October 29 & 30, 2003 Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee of the Food and Drug Administration to review the safety data on Topical Immunomodulators and Topical Corticosteroids.

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ADVISORY SUBCOMMITTEE

OF THE

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

8:06 a.m.

Wednesday, October 29, 2003

The Ballrooms
The Hilton Hotel
620 Perry Parkway
Gaithersburg, Maryland

AFTERNOON SESSION

(1:03 p.m.)

DR. CHESNEY: I think we're ready for the afternoon session, if everybody could take their seats please.

This is the beginning of the open public hearing, and the FDA has a new policy which I will read, or a new statement which needs to be read before public hearings.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

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

Is there anybody who would like to speak at our open public hearing? Is there a Mr. Jerry Roth here?

MR. ROTH: Thank you. My name is Jerry Roth. I am President and owner of Hill Dermaceuticals, which in today's society makes me a dinosaur in the sense of, so to speak, the side effects stop here.

During today I wanted to let you know that every corticosteroid possibly will not fall into the side effect range of what you've seen this morning. There were three things that have been mentioned by every speaker and that is the body surface area, the vehicle, and the volume of use or the amount exposed to. And I hoped that some of these questions would get answered in the safety data that I'm going to present. I will make it very brief since we've been here long, and I'm not used to sitting still this long myself.

First of all, Derma-Smoothe/FS is a fluocinolone acetonide in a peanut oil vehicle. We conducted two independent studies for the treatment of atopic dermatitis in ages 2 to 12, and I want you to understand that the criteria for atopic dermatitis was greater than 50 percent body involvement. The data that I'm about to show has been approved by the dermatology branch of the Food and Drug Administration.

I might add that you had a pre-conference document and it mentione fluocinolone acetonide topical oil. It's ages 6 to 12. Since that time, it has been approved for ages 2 to 12.

The study design as an open-label safety study. Once again, the patient criteria was moderate to severe atopic dermatitis involving greater than 50 percent of the body. The dosage was twice a day application to the diseased skin for continuous treatment for 4 weeks. The criteria is what you ve heard all day, the cosyntropin ACTH stimulation test and the serum cortisol levels both baseline and post stimulation.

The study design was prior to day 1 and day 29 the pre-stimulatio

serum cortisol level was assessed, immediately followed by stimulation with cosyntropin, and then the post-stimulation cortisol level was taken after 60 utes.

The total population was 34 patients. There's a typo in your pre-packet. You had 33. It was 34 patients.

But 18 patients had a body involvement of greater than 75 percent of the body. 16 additional patients were involved. The body surface area was 50 to 75 percent.

The other question that we'll get answered is the amount of volume of use and the amount exposed. The average patient used in the 30-day -- in the 4-week -- or 29-day level was 9.5 milliliters and I will come back to that in just a minute.

But the baseline cortisol levels did not change from day 1 to day 29. The p value in the first study was .6. The p value in the second study, .376. When you increased or did the stimulation, the increment was no difference from day 20 -- statistical difference between day 1 and day 29.

Just for those who are not physicians, we're talking about a considerable amount of body surface area, your chest, back, front of your legs, back of your legs, arms, and so forth. So once again, I want to point out that it is a significant body surface area.

Study 1, just to review. The baseline from day 1 and 21 on the cortisol levels -- or to 29 was not statistically significant. It was .6. The increment increase in cortisol after stimulation of day 1 and after 4 weeks was not significantly different either.

Study 2 showed pretty much the same. There was not statistical difference from day 1 to day 29 in their cortisol levels as well as the increment increase.

I mentioned drug exposure. Each patient was dispensed -- and it's been brought up by several of the advisory committee today. Each patient was dispensed a 4 ounce bottle and the average usage was 9.5 milliliters. Now,

within this 4 ounce bottle, there are 12 milligrams of fluocinolone. That means that the average patient had exposure of no more than 1 milligram of ocinolone, and that is not much. I mean, that's infinitesimal compared to what you've seen and the amount of usage in the studies that have been presented today.

The conclusion, of course, 4 weeks, twice daily application of Derma-Smoothe/FS, or fluocinolone acetonide in peanut oil, to diseased skin involving 50 to 90 percent of the body surface area, there was no change in the morning baseline value of plasma cortisol, nor did it affect the cortisol stimulation by the administration of ACTH.

It has been asked several times in here this morning about efficacy, and very briefly, these patients, the 34 patients, greater than 60 percent, actually 67 percent, 23 patients had a 75 to 100 percent improvement.

I want to thank you. I know you've heard a lot of data today. If there are any questions, I would certainly --

DR. CHESNEY: Any questions for Mr. Roth? Dr. Fink.

DR. FINK: Yes. Analysis of pooled data would hide potentially outliers who had adrenal suppression. Did any of the subjects in either study show evidence of adrenal suppression?

MR. ROTH: Not one patient showed adrenal suppression. I should have said that in the beginning

DR. CHESNEY: Dr. Stratakis.

DR. STRATAKIS: The question I have is again with regard to the test that you used to assess adrenal suppression. So I think it was very nicely put forward this morning that baseline cortisol values are not a good test to assess adrenal suppression. I think that this is evident from your numbers. In one of your studies anyway, you have a baseline value of 10.73 as e average and then you have a standard deviation of 5.1 with a mean value of cortisol of 10.73?

MR. ROTH: That was the range. I think that the accepted standard

here and what the agency requires for a test is the baseline cortisol and stimulation before the study. I believe Dr. Wilkin had mentioned that there's one of these patients that haven't been treated before. At this time, that is the best that the agency has. I'm only comparing my data to the same test standards that what you've seen this morning.

DR. STRATAKIS: Do you have the numbers of the ACTH stimulated values?

MR. ROTH: Yes. I believe they're on your chart. Is it not? The increment is on there.

DR. STRATAKIS: This is the increment.

MR. ROTH: Yes, the increment.

DR. STRATAKIS: The actual number.

MR. ROTH: The actual increment, yes.

DR. STRATAKIS: The actual peak --

MR. ROTH: It more than doubled on each of those patients, and I believe at 60 minutes the standard range is a double, and I believe that each of those, the increment wasn't more than doubled in each of the patients after the stimulation.

DR. STRATAKIS: Thank you.

DR. SCHNEIDER: Obviously, these results are a little bit at variance with what we've heard earlier. Let me ask you first. The total amount of steroid that the patient was exposed to during this 29-day period was 1 milligram?

MR. ROTH: Per day.

DR. SCHNEIDER: It was 1 milligram per day.

MR. ROTH: Per day. Once again, fluocinolone is considered a light to mid potency and this vehicle is possibly less because the vasoconstriction is even less than what this same active would be in something else. If you put this amount in an ointment or cream, the amount exposed would be many times more than that 1 milligram to cover the same body surface area.

DR. SCHNEIDER: You mean the amount that was applied.

MR. ROTH: Right. In other words, being in a peanut oil base, you e spreadability. That's why the average -- and we calculated each bottle returned -- was 1 milligram per day. If this same corticosteroid may have been in an ointment or something, you would have to apply a lot more to cover the same amount of surface. Therefore you would be exposed to far more than possibly the 1 milligram per day. It may take three tubes or four tubes.

DR. SCHNEIDER: Do you have any information on differential absorption? For example, if you put the material in peanut oil, is it absorbed less through the skin?

MR. ROTH: Well, we don't get much absorption. This the product on the market in a peanut oil. We didn't do it just for this study. It was previously on the market. It was done. I can't tell you that if you put it in plain mineral oil, it's going to be any different, but the product was approved way before we did these studies. The product was initially approved in 1988 and it was also approved under a different thing for scalp psoriasis. This has been on the market. It wasn't that we put it in the peanut oil just to check for this study. The vehicle is an NDA and because of the vehicle, it is an NDA drug not a generic equivalent.

DR. SCHNEIDER: I mean, your contention is since the efficacy was the same that you achieved this equal efficacy with less total skin exposure than if you put it in a cream or a lotion and, in addition, that you may also have less systemic absorption.

MR. ROTH: I'm not telling you that this works better than the cream.

DR. SCHNEIDER: Well, you don't have a head-to-head trial.

MR. ROTH: Okay.

DR. SCHNEIDER: But the response was certainly within the range of what we heard earlier for other drugs.

MR. ROTH: Yes. The response was, yes, and that's always been the

case. Efficacy studies were done. This was done as an efficacy approval and efficacy was done at many centers for efficacy results besides these 34 ients. This was approved as an efficacy study. Once again, we showed that oil sometimes -- it has been mentioned many times in here today regarding hydration or whatever, and there have certainly been many studies done on peanut oil with hydration. So that's not our claim in the label though.

DR. SCHNEIDER: Thank you.

MR. ROTH: Okay.

DR. CHESNEY: Dr. Ebert.

DR. EBERT: Your figure of 1 to 2 percent absorption is based on what --

MR. ROTH: That was the general accepted, I believe, in the textbook of corticosteroids by Dr. Maybach. I believe that that's their accepted of what is absorbed through the skin. That I believe is a range. I don't think that's amount. However, with just 1 milligram you certainly have room for a lot more. That 1-2 percent, of course, is higher for more exposure, volume of steroids.

DR. CHESNEY: Dr. Wilkin.

DR. WILKIN: Yes. We in the review division for this product were not made aware of the content of this particular presentation in the open public section, and so I would say that we're in the position of extreme neutrality in terms of the data and the conduct of the trial. We just simply didn't prepare. Had we known and if this is an important thing to discuss, we could have reviewed this efficacy supplement, but we did not realize this was going to be discussed.

DR. CHESNEY: Any other comments, questions?

(No response.)

DR. CHESNEY: Thank you very much.

MR. ROTH: Thank you very much for your time.

DR. CHESNEY: Is there anybody else who wanted to speak in the ope