it is fungal or dermatitis or whatever.

DR. DRAKE: Fred?

DR. MILLER: This is just a point of information. How costly is this preparation, when we talk about cost effectiveness?

DR. STERN: Correct me if I am wrong, it is about, average wholesale price is $1.50 or so a gram in a 30-gram tube. $45.00 average wholesale price for this 30-gram tube plus or minus $6.00. Is that about right? So, it ain't cheap.

DR. MILLER: So I think this is the point. Again, if we don't need the preparation, if, indeed, it is not a tinea and would respond to a lesser steroid, what should be used as we are trying to economize.

DR. DRAKE: I am going to go back to my question to the committee. Do you want to let stand this absolute, "Thou shalt not ever use this ever in any circumstances," or do you want to put a modifier on there, "Because it hasn't been studied."

I guess I am still very concerned. I am with Lloyd. I apologize. As a committee chair, I am supposed to be just a facilitator and I promise I am going to quit after this, but I would like a sense of the committee as to where you are on this issue because it may be just three of us. It may be just Lloyd, Dr. Chesney and myself.

But I would like to have you give a sense of the committee to the agency where you would like them to explore a method of not sending people to the courtroom or being forbidden to use something when they might see a particular need for it at a particular time for a short period of time.

DR. STERN: So you are asking also about the label, then, which already has that very direct--

DR. DRAKE: It already has it but I think we certainly have the right to suggest that, perhaps, a modifier be put on there because I don't like to see any drug ever restricted from a physician being able to use it in any patient.

DR. KILPATRICK: Madame Chair, we are in a "Catch 22" because we don't want to recommend a weakening of the language.

DR. DRAKE: But this is an absolute forbiddance. I don't think at any time a drug should be absolutely forbidden to a physician to use if they think that particular drug is going to help that particular patient. We have been protected by law on that for years.

I quit. I am not going to say any more. John? And then I am going to call for a sense of the committee so we don't dwell on this anymore.

DR. DiGIOVANNA: I tend to agree with you and I wonder where this wording came from. I get the

understanding that this is a new wording and that it is a response--I get the sense it is a response from Schering to the adverse events that have been reported.

I agree with you that, while I don't personally use the drug, I don't personally like the drug, I think it is abused, clearly, there are physicians who find it useful. I agree with you, we should carefully think if we are going to be extreme in what is said and going to put our force of rule or force of numbers behind it, then we should feel, certainly, that it is true.

While I think that, in most situations, it should not be used in children, I think, depending on how sternly that is stated is something that should be given consideration. Now that I have said that tersely, Dr. Stern.

DR. JORDAN: It is interesting. If you read the indications and usage of this product, it is for the topical treatment of the following dermal infections; tinea pedis, cruris, tinea corporis due to organisms. Of course, this is probably not where it is used.

But then, again, I think maybe to solve this problem, they do have verbiage here that the lotion is "not recommended" rather than "not used." Maybe that would be more appropriate for the physicians that use it for some of these other purposes.

DR. DRAKE: I would like to ask the sense of the committee because we could debate this all night. Please; I am going to ask the sense of the committee on the question. I am not going to word it because I want to leave it up to the FDA to take the sense of the committee, but I would like to know the members of this committee who feel that, perhaps, there shouldn't be an absolute ban but some thought be given into providing language that allows a physician to use it in certain instances only but without--I am going to ask for the sense of the committee now.

I want to know who is in favor of putting some kind of a modifier on there so that somebody is not in trouble if they choose to use this product. Please raise your hand if you are in favor of that.

[Show of hands.]

DR. DRAKE: So you have got ten. John, so that at least helps you. I think the committee does not think this product should not be widely used or even routinely used on the pediatric population, and certainly diaper dermatitis. However, none of us want to put it in such hard language that no physician would feel comfortable using it if they thought there was a need or be beneficial to one of their patients.

DR. MINDEL: Not none.

DR. DRAKE: Yes?

DR. MINDEL: I voted against.

DR. DRAKE: How many are against it? I'm sorry. I forgot. How many are against?

[Show of hands.]

DR. DRAKE: Two are against. So it is 10 to 2.

DR. BERGFELD: Can we have some discussion of why we are against?

DR. DRAKE: Yes.

DR. BERGFELD: The reason I voted against it is because, under question 3, I have here--

DR. DRAKE: But those are not the questions we are using today, Wilma. Those were old in the book. They are not the questions we are using.

DR. BERGFELD: The point of fact is the sponsor proposed a pediatric-use labeling. Is that not the same?

DR. DRAKE: There were some documents that were removed from the packets earlier and then Wilma got a late packet. That is a late packet and that is not what is before us. The questions that are before us are on this document right here.

Is there anything anybody else wants to add to Question 4? I am going to go to Question 5. I am trying to get us done halfway on time here.

Question 5 is, "Should the pediatric section, in addition to other labeling sections for Lotrisone Cream be

changed to mirror labeling for Lotrisone Lotion as discussed in the above question?" That is sort of what we discussed earlier, should there be any difference.

I would like the committee to vote on this. If there is discussion, fine. If not, I would entertain a motion.

DR. ROSENBERG: Make them the same.

DR. DRAKE: Is that seconded?

[Second.]

DR. DRAKE: All in favor, please raise your hands.

[Show of hands.]

DR. DRAKE: Bingo.

Question 6, "Does the committee have recommendations regarding additional ways," now this is where you can get into some information that you have been on the table a lot for the committee. We have about ten minutes before break. "Does the committee have recommendations regarding additional ways to address the use of products containing superpotent topical corticosteroids in children and infants?"

Jon?

DR. WILKIN: If we could amend that to instead of saying "superpotent," just, "at the higher end."

DR. DRAKE: Okay; saying, "higher-end topical corticosteroids." Now is the time for you guys to give all

your very good ideas that we have heard here.

DR. ROSENBERG: I make a motion that the agency consider a baby product with half percent hydrocortisone in it.

DR. DRAKE: Just a second, Bill. May I ask a point of order. Is it up to the agency to consider it or is it up to a company to present it to the agency?

DR. WILKIN: Well, you know, if a sponsor presents us anything, we will consider it. I think he is encouraging a sponsor to consider--

DR. ROSENBERG: It is sort of like "Field of Dreams." If you approve it, the companies will come, I think.

DR. WILKIN: I will say to that, we will promise to consider it.

DR. PLOTT: I think that the clinical-trial data has to support the rationale for using a combination product. Historically, I have personally been involved with another combination product which did not come to the market because it could not meet that justification.

I think the problem with having a lower potency topical steroid probably has something to do with being able to meet the requirements of a combination product, not that the utility would not be appreciated, simply it does not meet the hurdle that is necessary.

DR. DRAKE: Then, Bill, that makes your motion appropriate because what we are hearing from Todd is that even if they wanted to, there are rules in place that would preclude that. So, do you want to make a motion that the agency consider some new rules or additional rules. I see Jon is reaching for the mike.

DR. WILKIN: I am not sure exactly what Dr. Plott's product seemed, in their minds, to fail to meet some sort of endpoint. I would say that when we think about antifungal corticosteroid combination products, we are really looking for the antiinflammatory aspect. The sponsor can select the time from phase II trials where they think they are going to have the greatest delta, and they can end up powering it to where they--if there is an effect, I think they can achieve that effect.

DR. DRAKE: Bill?

DR. ROSENBERG: I don't want to preempt this, but I think we are really talking realistically. Let's back up. The word you used earlier, Jonathan, I forget what it was but it was very good. Let's back up on the entry-level criteria for the study. Let's envision the real world settings in which these products are used which are in primary-care settings, often as, by the way, where we don't need to upgrade and add cost and so forth, "Do you think this might be a ringworm? What should we do?"

Let's do a study with those kinds of patients, not in dermatologists' offices. Let's do it in offices where they have no CLIA certificate and where they don't do a KOH, and let's let the doctors put these different armed, coded products on those kinds of walk-in patients and see how the combination, the lesser combination, would do as compared to a plain Lotrisone.

I bet it would do a lot better because I bet 80 percent are not fungus of the ones who get it. But these are the ones that the doctors who are seeing these patients, and appropriately seeing these patients. This is the way the system should work.

If these doctors think this may be a fungus, and would take part in this kind of a trial, I think you could do it with data and you could show that, perhaps, the combination has utility and efficacy over anyone of the single agents.

DR. WILKIN: If I could respond to that. I think it is a philosophical approach to what is the kind of information one wants from the phase III trials. I would argue that if you can differentiate the patient, if you can actually figure out what is the cause of the redness and the scale, that you actually have a better database.

If it turns out that the product would work for both a tinea and also for an eczematous condition that

doesn't have tinea, then I think it would be from a much more informed position that the physician who would choose to use this without doing the KOH and the culture, they would have the certainty that it would work in both circumstances.

DR. DRAKE: We have five minutes left. I want to make sure we get everything in that we want to, so, please, for the panel, try to keep your suggestions concise. I see Dr. Chesney, John, Joe and Mary. Mary, is yours pertinent for right at the moment?

DR. SPRAKER: Any time.

DR. DRAKE: Dr. Chesney, John, Joe and Mary.

DR. CHESNEY: Just a comment. I don't know if you are all aware that the NIH has funded eight to ten pediatric pharmacokinetic research units across the country now, and they are in fact, right now, looking at an antifungal Fortinia. They are requiring a mycological diagnosis and coming up with some very, very interesting information.

So the mechanism is there for doing these studies in children. You don't even have to go to primary-care offices. These are very sophisticated pediatric pharmacokineticists and physicians who are totally set up to do these studies now.

DR. DRAKE: John?

DR. DiGIOVANNA: I would respectfully like to

disagree with Dr. Rosenberg, for the first time, in that I believe it was Senator Moynihan who coined the phrase, something about the dumbing down of medicine. I think that the fact that we have come to a point where there are people who are using less sophisticated, less accurate, techniques for larger percentages of the population doesn't necessarily empower us to go ahead and try to develop less active, less dangerous, medications to fit that need.

I think that if we had a medication that was really great for all diseases, maybe we would all have to find another specialty and that would be fine. But I do think that, while if a medication is useful, it should be available, I don't know that the best course is to go and try to find medications which are effective when the best, most sophisticated techniques we have are simply on available or not useful.

DR. DRAKE: Joe?

DR. McGUIRE: Two brief ones. First, I am sure the sponsor is already planning to put out a "Dear Doctor" letter that would contain the changes that you now have in the product information sheet. Unfortunately, I think that is going to have to go to all pediatricians, which is a big mailing.

The second item, which is something that I believe the agency has to think about, is that we have left out a

very large part of the population which is the geriatric group who have pruritus of the scrotum, pruritus of the anus, pruritus of the vulva. They get this product and they use it over and over again.

I hardly ever use class 1 or class 2 steroids in older people, whatever "older" means. I will talk to Rob later. But they get very atrophic very, very quickly.

DR. DRAKE: I think that is a wonderful comment, Joe. Thank you for bringing us back to what we are supposed to be doing and that is giving suggestions to the agency.

Mary?

DR. SPRAKER: Would the committee like to recommend to FDA that the sponsor be asked to present a specific plan to the agency regarding how to further educate pediatricians about the problems associated with inappropriate Lotrisone use?

DR. DRAKE: How does the committee feel about that? Would you like to have the sponsor present a formal plan to the agency? Let's get a sense of the committee. How many would like to do that, raise your hand.

[Show of hands.]

DR. DRAKE: That is sort of like voting for Motherhood and Apple Pie. Todd, I don't think that is too restrictive.

DR. BERGFELD: I think that it is too limited,

just to pediatricians. I mean, if you looked at the statistics, the family-practice docs and the internists were really the high users. So I think that has to be a very large program of education. Pediatricians could be focused because we are dealing with wee ones and we are all sympathetic to that, but there is a larger population at risk.

DR. KILPATRICK: Madame Chairman, may I add to that also.

DR. DRAKE: Yes.

DR. KILPATRICK: On the handout that we were given by the agency, there is a suggestion for postmarketing surveillance. It may be that the two could be combined in some way so we know who is doing what.

DR. DRAKE: That is a very good suggestion. Jim, you just earned your keep today.

DR. KILPATRICK: I earned my $33.00.

DR. DRAKE: You did. That is a very good suggestion. I like that a lot.

John?

DR. DiGIOVANNA: There is a little bit of a conflicting statement here. If you are going to label that it shouldn't be used at all in children under 12, why would Schering want to have it sent at all to pediatricians.

DR. DRAKE: We have just suggested that labeling

be modified just a tad.

DR. McGUIRE: Because that is a group whose practice is going to be modified the most, and they need to know.

DR. DRAKE: Would the committee like to have the FDA report back to us in some future meeting about what Schering is doing to address these concerns? No? Okay. Oh; yes? How many would like to have a follow up on this: Raise your hand.

[Show of hands.]

DR. KILPATRICK: By E-mail.

DR. DRAKE: By E-mail. We would like to have something, Dr. Wilkin. The committee would love to learn what Schering has got in mind to further this educational program.

I have one suggestion. I think that the information that has been presented here today, particularly by Dr. La Grenade, I think that kind of stuff is really interesting. I think the whole thing should be presented. I would certainly encourage anybody at this table, or the FDA, themselves, or Schering, to think about getting this written up so that it appears in multiple journals.

People still look at their journals so I would strongly think about publishing it in journals in different capacities.

I am going to do one last thing. I am going to ask each member of the committee what ideas they might have plus I am going to go back and hit you guys. Give me your best idea for the committee.

Eduardo; what is the best idea you have got to make this better?

DR. TSCHEN: I think there are two things; the information in the package and in the tube as well as the education to the physicians who are going to be prescribing it. I think the drug rep is a big source of information to most of the clinicians. I think it is an incredibly good source of information for most of the clinicians who are practicing in this field.

DR. DRAKE: John?

DR. DiGIOVANNA: I think one point that has been made and I think would be very useful with respect to Question 6 is including information about the specific known adverse events in a way that is clear for people using it and the parents of infants using it so that they are aware of the differences in the risks in children and adults with respect to the adverse events which have been observed, mainly atrophy and striae.

DR. DRAKE: Fred?

DR. MILLER: I would just echo what they said but, again, I would say that I don't think that the educational

process can reach everyone. I just think there are too many lacunae and people will slip through. So it needs to be, again, the label on the tube.

DR. DRAKE: Bob?

DR. JORDAN: I agree with labeling the tube and the box, particularly when it comes to the pediatric group. But I think one point maybe the sponsor should understand, we are all not very comfortable with the strength of this corticosteroid in this product.

I would like to see something, at least some statement, as to the strength of this.

DR. DRAKE: And the side effects from it.

Yes?

DR. BERGFELD: I have only a brief addition. In the product information piece, as one reads through it, for the division of the component active ingredients, I am not hit by anything that I should be particularly worried about. As stated, in dermatology, we are very worried about skin atrophy and striae. In some way, I would like that brought out in this piece as well as in the patient information.

DR. DRAKE: Dr. Chesney?

DR. CHESNEY: Pediatricians need to be educated but please be sure to include family practitioners in any "Dear John" letter because they also treat many, many children.

DR. DRAKE: And internists, because they take care of the elderly, the geriatrics.

Rob?

DR. STERN: Nothing to add.

DR. DRAKE: What? Jim.

DR. KILPATRICK: Some of you may not realize, but the FDA does not pay for overtime. I have earned my keep today, so I have no other comments.

DR. DRAKE: Bill?

DR. ROSENBERG: I have a recommendation for the Chair. I know that the Chair spent her year on Capitol Hill on the Senate side with Bob Dole, but I think adoption of the House policy of allowing members to come back and talk into the microphone under special orders when everybody else has gone home would be useful. That would help some of us.

DR. DRAKE: When everybody else has gone home?

DR. ROSENBERG: Yes; that is my suggestion.

DR. DRAKE: I have instituted this policy of really forcing all the members to talk because, sometimes, one or two members talk and nobody else does. But I have tried to force everybody to talk. We have been a little bit restricted on time, but I agree with you. I think these committees have so many good ideas.

Joe?

DR. McGUIRE: Thanks, Lynn. I have said what I

wanted to say.

DR. DRAKE: Joel?

DR. MINDEL: I hate to be serious again.

DR. DRAKE: That's okay.

DR. MINDEL: But the studies on which this present drug is based were done twelve years ago. The drug on which we are saying we have to have the duplicate labeling was done twelve years ago with the present modification.

I would like to see this new drug limited to a seven- or eight-day labeling maximum use, period.

DR. DRAKE: Okay; that is a thoughtful suggestion.

Now, you experts have had a chance to think. Dr. Epps?

DR. EPPS: One recommendation for wording may be two separate sentences such as, "Not to be used in diaper dermatitis due to striae and whatever side effects." And the second one, "Not recommended under the age of 12."

DR. DRAKE: Ted?

DR. ROSEN: I have nothing further to add. I think you all have heard the same recommendations multiple times. They are all good ones.

DR. DRAKE: Steve?

DR. FELDMAN: We talked about this drug has been proven safe. Safety, in small trials, doesn't really tell you about safety for less common events. It is clear from

the postmarketing data there have been a lot of adverse events. That could be listed under adverse reactions much more prominently.

Again, it raises the issue--I don't think we should say that this drug has been proven safe. On the contrary, the postmarketing data has shown that there are adverse events reaction with this drug with the labeling that has been out there limiting its use.

So I think the committee should feel really comfortable making decisions that say the labeling needs to be strengthened or its use should be curtailed in some way. I think it was an excellent point that was brought up that the new product really has not been shown to add anything over existing product and even the old product that was out there hasn't really been shown to add anything over existing products.

I think the idea of comparing the numerator and denominator of the adverse-event profile of Lotrisone to Diprosone would be very important because if you did find that the adverse events are much more common with Lotrisone, when you know that the drug is equally potent in terms of its steroid effects, then you would really say that something is going on with the marketing of the product or the use of the product that is of serious concern given the risk/benefit ratio.

DR. DRAKE: Mary?

DR. SPRAKER: Echoing Wilma. When you read the package insert, there is a word or two about the adverse events. I think a whole paragraph on the problem in children, how many children have been seen with striae, the adverse reports that have been reported would help emphasize and give the practicing physician more information go to on.

DR. DRAKE: I think you earlier even said about a black box. We never got back to that, but they might want to consider that.

DR. DRAKE: Mark?

DR. ELGART: As I sit here listening to this, I think that probably 20, maybe more, percent of my practice is off-label use of drugs. I think that most of us do that. I think that no matter how aggressive we are on the label, we cannot, as you have said, restrict totally the use of these medications.

That is probably good. You can lead a horse to water but you can't make him drink. You can lead a family practitioner to what the right way to use this is but, if he wants to use it another way, he may be right, for him.

So I think that we can't be too obstructionist in the way that we put this material out.

DR. DRAKE: Lloyd?

DR. KING: Actually, I am struck by how visual we

are and, in the coming of the E-commerce area, I am struck by the pharmaceutical industry is becoming worldwide. If we can develop symbols for smiley faces and all this for the computer, a shorthand for "I'm happy," "I'm sad," would it not be a challenge like developing international signs for a roadway, for bathrooms, et cetera, if we could come up with some kind of symbolic language that says, "Don't use this," with an X mark, some improvement on the skull and crossbones.

So I think the challenge is people are visual. They are not going to read all these things if they are illiterate. But they see a skull and crossbones, they get the message. So I think we could take a lead from E-commerce and say smiley faces. These things may be the challenge of the future.

May I ask a question from all the folks from the agency. Do you have what you want? Do you have what you need from us at this point?

DR. WILKIN: Yes. I would like to thank the sponsor, Dr. Plott, for his presentation, the invited guests, experts who presented and the committee who deliberated in great depth over these, I think, difficult questions because they had both scientific aspects and they also had societal values imbedded.

Let it be said that dermatologists considered

their colleagues in other specialties. We heard that message as well. I would thank you, Dr. Drake. We got very good information which we will take back and think about. We heard the charge. We will report back.

DR. DRAKE: I, too, want to thank the sponsor. I want to point out there are lots of people in the audience here today who have antifungal products and what not. I think you have heard a lot of very positive suggestions. Bill, "Tinea/Baby?" What was it? I don't remember. But you have heard a lot of position suggestions. Please don't let us stop you from developing something new. It is always good for our patients.

Now, we have kind of run over. I am going to have a seven-minute break. I am going to reconvene at 4 o'clock because, if we don't, we won't get out of here and it is not fair to the next company. So I want to reconvene at 4:00.

[Break.]

NDA 20-966 - Dermex II (zinc oxinate) Ointment

Dermex Pharmaceuticals

For Treatment of Actinic Keratosis, Basal Cell Carcinoma and Squamous Cell Carcinoma

DR. DRAKE: We are reconvened. The last thing on our agenda today is the open session. Mr. Henriquez, would you please do the conflict of interest statements.

Conflict of Interest Statement

MR. HENRIQUEZ: The following announcement addresses the issues of conflict of interest with regards to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting when evaluated against the agenda.

We would, however, like to disclose for the record that Dr. Lynn Drake has interests which would not constitute a financial interest within the meaning of 18 USC 208-A but which could create the appearance of a conflict. The agency has determined, not withstanding these interests, that the interests of the government and her participation outweigh the concerns that the integrity of the agency's programs and operations may be questioned.

With respect to the FDA's invited guest, Dr. Stephen Feldman, Dr. Theodore Rosen and Dr. Mary Spraker have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Feldman would like to disclose that his department has a grant with Dermex for a pending NDA. Dr.

Theodore Rosen would like to disclose that approximately six years ago, his department received a grant from Allergan for a study of Naftin. Dr. Rosen was an investigator on the study but received no personal remunerations. In 1999, Dr. Rosen received an honorarium from Allergan for a lecture concerning Naftin.

Dr. Mary Spraker would like to disclose that she is a speaker for Dermex' Distinguished Lecture Program. Dr. Spraker's talks to do involve speaking about any of Dermex' products. In the event that the discussions involve any other products or firms not already on the agenda for which the FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvements with any firms whose products they may wish to comment upon.

DR. DRAKE: Thank you.

Dr. Wilkin?

Introductory Remarks

DR. WILKIN: This afternoon, we will consider the zinc oxinate ointment product. Dr. Ko will give the agency presentation. At the end, what we are interested in does

the committee have comments. We actually have no specific questions to give to the committee. I think it will be explanatory after Dr. Coe's presentation.

DR. DRAKE: I guess the first presenter is the FDA and that is Dr. Hon-Sum Ko.

FDA Presentation

NDA 20-996 Dermex (zinc oxinate) Ointment

DR. KO: Thank you, Madame Chairman.

[Slide.]

My presentation will be on NDA 20-996 from Dermex Pharmaceuticals.

[Slide.]

They have a product called zinc oxinate which is a chelate of zinc chloride with 8-hydroxyquinoline in an ointment base. Now, its active ingredient is said to be at least, in part, a metal-ligand complex formed by the reaction of 1 mole of zinc chloride with 2 moles of 8-hydroxyquinoline in situ during the manufacturer of the drug product.

As well, the sponsor states that an excess of zinc ion is needed for its activity.

[Slide.]

Zinc chloride has been used in Mohs surgery as a fixative. It is also available for nutrition supplementation when diluted. For 8-hydroxyquinoline, it is

used as a chelating agent, for example, in nuclear medicine to chelate indium, radioactive indium. It also has antibacterial properties and so it may be used in some topical products.

[Slide.]

The proposed indications for this NDA has changed with time. When the NDA was first submitted in March, 1998, six indications were requested; squamous-cell carcinoma, basal-cell carcinoma, actinic keratoses, Kaposi's sarcoma and also genital warts and verruca warts.

When a resubmission was given to the agency in September of 1999, only three indications were sought. These were squamous-cell carcinoma, basal-cell carcinoma and actinic keratoses.

[Slide.]

In the submission of 1999, a clinical protocol was provided. It is included in your briefing package in Attachment 1.

[Slide.]

Basically, the protocol involves having patients biopsied to verify the diagnosis and have photographs before and after treatment. There were two phases in the study. A patient may be given 8-hydroxyquinoline or zinc chloride or vehicle in the blind phase which is followed by an open phase with the Dermex product.

Up to three applications may be given. And then, as mentioned, there would be a post-treatment biopsy.

[Slide.]

We are going into a summary discussion of the clinical data.

[Slide.]

This table provides the material that we have received from the sponsor for the three indications; actinic keratoses, basal-cell carcinoma and squamous-cell carcinoma. There were descriptions of ten patients of actinic keratoses in 1998 and one more in 1999. Basal-cell carcinoma, we had fourteen patients in 1998 and eight in 1999. There was one squamous-cell carcinoma description in 1999.

In both submissions, the same photographic cases were presented. There were five of them. They are also present in the sponsor's package which I think you have with you right now.

[Slide.]

I am going into just a very brief discussion of the clinical data of the 1999 cases. These were more representative and were presented in greater detail as there was also histological information.

There was one case of actinic keratoses in a 60-year-old Caucasian female having multiple lesions on the face. Treatment with the product resulted in necrosis after

the application.

[Slide.]

For basal-cell carcinoma, eight cases were reported in the 1999 submission with seven males and one female. The age range was between 42 and 81. There were seven Caucasians and one black. These patients had disease duration lasting between six months to 30 years. The lesions were almost all in the head and neck area except one which was in the right hand.

Serial histological specimens showed that four out of the eight patients showed no tumor on the last follow-up biopsy after treatment.

DR. ROSEN: Can I interrupt you a second. Does that mean that the other four out of eight did have tumor on the last biopsy submitted?

DR. KO: Yes.

[Slide.]

The third indication is squamous-cell carcinoma. There was one case report of a 72-year-old Caucasian male having skin ulceration over the cheek. Serial histology still showed presence of squamous-cell carcinoma at the last biopsy.

[Slide.]

There is limitation of the efficacy data because, really, the data is regarded as anecdotal. The investigator

for the submission in 1999, his qualifications have not been verified. The endpoints have not been clear-cut, defined, a priori and there are issues on study design including randomization and blinding which have been problematic.

The sponsor did also present some animal data apart from the human data. However, these are not appropriate to support a human indication.

[Slide.]

Concerning the safety data, the cases presented in 1999 did not, really, provide any safety information to support the adverse-reactions section of the label which lists a number of possible side effects including burning, inflammatory response, contact dermatitis, increased sensitivity to sunlight, itching, oozing, soreness, darkening of the skin and scaling.

[Slide.]

In your package, under Appendix 1, you have the regulations concerning adequate and well-controlled studies. This slide is really just a summary of what the agency regards as adequate and well-controlled studies to support indications in an NDA.

The student needs to have clear-cut objectives and a summary of methods of analysis. It should be properly designed to allow valid comparison with proper control. It needs to have good subject-selection criteria to assure that

programs actually have the disease or condition to be studied.

Methods of assigning patients to the treatment would minimize bias such as by randomization with or without stratification. There should be measures to minimize bias on the part of subjects, observers and in the data analysis. The evaluate of response needs to be clearly defined and reliable and there should be adequate analysis of the results of the drug effects.

[Slide.]

This slide shows the regulatory history of this application. The original submission in March of 1998 was not fileable because of deficiencies. Subsequent to this, the applicant requested conference with the agency and this was held. The application submitted new material in 1999 and requested the agency to file the application for review.

Despite deficiencies, the regulations to allow the agency to file the application. So this was filed and reviewed.

[Slide.]

The clinical biostatistical review showed the following deficiencies. The application lacks proper format, content and information on compliance with IRB regulations. There were no adequate and well-controlled studies to support safety or efficacy of the Dermex product

in the treatment of the requested indications, actinic keratoses, basal-cell carcinoma and squamous-cell carcinoma.

[Slide.]

Other review disciplines also found deficiencies with the application. The chemistry, manufacturing and control team noted that this NDA lacks specifications such as quality attributes, analytical methods and acceptance criteria for starting materials, active pharmaceutical ingredient or drug substance or proposed finished drug product.

Without the analytical controls, the identity, strength, quality and purity of the drug product cannot be ascertained. It also lacks stability data to support the expiration date and data to evaluate differences in formulations between batches used for the clinical studies and the proposed to-be-marketed drug product.

[Slide.]

There are also issues of the manufacturing microbiology part because this NDA does not provide a statement indicating whether the product is sterile or non-sterile. If it is sterile, then information on the sterilization process validation data needs to be provided.

If non-sterile, then it would need microbial limits-testing methodology and corresponding acceptance criteria or scientific rationale for lack of this testing.

Also, if it is non-sterile, then there would be a need to provide a preservative, if any, its effectiveness validation data or demonstrating that the antimicrobial properties are inherent in the non-preserved product.

Also, if it is non-sterile, it needs microbiological stability data.

[Slide.]

Pharmacology, toxicology discipline issues relate to the lack, in this NDA, of in vitro and preclinical animal data routinely collected to help identify potential toxicities of the product, or studies that can help bridging existing data on individual components of the Dermex product.

[Slide.]

Because of these deficiencies in the application, it really precludes approval of this application. The agency brings this to the committee to see whether you have any recommendations.

DR. DRAKE: In the interest of time, would it be worthwhile to hear from the sponsor immediately and then we can kind of address or comments all together.

Dr. Potestio, welcome. Please proceed.

Sponsor Presentation

Summary of Company

DR. POTESTIO: My main purpose here is to

introduce our company. Our company is an extremely small company. It consists of three people. The first one, Dr. Russell Jordan who did all the formulation for this drug, is home, extremely sick. He is in heart failure, terminal stages of hepatitis C, uncontrollable diabetes and nephrosis and his doctor, as you can obviously tell, has kept him at home.

Our second member of this is Mr. Carl Hanson who is a registered pharmacist who is compounding our medications and presenting this to the FDA. He has also been in research with Abbott Laboratories. I am a retired, board-certified obstetrician-gynecologist. The reason that I am retired is because I lost my right eye back in 1998 due the retinal detachment.

The reason this company was formed was originally not because of the skin-cancer cure that we have but because of the fact that my wife came down with a right upper-quadrant pain, and we buried her five-and-a-half weeks later. The next day after she had her pain, we brought her in to the internist who did not discover any gall stones but a wild-growing pancreatic cancer.

She underwent bypass surgery to avoid obstruction and was put on 5FU for chemotherapy. Everybody in the hospital at that particular time knew that 5FU caused severe nausea and vomiting except our learned oncologist. I quit

being a doctor and became a husband and looked all over for any kind of cure and called all the pharmaceutical companies to see if they had anything. They had nothing.

Finally, the name of Russ Jordan came up and the reason I knew Russ Jordan was because he did oncology and research all his life. When I first met him, he was at National Jewish working in immunology at that particular time. I took care of his wife and daughters while I was in private practice.

I called Russ and told him what my problem was and he formulated some oral medication, the lowest possible dose to give to my wife. With this medication, ladies and gentlemen, she had no nausea, no vomiting and no side effects.

In spite of the fact that it was the lowest possible dose and she only took it for two weeks before she died of pulmonary edema, the tumor began to recede. Two months later, after her death, he called me up. We had lunch and he discussed starting a pharmaceutical company. He had done all of his work through a Dr. Marie Gonzalez in the Free Clinic of Mexico where they had treated at least over 100 skin cancers.

Every one of the skin cancers was first diagnosed by biopsy, treated, post-op biopsy to verify it and at least a five- to ten-year follow up to make sure it didn't recur.

The controls were usually the same person as they had multiple lesions.

We started the company, but my main purpose was not the skin. My main purpose was the oral as I knew he had a cure for breast cancer, lung cancer and GI cancer, from what I could see. But we needed a lot of money and a lot more research to bring it on the market.

So we decided to start crawling before we started walking and came out with our skin-cancer product. Ladies and gentlemen, I have used this product. It is totally different than what I just heard a few minutes ago from the previous speaker. Every time I have used this product, I have seen virtually no side effects. I have seen the tumor disappear after only one application and a short follow up. I have seen no recurrence.

There is going to be one out of every five humans in this world that is going to come down with cancer of the skin. Ladies and gentlemen, we do have a drug that needs to be out there that does work. It is most unfortunate that this drug is in the hands of a small pharmaceutical company with limited money. But we will bring it on the market with the blessing of the FDA as we do not want to go herbal because skin cancer is too serious of a disease to put in the hands of the lay people and it should be in the hands of the professionals who know what they are treating and how

they are treating it.

Thank you so much.

DR. DRAKE: Thank you.

Mr. Hanson?

Updating the Committee on Dermex

MR. HANSON: I will try to make this a brief as possible. You have the handouts. One thing I would like to correct and ask Dr. Ko--you said the animal studies did not pertain to the human cancer cells; is that correct? I want to ask you that now.

DR. KO: I didn't say that.

MR. HANSON: I think you did. You said that animal studies did not pertain--squamous cell in the cow does pertain to the human. A hundred studies were done. They were included in the filing that we made. I just wanted to make that correction.

A lot of the deficiencies that are in there for the analytical part of it, we have limited funds. We are a small company. So we did not start with the manufacturing entity until March when we found out that it was in the final stages for this advisory committee.

At the time, I called for an inspection. We have received an inspection. All of the supposed deficiencies on the analytical has been addressed. The microbial problem is taken care of. We have hired and contracted a microbial--

actually, Nelson Laboratories in Utah is going to do our microbial work.

We have installed a pure pharmaceutic water system. We have the machinery now. The analytical part was not done before because, in my experience in manufacturing from Abbott and from my own compounding, I have 48 years of experience in pharmacy.

We did not start any of the analytical work because it was a moot thing because I was doing a mortar-and-pestle up to that time. We have an ANDA in place for the equine horse which we are waiting the final approval on. We also have an IND in for the squamous-cell cow. We are working on the dog. We have 44 indications for the dog. It sounds like kind of an overall type thing.

If there are not any more questions on that, I would like to get on with the handout, if I could. I will briefly go through that.

I inclosed a letter that I wrote to this Mr. Castle. I informed Dr. Jonathan Wilkin that there was a lot of dysfunctional letters and correspondence that evolved after we were notified that we were going to be before the advisory committee. I had eight phone calls in to one gentlemen with no answer. I would hope that the FDA would treat small companies better than we were treated at this time.

The treatment that we received from Dr. Wilkin's division was exemplary. I want to comment and thank Dr. Wilkin and also Mary Jean. At one point, I had no idea of the language needed or what was needed and I told Mary Jean at one point that, "I am a farm boy who came to town on a load of turnips and fell off." At that point, she was very gracious.

Let's go to the archival information. The original application was for more indications but Dr. Jordan had a tremendous amount of valuable clinical work in his office. His office was inundated with twenty to thirty feet of water at the same time that Colorado State University lost their library. We lost a tremendous amount of information.

But it was our decision, at that time, to go ahead with what we could salvage at that time and work from there. So we do have some information on the--quite a bit on the warts, but it seemed like a moot thing to do that at this time, to cloud the issue. Kaposi's sarcoma, he had many, many cases. We were able to salvage one which was not applicable at this time.

If you will notice, we limited down to the three. The reason, now, also, I am putting this in the archival, we asked, at this time, for the accelerated approval with expedited review. Expedited review is an executive order

asking that, due to small companies with limited assets, that they expedite the review which Dr. Wilkin and his staff did

The accelerated approval, the reason we placed it there is that it would remain in postmarket clinical studies. In other words, we didn't feel that we had a complete case to file, but we placed ourselves in that position so that it would be under the direction and the guidelines of a protocol that would be substantial to substantiate the work that has been done.

We also realized at this time, we were trying to seek more clinical help. I know there are quite a few dermatologists here, but I was appalled. We approached four very prominent dermatologists in Denver. Each one of them gave the same response. One was a good friend of Dr. Potestio's. The response that he got from his friend was, "Frank, we have two rooms going with surgical procedures that we average $2,000 to $3,000 from. Why should I get a product on the market that might eliminate my surgery?"

I am sorry about that, but we did make a very good effort to try to set up a clinical study in Denver which is a good place for it, but we came against a brick wall.

We did give the reasons why we thought it should be an expedited marketing position. It provides a very meaningful advantage over the existing treatment which is

surgical excision, radiation and electrodissection.

I will go through these very fast. They are kind of mundane. Demonstrates reliability and effectiveness in the following. The supportive evidence is covered by Subpart E. Procedures; complies within the scope of serious and life-threatening criteria, which we discussed with a member of the division in 1997 and 1998. We confirmed it. We complied with the fact that it had to be within the six months previous to a filing.

I don't see any mention of this in any of the correspondence we received. Supporting evidence should provide the effect of a surrogate endpoint for Dermex. Distribution and use will be restricted during the specified time administered by the FDA, Dermex II will comply with--anyway. We had decided on this protocol that we will comply with the protocol in a postmarketing condition in a very, very strict sense and limit the marketing very rigidly.

We actually have found and have made the first approach to Kaiser. I am a consultant for geriatrics with Kaiser at the present time, part-time. We found that, basically, economically--you can see No. 7 is economic importance.

HMOs and Medicare are trying to save money. This product will save a tremendous amount of money for Medicare and for HMOs. We have found great favor in approaching some

of the HMOs, particularly Kaiser. They are not in the position of trying to do surgery to make money. I am sorry to have to make that statement, but I have been in the medical profession for more years than I care to talk about.

Information available reveals that there is no other chemical treatment available for the indicated illnesses. Highly selective. We have data here from a Sir Alpert which I am going to include in there. Sir Alpert started working with chelation as far back as 1930, 1940 and 1950.

Chelation is not a chemical reaction, as purported. It is actually a claw where the two chemicals come together, which brings me to the point that one is 8-hydroxyquinoline which is not under any prescription control. Zinc is definitely not. We have two entities here that are not under any control at the present time by prescription.

Dr. Jordan has accumulated sufficient evidence in treating topical Kaposi's sarcoma. We are going to pursue this more aggressively in postmarket clinical studies. I tried to eliminate a lot of the information that we have. Bridging from the information that we provided, which they said was not done for toxicology and pharmacology, I believe we sufficiently gave enough information which, according to the CFRs that I studied, were allowed, if it has been used

previously, either component has been used previously, in a manner that would pertain internally or externally. Both of these products meet that.

I put in there selected toxicity mainly to show you that 8-hydroxyquinoline has been used and it is in most of the USPs and formularies around the world. Diaper dermatitis; I know I listened to a lot of discussion this day on Lotrisone. I think there was some opposition. I would make one suggestion at this time. If you want to know what the pharmacist is going to on labeling, you should talk to a pharmacist.

Effective oxyquinoline ointment on diaper dermatitis, when you consider the amount of area on a child, on a baby, what, 25, 30 percent of the body area is buttocks, so it was used on that. Activity with some of the things here. We have potential amebocide for 8-hydroxyquinoline. The thing was brought up about a preservative. The original talks that Dr. Jordan had with the division was to use eucerin which has nickel in it which actually interferes with the zinc and would replace it. So we went to a plasty-base, which is Squibb's original product.

We have antibacterial, antifungal, activity for the oxine. That is the next page, 11, I think it is. I don't have my pages numbered here. There is sufficient

evidence. We tried to highlight most of it so that you could just review it.

Indium 111 is a very important one for us because I did work on the IND for--I was a nuclear pharmacist and I worked on the IND with indium 111 with a Dr. Klingan-Smith. This actually is an isotopic follow through the body of 8-hydroxyquinoline. If you look under mechanism of action and effect, labeling of leukocyte, which we did within the cell, the radioactive indium dissociates from oxyquinoline and becomes firmly attached to the cytoplasm components while the nonradioactive oxyquinoline is released by the cell.

They also established, in these studies, the fact that carcinogenicity, you go to the other page, here, is, "Although earlier studies suggested oxyquinoline might have carcinogenic potential, recent studies have not shown the carcinogenic effect in rats and mice given oxyquinoline in feed concentrations of 1500 or 3000 parts per million."

"Indium 111 is excreted in breast milk," and such like that, which we did find.

Toxicology and carcinogenesis studies of 8-hydroxyquinoline; profound. We have got survival of dosed male and female rats and mice in two-year studies comparable to that of the corresponding controls, the high-dose rats and mice of each sex exhibited slight decreases in mean body weight and decreased feed consumption.

"In vitro, 8-hydroxyquinoline did not induce either unscheduled DNA synthesis in rat hepatocytes or transformation--"" "An audit of the experimental data for these carcinogenesis studies on 8-hydroxyquinoline was conducted. No data discrepancies were found." I rushed that.

Let's go on to zinc. Zinc oxide has been preferred--when my wife and I were raising our nine children, we used zinc oxide and didn't have any Lotrisone. We also used calcium and zinc undecylenate with very good success, a product called Keldicine.

We have got oral zinc. Strength usually available for zinc chloride, we have got zinc gluconate, but it is zinc, 1.4 milligrams of elemental goes down to 60 milligrams of elemental zinc. Canada has 10 to 50. I was told I had a high PSA and they recommended that I take zinc orally. I am taking 30 milligrams a day. Zinc chloride has been used in an injection form, no apparent problems.

Zinc-chloride mouthwash on plaque and zinc levels on surface enamels. That is pretty self explanatory. Zinc chloride paste for the debridement of chronic leg ulcers. I think that is self-explanatory.

Zinc chloride spray--magnesium hydroxide ointment. This spray was used, and I don't think I highlighted that, but it was used in the incision and OB procedures,

vaginally.

Does zinc really cure common cold? Zinc has been profoundly taken internally as lozenges and whatever have you. Zinc deficiencies. Okay; on a chelate, the worst possible scenario is that the chelate releases the zinc. So what do we have in the pharmacokinetic range? We have zinc and we have 8-hydroxyquinoline.

8-hydroxyquinoline and zinc, as a chelate oxine, is very stable. Sir Alpert did about five years of work on stability and, as far as the stability of the product goes, we did confer and provide mathematical constants for the chelation.

Chelation, I might address. I just received--I have two friends of mine that are pharmaceutical chemists. They are professors, Ph.D.s at the University of Idaho. Both of these people have been working on a good assay.

The assay for the chelate is very hard to do because it is non-ionic. You can't draw it out. So the best possible way is to break it up and bring it out so you don't have--then, you don't have a good assay. But we have found a way to analyze a chelate which we are now working on and will have in place.

By the way, our inspection, we gave a deadline of September 1 to have all of the problems solved and we are well on the way. We have got about 50 percent of them done

already.

Zinc, the super mineral. Self-explanatory. Okay; we have got, important in wound healing, zinc. The element also functions as an antioxidant. Helpful in treatment of acne. Hastens healing of peptic ulcers.

What diseases are associated with zinc? They have got pig studies and whatever there. Zinc's little-known tie to immunity. Zinc, an unsung mineral. This, by the way, is one-tenth of the information references that we gave to the division. Zinc and the common cold. Zinc in plasma. I am not going to spend any time with these. I think they are pretty--zinc deficiency.

What we have here is we have a product that is made of two components that are not under the direct division of the FDA, if I may be corrected on that, Dr. Wilkin? 8-hydroxyquinoline was used in baby oil for many years. I don't know if many of you are familiar with that. 8-hydroxyquinoline is not in bagbone. Many pediatricians are writing bagbone for diaper rash. I call them back and tell them not to use it, it has too much phenol in it.

We then put in Dr. Jordan's curriculum vitae to establish the fact that here is a man that did these clinical studies in Mexico, at that time under the protocol set by the FDA which is not the same as it is today. But he did comply with them.

You can see that he was in charge of research at many places. He has a Ph.D. in microbiology and virology from the University of Michigan. We could not establish--he is very ill. Only his wife and the physicians at this time are able to confer with him, but it kind of establishes the fact that here is a man of very high quality. As a matter or fact, he worked for Kettering, Charles Kettering Institute. He was director of that.

Let's go on and--are we running out of time?

DR. DRAKE: Mr. Hanson, we are very appreciative--

MR. HANSON: Could I go through the slides? I don't want to seem abrupt, but I will be. To give a whole day on Lotrisone and then give us about twenty minutes to give a presentation on a very viable product--I would like ten more minutes.

DR. DRAKE: May I finish, though.

MR. HANSON: Sure.

DR. DRAKE: Just so you know, the company, the sponsor's portion was thirty minutes and they were held to that. So your thirty minutes is up but we would happy to give you a few more minutes to go through the pictures.

DR. DRAKE: I will skip and go to the--all right; I'll tell you what. Let's go to the pictures. All of the advisory committee has the pictures?

DR. KILPATRICK: Sir, would it not be more

advantageous to you and your colleagues if you could get some of the reactions of members of the committee to what you presented and what we have in front of us rather than spending the time taking us through things--

MR. HANSON: Could I show the slides?

DR. KILPATRICK: I am not the chair, but--

DR. DRAKE: Number one, the agency said that they are not going to approve it as it stands now. We are very appreciative that you gentlemen have brought this forward. I think it is wonderful that three people have made this gallant effort to start a company and do it on your own. It is very admirable.

By the way, Dr. Potestio, I want to tell you how sorry we are about your wife and about the tragedies that led you into this, but thank goodness you are using it for something very positive.

So we are very grateful that you brought this forward. I really admire you guys for doing this. It is really important that people--America is founded on individual people doing something or trying to do something great. My question to you, and I am happy to use the time either way, is we can spend the next twenty-five minutes, which you have--which you don't have but the whole committee has--trying to help you maybe be successful by giving you some strong or good advice.

Or we are happy to go through the pictures. But I honestly believe that, if I was in your position, this group is the one that is going to approve it. Maybe you would like to hear from this committee on how to do your job more effectively so that you can move forward.

MR. HANSON: All right. At this time, I would like to make another statement. Dr. Jordan, at one of his last visits, said that if we have too much problem, let's just go herbal. We have a product that we have made, I have made and compounded herbally, that we have used on animals, squamous-cell on cows' eyes. It is a totally herbal product.

We are in a position to go ahead and manufacture that but we are trying to keep this under the auspices and the guidance and the protection of the medical profession. If this was released, organically chelated zinc for skin care, it would be horrendous. It is something that we just want. Our patent does state that we do have that ability, and we do have that ability.

So I would like to make that statement at this time.

DR. DRAKE: Thank you. I think now what I would like to do is, again, thank you for coming forward and thank you for your efforts. I think this entrepreneurialism is wonderful.

Committee Discussion

Now, I would like to turn it back to the committee and ask the committee to give you some suggestions. I would like the committee to be helpful. I would like to start with Jim and then Rob.

DR. KILPATRICK: You haven't met members of the committee, sir, but you should know that I am a medical statistician from the Medical College of Virginia in Richmond, Virginia. I have been there for thirty-five years. I have been involved in collaborative research all that period.

I am currently collaborating with residents in orthopedics. I have been forced to tell them something which I think may be applicable to this situation. In real estate, there are three major factors in buying a piece of real estate; location, location, location. I have used that as an example to tell my students who are working with me there are three major factors in research; focus, focus, focus.

What I have heard is that you and your colleagues strongly believe that you have a safe and effective product. What I would suggest, very humbly, sir, is that you pick out the one aspect that you think is most easily demonstrable--the one aspect that is most easily demonstrable--and, if you want FDA approval, take that particular aspect through the

phase I, phase II, phase III protocols that you have heard from the rest of us.

This is my contribution to where I think you have to go.

MR. HANSON: Thank you very much, Doctor.

DR. DRAKE: Dr. Stern?

DR. STERN: I had a question and, perhaps, a suggestion. Since we just received this, there may be this material, but it wasn't clear to me in either presentation about the status of human studies, committee review, IRB review for the various protocols that have involved humans. Certainly, it is my impression that the only information gathered with appropriate approval of the Human Studies Protection Committee can be, in fact, even entertained by the FDA.

DR. DRAKE: Dr. Wilkin?

DR. WILKIN: There are not IRBs exactly everywhere. Europe has a somewhat different system. It is the Declaration of Helsinki.

DR. STERN: Right; but some sort of protection.

DR. WILKIN: Yes. It is in our regs that that is to be an important component of the information that comes to us. Now, the IRB regs, I think, go back to possibly 1978, 1979, something like that. Sometimes, there are data that precede those. We are not excluded from considering

that.

If we have a product that is out there that was studied under questionable circumstances but it is for a life-threatening kind of situation, it is something that we would think about, looking at the data; yes.

DR. STERN: But is it not helpful to an investigator to review their protocol with the Committee for the Protection of Human Subjects?

DR. WILKIN: Oh; it is expected that there will be either the IRB, Declaration of Helsinki and that there will be consent form.

DR. STERN: Informed consent.

DR. WILKIN: Yes.

DR. DRAKE: Dr. Bergfeld.

DR. BERGFELD: I would like to make a few statements. First of all, I laud you at your attempts to coming forward with a nonsurgical approach to skin cancers and, perhaps, others. I think that the clinical photographs that we have all been looking at are very nicely presented. One, we can see what has happened.

I think that the loss of your databank due to flood is a major insult to your credibility in moving forward. I think that you have a great need to somehow associate yourselves with someone or some company that has more funds than you do to allow you to go forward with the

studies because I think this would be a worthwhile new therapy for us in medicine.

I wouldn't want to be discouraging here because you have presented us a very unique idea and a very unique product. We have had some experience with the old Mohs technique with the zinc chloride as well and we do know, in dermatology at least, that this was a very effective therapy and now currently being used for melanoma.

I had leaned over to Dr. Jordan here to ask him if there had been any clinical studies on Dr. Mohs' cases and I don't believe there have been. They never came for review by anyone.

DR. DRAKE: So we are a step ahead. They at least came.

DR. BERGFELD: You have come. So I think that gathering up some information, putting it together a little bit tighter, focusing and perhaps getting one of other colleagues over here interested in what you have had to say, might allow you to go forward.

DR. DRAKE: Other comments?

MR. HANSON: If I could make a statement right here. Dr. Jordan did have clinical studies that he did in Mexico on malignant melanoma. He did have excellent results.

DR. DRAKE: Dr. DiGiovanna?

DR. DiGIOVANNA: Just a point of clarification. On page 42, it says that Dr. Jordan is an M.D., Ph.D. He is the one who did the clinical studies?

MR. HANSON: We could not verify that. Due to his illness, we could not make proper contact so we sent a letter back to Dr. Wilkin and his division saying that we could only verify his Ph.D. at this time. So I want to clarify that. We have clarified that--someone assumed that he did have an M.D. There was evidence that he did, but we could not authenticate it.

So I sent a letter to Dr. Wilkin and Mary Jean. You did get that letter? Yes; thank you. That is a good point.

DR. DRAKE: Other comments from committee? Dr. King?

DR. KING: I just had a simple question. It kind of threw me off looking at the data, and I didn't look at it very much. I was trying to figure out what the difference was between using zinc as a fixative and, say, formaldehyde. It wasn't clear to me you were fixing the tumor or the process in the skin and then there is surgical removal because it is almost like repeating so-called Mohs surgery where you fix it and then cut it out, because when I was looking at the animal, the cow data, or maybe it was the Yorkie, it looked like you had fixed it with zinc and then

you had gone back and repeatedly cut it out.

I guess I am having trouble with what is the exact protocol.

MR. HANSON: Mode of action?

DR. KING: No, no; I know what the mode of action is in one sense. It is a fixative. So you use it for electron microscopy. What I was asking is what is the protocol? Is it zinc chloride fixative and zinc interactions and then you cut it out or you just put it on there like another chemical Effudex and seeing what happens.

The protocol is the problem; I don't know what you are doing, actually.

MR. HANSON: I see. With the Yorkie, he actually put it on, but he was having trouble getting it to stay on with the dog. It was such a large fibrosarcoma. So he called and actually what he did was he put it in an ointment, which is kind of crude. Anyway, he made a solution out of it and injected the fibrosarcoma.

DR. KING: That would be a version of injecting formaldehyde or formalin and fixation. It looks to me like you are doing chemical fixation and then debriding it. That is a different issue. That is why I was asking you is it just topical and watch what happens with no scarring or is it doing surgical removal after fixation?

MR. HANSON: No; it wasn't. Actually, the

debriding that he made was due to--the healthy tissue was actually interfering with his work so he had to debride it to continue on with the topical application. But the topical application was the final--I see what your point is.

DR. KING: I am just having trouble. Rubbing on the cream is different from rubbing on the cream and then cutting it out. I never saw a tumor get out of formalin if it was adequately excised.

MR. HANSON: It is kind of interesting. Go ahead, Dr. Drake, if you want to make some other comments.

DR. DRAKE: I think Wilma hit the nail on the head. I think everybody in dermatology would be very enthusiastic and eager to have a nonsurgical approach to skin cancer, or for any other cancer, for that matter. But, clearly, this is an area in which there is a great demand. I couldn't support Rob Stern any more by saying that it really needs to be focused.

Finally, I think you need to get--whether you approach some venture capital folks, or maybe somebody in this audience that has a company might have an idea to partner with you, but I think, conceptually, you need a partner of some sort so that you can do the necessary work that is credible and scientifically valid so that the agency and this committee can consider it seriously.

But, in terms of concept of needing a nonsurgical

approach, that would be very interesting to this committee.

MR. HANSON: I have some of the product that we have made. This was sent for a chemical analysis, by the way. You can see it is kind of a yucky green. I am going to do something here in a minute. This actually only attacks cancer cells. I just put some on my skin and there is no reaction. I am going to eat it. Isn't that neat? Call 911, would you?

DR. DRAKE: Mr. Hanson, you know what I am going to do now so that we can use our time wisely, I am going to poll the panel and ask the panel to each person give you their single best idea, including you guys.

MR. HANSON: That would be great.

DR. DRAKE: Let each member of the panel, much as we did with Schering, I want to ask the panel members to each give them their one best idea on how to be helpful to you. I am going to ask the panel to be original. If it has already been said, think of something new.

Eduardo.

DR. TSCHEN: An interesting idea. I think more formal clinical trials will be a great idea, formal clinical studies.

DR. DiGIOVANNA: I am not that original. I have to agree with Wilma. I think partnering with someone who has extensive knowledge in formal trials would be helpful.

DR. MILLER: The FDA has listed the things that need to be complied with with the NDA, so each of those items would have to be complied with before you would be able to go forward.

MR. HANSON: We are addressing those aggressively. Yes.

DR. JORDAN: I think the notion to focus this, maybe just pick one of these tumors, like basal-cell, and focus in on those studies, but do them well.

DR. DRAKE: That is an excellent idea; do just one tumor. Wilma, go ahead. You are not off the hook.

DR. BERGFELD: Because I am an entrepreneur-like therapist, I would say that I would hope that you would go forward. It sounds very interesting to me.

MR. HANSON: We will. We are, aggressively.

DR. DRAKE: Dr. Stern?

DR. STERN: I think I made my suggestion. I think it will also help to be in contact with an institutional review board and Protection of Human Subjects.

MR. HANSON: Thank you.

DR. DRAKE: Jim?

DR. KILPATRICK: Again, three words; focus, focus, focus.

DR. STERN: Very good.

DR. DRAKE: Actually, I gave Rob credit for that,

but it was you. You are exactly right. I'm sorry. Sorry, Jim. You are the one that had that good idea.

DR. STERN: Dr. Kilpatrick just says what I think.

DR. DRAKE: Bill?

DR. ROSENBERG: I just think you have to realize that, over the years, individuals have come forward and said this or that would cure cancer. There are people with cancer who will turn anywhere for help. Now, with skin cancer, we have treatments that work. I think to suggest that we are going to be able to treat to people until we know so is wrong.

So I think the studies need to be done with people who understand that--either people or animals. I think starting with animals makes more sense. It is easier to get permission to study cancer in animals. I think if you were to work with a veterinary group or an academic veterinary group and see if you can cure skin cancer in animals, I think the world would beat a path to your door.

But I think you must be very cautious, or more than cautious. I think you just must realize that there are too many people who have cancer and are too upset and too sad who can't just think that somebody has got a cure for it. You don't want to be in that category.

MR. HANSON: I agree with you wholeheartedly. Too many of my friends have beaten the path to Mexico to look

for the wonder drug. When you say there are treatments for it, are you talking about the excisions? There is no topical--I think Effudex is no longer recommended for any type of skin cancer, actinic keratoses.

DR. ROSENBERG: There is actually something that is being studied now.

DR. DRAKE: I don't want to go there. I would like to continue, please, because we are getting close to adjournment hour and I would like to call on Joe. We are going to do this other table, too. So, Joe?

DR. McGUIRE: You have a concept and you have a product and you are frustrated because people are skeptical. That is the way it is going to be until the information is presented in a way that someone other than you can understand it. It is very hard for me to understand your data, here.

I think you need to sit down with some friendly but smart person and ask them how to get your data in shape so that it is interpretable by someone else. This was a lot of work but it is also very difficult for an outsider to understand.

DR. DRAKE: Joel?

DR. MINDEL: Nothing. Thank you.

DR. DRAKE: Jon? I want to go back down here. Dr. Epps?

DR. EPPS: Once you have your protocols and your process together, have as many subjects as you can and also some controls.

MR. HANSON: The control, by the way, was done by Dr. Jordan down there. He used the same patient. One of those photos was the cheek. That was a surveyor that was in Mexico. He put the separate components on other lesions that this man had and the base and used that type of control. In other words, the same immune system, the same person, persons. That was his control.

DR. DRAKE: Mr. Hanson, what I want to say is you are using--another thing, if you are going to come before this committee again, I think you have to have credible people. We don't even know, and you don't even know, what credentials Dr. Jordan has, or Mr. Jordan, or whatever he is.

I think you really have to go back and look at the credibility of your work because the outside world is not going to buy in until they understand who is doing the work. By controls, I guess I would like to elucidate a little bit. By controls is, you may treat a tumor with this product and then you go back and remove it by an excisional method, the traditional way, and look at it histologically and see if the tumor is all gone.

So that is what I am thinking of. When I think of

controls, I want to make sure that the tumor is gone and that this product will do the job.

MR. HANSON: Yes; I do

DR. ROSEN: Not only focus, focus, focus, but data, data, data. It is not only the quality of data but the quantity of data. There is more than one method of treating skin cancer now, not only excision. Effudex is still used in actinic keratoses. Superficial multicentered basal-cell, intralesional interferon. There are immune-modifier-response drugs that are being studied now for the treatment of skin cancer.

You will have to have data that is in comparable quantity to perform comparably so that you show that your product is equally good to the other options but has an advantage of no surgery, smaller recuperation time, better cosmetic outcome or something. But you have to have a quantity of data that will be comparable to the other methods that are available.

I would also echo one of the other comments on the other side of the room. Human data is, A, hard to come by and it is risky and requires institutional review board. Having lost a pet to a very aggressive sarcoma, you could easily, probably more easily, partner with a veterinary academic group and do a world of good for treating animal tumors. You are held to somewhat less stringent standards,

if you wanted to start there and at least prove the viability of your product in one group of mammals.

MR. HANSON: Thank you.

DR. DRAKE: Steve?

DR. FELDMAN: I feel more comfortable if the studies were clearly blinded as well as controlled.

MR. HANSON: Thank you.

DR. DRAKE: Lloyd?

DR. KING: It has been my experience in life the great idea whose time has not come is a failure. It oftentimes fails because it is not presented in a way that users, or the people who need to concept, understand. So I think you are going to have to do the focus and set up this in a way--you have got to speak English to English and French to French.

This is, so far, more a testimonial and not in the usual format. So I think you have a great idea. You are just not convincing because you are speaking French to English folks.

DR. DRAKE: With that, the hour is getting quite late. What I want to do is I want to thank you, Mr. Hanson, and you, Dr. Potestio, for coming and, once again, warmly welcome you to the world of investigation. I hope our comments have been helpful.

With that, I would like, then, to--

MR. HANSON: If I could take a minute and thank the advisory committee for their patience with us and good advice.

DR. DRAKE: We wish you great success.

MR. HANSON: We are going to market this. Thank you.

DR. DRAKE: Dr. Wilkin?

DR. WILKIN: Dr. Drake, we thank the invited guests, the experts, the sponsor for their earnest presentation, the members of the committee and you, the Chair, for the comments. They have been helpful for us. They were directed at the sponsor, but they were helpful for us to hear as well. Thank you.

DR. DRAKE: Is there any further business to come before this committee? We stand in recess until tomorrow.

[Whereupon, at 5:15, the proceedings were recessed to be resumed at 8:30 a.m., Friday, June 30, 2000.]

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CERTIFICATE

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