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Martin Okun, M.D., Ph.D.
Susan Walker, M.D.

C O N T E N T S

NDA 20-010 - Lotrisone (betamethasone diproprionate and clotrimazole) Lotion
Schering-Plough, Inc.
for Treatment of Tinea Pedis, Tinea Cruris and Tinea Corporis

C O N T E N T S (Continued)

NDA 20-996 - Dermex II (zinc oxinate) Ointment
Dermex Pharmaceuticals, LLC
for Treatment of Actinic Keratosis, Basal Cell Carcinoma and Squamous Cell Carcinoma

P R O C E E D I N G S

Call to Order and Welcome

DR. DRAKE: Good morning. I am Lynn Drake from the University of Oklahoma, currently, and, as of July 1, from Harvard Medical School. I would like to welcome you to the fifty-second meeting of the Dermatologic and Ophthalmologic Drugs Advisory Committee for the Center for Drug Evaluation and Research of the Food and Drug Administration. The date is June 29, 2000.

The first thing I would like to do, before introductions, is make a primary introduction. I would like to introduce our new executive secretary, Jaime Henriquez.

MR. HENRIQUEZ: Welcome.

Conflict of Interest Statement

MR. HENRIQUEZ: The following is the conflict of interest statement. 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 with the following exceptions.

In accordance with 18 USC 208-B, full waivers have been granted to Drs. Joel Mindel and Robert S. Stern. Copies of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office located in 12A-30 in the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Lynn Drake has interests which do 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, Drs. Stephen Feldman, Mervyn Elgart, Theodore Rosen and Mary Spraker have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr Elgart would like the disclose that he speaks for Vertex concerning Mentax. Dr. Feldman would like to disclose that his Department of Dermatology received a teaching grant from Ortho for Spectazole and a teaching grant for Allergan grant for Naftin Cream and research funding from Ortho from Spectazole Cream and NDA 21-026 His

department has also received similar research funding in the past from Glaxo for Oxistate.

Dr. Theodore Rosen would like to disclose that his department received a grant from Vertex for a study of Mentax. 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. Dr. Rosen has also given talks concerning Mentax for Vertex and received speakers fees from 1998 through 2000. In 1999, Dr. Rosen received an honorarium from Allergan for a lecture concerning Naftin.

Dr. Mary Spraker is an investigator on unrelated studies for both Schering and Glaxo. 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.

The agenda is very busy this morning. It is a very interesting agenda. The first thing I would like to do

is introduce the panel. I think most of us know each other but there may be some who don't and there also may be people in our audience who would like to know who the participants are.

I guess I would like to start from this side of the table with the FDA folks and we will wander around the table. Please identify yourself and your affiliation.

DR. LaGRENADE: I am Lois LaGrenade with the Office of Postmarket Drug Risk Assessment at the FDA. I am a medical officer.

DR. OKUN: I am Marty Okun with the Division of Dermatologic and Dental Drug Products, FDA.

DR. LUKE: Markham Luke with the FDA, Center for Drug Evaluation and Research, Dermatologic Division.

DR. WILKIN: Jonathan Wilkin, Division Director, Dermatologic and Dental Drug Products.

DR. MINDEL: Joel Mindel, Mt. Sinai School of Medicine, Departments of Ophthalmology and Pharmacology.

DR. McGUIRE: Joe McGuire, Stanford, Dermatology and Pediatrics.

DR. ROSENBERG: Bill Rosenberg, Dermatology at the University of Tennessee.

DR. KILPATRICK: Jim Kilpatrick, Biostatistics, Medical College of Virginia, Richmond, Virginia.

DR. STERN: Robert Stern, Dermatology at the Beth

Israel Deaconess Medical Center at Harvard Medical School.

MR. HENRIQUEZ: Jaime Henriquez, FDA.

DR. BERGFELD: Wilma Bergfeld, Cleveland Clinic, Departments of Dermatology and Pathology.

DR. JORDAN: Bob Jordan, Dermatology, University of Texas, Houston.

DR. MILLER: Fred Miller, Geisinger Medical Center, Dermatology.

DR. DiGIOVANNA: John DiGiovanna, Dermatology, Brown University and National Cancer Institute.

DR. TSCHEN: Eduardo Tschen, Dermatology, University of New Mexico.

DR. DRAKE: This panel, just for the audience's pleasure, are our invited experts. Please.

DR. EPPS: Roselyn Epps, Children's National Medical Center, Washington, D.C.

DR. ROSEN: Ted Rosen, Department of Dermatology, Baylor College of Medicine, Houston.

DR. FELDMAN: Steve Feldman, Department of Dermatology and Pathology at Wake Forest University School of Medicine.

DR. KING: Lloyd King, Vanderbilt University and Nashville V.A., Dermatology and Dermatopathology.

DR. DRAKE: I would like to thank all the committee and our experts for your time. I also want to

thank the FDA for the very nice presentations, that we have received the documents ahead of time which is nice because we have had an opportunity to review them and we look forward to your presentations.

I guess we would like to start with Dr. Wilkin, who is Chair of the Dermatologic and Opthalmologic Drugs Division. Dr. Wilkin, would you give us an overview, please, of what we discussing today.

Overview of the Issues

DR. WILKIN: Thank you, Dr. Drake. What we are going to be looking at later this morning is Lotrisone Lotion which is currently under review as an NDA in our division. You will hear the regulatory history of Lotrisone Lotion. You will learn that it received an approvable letter in past. I can tell you that the sponsor has met the conditions spelled out for approvability and so the intent is, in the very near future, that I will be signing an approval letter for this product.

This product is, of course, a line extension from the Lotrisone Cream which has been of interest in the literature to dermatologists and different comments have been made. We have invited guests to speak to some of those very specific Lotrisone-related issues.

What we hope to hear from the committee and also from the guests is constructive suggestions for labeling

that might address some of these issues.

Before we get into the very specific aspects of this particular antifungal corticosteroid combination product, we would first like to begin the morning session with an overview of antifungal/corticosteroid combination product policy and ways of thinking about the attributes of these products and how they might be labeled.

Again, in general, we will not be talking about a specific product but I think those kinds of answers will then help inform the specific questions that will follow on this particular product.

DR. DRAKE: Thank you very much.

I think we will move, then, onto the main part of the program. Dr. Okun, would you like to begin?

Presentations - FDA

Fixed Drug Products Combination Policy:

Antifungal Plus Corticosteroid for Tinea Infections

DR. OKUN: Good morning.

[Slide.]

As Dr. Wilkin indicated in his introduction, my purpose here is to present an overview of how the agency's combination policy is applied to topical drug products containing an antifungal agent and a corticosteroid agent.

[Slide.]

First, I would like to define some symbols that

will be used in the presentation. AF+CS refers to a fixed-drug combination topical drug product containing and antifungal and a corticosteroid agent for treatment of tinea infections. AF refers to a topical drug product containing an antifungal agent. CS refers to a topic drug product containing a corticosteroid agent.

[Slide.]

21 CFR 300.50 spells out the informational needs for approval of fixed combination prescription drugs. Each component of the combination must be shown to make a contribution to the treatment effect. The dosage of each component is such that the combination is safe and effective for a patient population requiring combination therapy as defined in the labeling of the product.

[Slide.]

This slide describes the informational needs for approval of an antifungal/corticosteroid combination drug product for treatment of tinea. When I say tinea here and throughout this presentation, I am referring specifically to tinea pedis. The agency view is that the treatment of tinea pedis is the highest hurdle for assessing efficacy of antifungal agents and that treatment of tinea cruris is the appropriate disease model to assess local adverse events for safety.

First a word about entry criteria for patients

enrolling in tinea pedis studies. The patients must have the clinical signs and symptoms of tinea infection at baseline. They must have a positive KOH at baseline. Fungus culture is collected at baseline and patients whose culture turns out to be negative are subsequently excluded from the efficacy analysis.

Informational needs for approval are that the contribution of the antifungal and of the corticosteroid components be demonstrated, that the antifungal/corticosteroid combination be demonstrated to safe and effective for tinea infections and that the population requiring combination therapy be identified.

[Slide.]

What are the potential benefits to patients with tinea of using an antifungal/corticosteroid combination product? The antifungal component is going to treat the infection with the point of cure occurring approximately five weeks after the start of treatment.

The corticosteroid component will relieve the symptoms of infection early, usually about one week after the start of treatment. The antifungal/corticosteroid combination, then, relieves symptoms of infection early and treats the infection.

[Slide.]

In comparing the antifungal/corticosteroid

combination with the antifungal stand-alone product, an antifungal stand-alone product relieves the symptoms by the point of cure as the infection is cured. The antifungal stand alone may provide some relief of symptoms early as the infection begins to clear.

The only potential benefit of antifungal/corticosteroid combination, compared to antifungal, is if the antifungal/corticosteroid combination provides more symptomatic relief early.

[Slide.]

I am going to use the following abbreviations for the rest of this talk on my slides: ROS to stand for relief of the signs and symptoms of tinea infection such as itching, erythema, scaling early in the treatment course; TTI referring to the treatment of tinea infection which includes mycologic cure and relief of signs and symptoms of tinea infection, usually occurring late in the treatment course or post-treatment.

[Slide.]

To demonstrate the contribution of the corticosteroid component in antifungal/corticosteroid combination products, the antifungal/corticosteroid combination must be shown to be superior to the antifungal stand alone in relief of symptoms early in the treatment course.

This condition applies regardless whether the corticosteroid stand alone is equivalent to the component product with respect to the relief of symptoms or if the corticosteroid stand alone is inferior to the component product with respect to the relief of symptoms.

The experts on clinical-trial design here are probably blanching at the notion of demonstrating equivalence in the clinical study. In fact, the equals sign is really a shorthand for demonstrating noninferiority within a prespecified confidence interval.

Scenario No. 1 where the corticosteroid arm is superior to the antifungal/corticosteroid combination with respect to the relief of symptoms is a scenario that I will discuss the ramifications of in a few minutes.

[Slide.]

To demonstrate the antifungal component in an antifungal/corticosteroid combination, the combination must be shown superior to the corticosteroid-only arm in terms of the treatment of the tinea infection. This condition applies regardless whether the antifungal is inferior to the component product with respect to tinea infection.

The ramifications of scenarios 2 and 3 where the antifungal arm is equivalent with respect to the combination for treatment of tinea infection or where the antifungal arm is superior to the combination arm with respect to treatment

of tinea infection will be discussed in just a few minutes.

[Slide.]

Let's return to one of the previously identified scenarios, Scenario No. 1. To refresh our memories, in Scenario No. 1, the combination product is demonstrated superior to the antifungal arm with respect to the relief of symptoms which demonstrates the contribution of the corticosteroid component. Also, the combination product is demonstrated superior to the corticosteroid-only arm with respect to the treatment of tinea infection; this demonstrates the contribution of the antifungal component.

What if the corticosteroid-only arm is superior to the combination product with respect to the relief of symptoms. Under this scenario, the combination product has risks and benefits associated with its use. The risk is that the antifungal component in the combination product is impairing the early relief of signs and symptoms.

The benefit is the antifungal component is providing treatment to the tinea infection. Very obviously, in this scenario, the benefits of a combination product is outweighing its risks.

[Slide.]

Let's consider Scenario No. 2. Let's assume that the combination product is superior to the antifungal arm with respect to the relief of symptoms. Again, this

demonstrates the corticosteroid contribution. Let's assume the combination product is superior to the corticosteroid-only arm. This demonstrates the contribution of the antifungal component in terms of treatment of tinea infection.

Let's assume the combination product is equivalent to the antifungal stand-alone arm with respect to the treatment of tinea infections. Under these circumstances, the question for your consideration is should such an antifungal/corticosteroid combination product with these properties be labeled for all tinea or should it be labeled only for the more inflammatory tinea that warrants the use of an antiinflammatory treatment.

[Slide.]

Let's consider Scenario No. 3 now. In this scenario, again the combination product is superior to the antifungal with respect to the relief of symptoms, again demonstrating the corticosteroid contribution. The combination product is superior to the corticosteroid arm with respect to the treatment of tinea infections, again demonstrating the contribution of the antifungal component.

What if the antifungal arm is superior to the combination arm with respect to the treatment of tinea infection? Under these circumstances, combination product has risks and benefits associated with its use, the

principle risk being that the corticosteroid component is impairing the treatment of the tinea infection.

The benefit is that the corticosteroid component is providing early relief of the signs and symptoms of infection. Under this scenario, only patients with clinically significant symptoms at baseline could benefit from use of the combination product.

A question for your consideration is how could labeling of such a product identify which patients could benefit from an antifungal/corticosteroid combination drug product with these properties.

[Slide.]

I would like to turn now to a discussion of some aspects of the clinical-study design for antifungal/corticosteroid combination drug products. The original paradigm that has been used for study of these products is a three-arm or sometimes a four-arm study where the arms are antifungal plus corticosteroid combination, another arm being the antifungal stand alone, another arm being the corticosteroid stand alone, and, in some circumstances, a fourth arm being the vehicle for all the other arms.

There are some shortcomings of including a corticosteroid arm in a clinical study of treatment of tinea infections in that anecdotal experience and publications

suggest that the corticosteroid component may interfere with the host-immune response against a fungus.

[Slide.]

This leads us to wonder if we can reconsider clinical-study design to fulfill the informational needs of the combination policy without enrolling the study subjects in a corticosteroid stand-alone arm.

[Slide.]

A new paradigm under consideration is a three-arm study where the three arms are composed of antifungal plus corticosteroid combination, the antifungal stand alone and the vehicle. In this paradigm, if the combination is superior to the antifungal stand alone with respect to the relief of symptoms, this demonstrates the contribution of the corticosteroid component.

If the combination product is superior to the vehicle with respect to the treatment of tinea infection, this demonstrates the contribution of the antifungal component under the assumption that the corticosteroid is not contributing to the treatment of tinea infection.

So we have demonstrated, under this paradigm, the contribution of each component. What information is lost by not having a corticosteroid stand-alone study arm?

[Slide.]

Under the three-armed study where there is a

combination arm, antifungal arm and vehicle study arm, in the absence of a corticosteroid study arm to demonstrate antifungal contribution, the combination product must be shown to be superior to the vehicle with respect to treatment of tinea infection.

If the combination product is demonstrated to be superior to the vehicle with respect to relief of symptoms, this may be due either to the contribution of the corticosteroid component or to early antiinflammatory effect of the antifungal component or, potentially, both.

For a sponsor to claim that the antifungal component provides relief of symptoms early in treatment comparable to that of a corticosteroid component, the sponsor would have to demonstrate that the antifungal arm is equivalent to the corticosteroid arm with respect to the relief of symptoms and that the antifungal arm is superior to the vehicle with respect to the relief of symptoms and that the corticosteroid arm is superior to the vehicle with relief of symptoms. This claim is not possible without a corticosteroid stand-alone arm.

A question for your consideration is whether the knowledge obtained from including a corticosteroid arm compensates for the previously mentioned shortcomings of having a corticosteroid arm in a clinical trial for treatment of tinea infections.

This concludes my presentation. Thank you.

DR. DRAKE: Thank you very much. You did a great job. That is complex and you did it in a manner that all of us understand. Thank you.

DR. OKUN: Thank you.

DR. DRAKE: There has been a lot of thought gone into that presentation.

I would like to ask Dr. Wilkin, would you like to consider these questions now? Is this an appropriate time?

DR. WILKIN: I think it would be. The questions that are limited to this.

DR. DRAKE: The three questions he has?

DR. WILKIN: That's right; just to the antifungal/corticosteroid combination policy types of issues. Yes.

DR. DRAKE: Let's consider the questions, then, at this moment, since this is fresh in our mind, of just the policy issues, the three questions that were outlined. I am going to pose the first question, then.

The first question is, "Is the proposed set of decision rules for antifungal/corticosteroid combination topical products acceptable for documenting the contribution of both components?" That is the question.

I would like to ask for a point of clarification. I have read it, but I think, for the whole committee's

benefit, the proposed set of decision rules we have before us or we been just given questions. We don't really have the proposed set on a slide yet.

Jon, is the proposed set of rules before us? Do you want to elucidate a little bit on those?

DR. WILKIN: If you like, Dr. Okun has them in his slides.

DR. DRAKE: Could we go back to the slides? I would like to go back so we are all talking the same set of rules.

DR. OKUN: I am just trying to think of which would be the most appropriate slide.

DR. DRAKE: I think one of the questions that pertained to this was on Slides 13 and 15. One of the things you wanted to know is the corticosteroid arm important for this. That was Slides 13 and 15.

DR. OKUN: Certainly, we can start with that. If we consider the utility of the corticosteroid-only arm, let's go the Slide No. 15.

[Slide.]

This is the three-armed paradigm in which a corticosteroid-only arm is excluded. In this paradigm, for us to demonstrate the contribution of each component, again, there is the combination arm, the antifungal stand-alone arm and the vehicle arm. The antifungal combination

corticosteroid arm must be demonstrated superior to the antifungal arm with respect the relief of symptoms.

I should mention, parenthetically, that implicit in this is also that the antifungal/corticosteroid combination arm is superior to the vehicle with respect to the relief of symptoms. In addition, the combination arm must be shown to be superior to the vehicle with respect to the treatment of the tinea infections.

The latter demonstrates the contribution of the antifungal component. So our Question No. 2c, "Is it sufficient that the corticosteroid does not reduce the antifungal activity--" Dr. Drake, what question are we on? I'm sorry.

DR. DRAKE: Let me back up. Maybe I didn't make myself very clear. On Question 1, one of the questions that I think probably everyone has is is the proposed set of decision rules for this combination product acceptable for documenting the contribution of both components.

I think we may be a little weak, at least from my personal perspective, on exactly what are the proposed set of rules which I don't think I actually know for sure exactly what we are proposing. Or is that what we are supposed to decide? Do you want advice on what we would propose?

DR. OKUN: I think I can help you out.

DR. DRAKE: Good. I could use some help.

DR. OKUN: I apologize. I should have made this a little more explicitly clear. Obviously, several decision rules were bandied about in my presentation. I wasn't very explicit in terms of referring to which we were talking about here.

DR. DRAKE: While you are looking, I am going to take a couple of comments from the panel. Dr. Stern?

DR. STERN: One of the interesting things about these rules is that they are in the complete absence of any rules about risk. Somehow, we have gotten into thinking a lot about tinea pedis where the risk of these agents, except for what is in the rules, is probably minimal.

But, in fact, these combination agents are used in a variety of other sites where there may be greater desirability to avoid corticosteroids where possible. So, if you are just looking at inflammation at eight days and fungal cure at 35 days, I am not sure that these rules can be generally applicable unless you have it as the caveat and in a site where you don't really care whether you are using steroids for a week or two.

That is the one thing that seemed to be a little bit absent from this discussion which I know is very much a concern for the specific agent we are going to be considering later.

DR. WILKIN: I think the point is well taken. I think actually your concern is incorporated into one of the decision rules. Perhaps, the best place, rather than the slides where we would be looking at the individual rules, if you look at this document that came to you, the Overview and Questions, if you look at the top of--

DR. DRAKE: Jon, was this in the material that was mailed out to us ahead, or is it in our packet today?

DR. WILKIN: It is material that was mailed to you.

DR. DRAKE: It is in the mailed packet; okay. Let's just make sure we are on the right thing.

DR. WILKIN: It is under Tab 1.

DR. STERN: Are these the three, the last page of Tab 1.

DR. WILKIN: At the top. It starts, in parenthesis, if the antifungal is superior to the combination for antifungal activity, that could be anticipated for many products, and, antifungal is non-inferior, essentially non-different, from the combination for antiinflammatory activity, then the question is one could approve the antifungal alone for all tinea regardless of the inflammatory component because, once again, the antifungal alone is superior to the combination for antifungal activity and the sponsor has not been able to

demonstrate a difference between the combination and the antifungal alone in treating the antiinflammatory part.

So that would be the first decision rule. The question is does that particular outcome and how we would go with that. So this would not be a combination product. It would be approval of the antifungal alone.

DR. STERN: But implicit in that, would you not approve a combination product where the antifungal component, in fact, gave you these results, superiority with respect to mycologic cure and equivalence with respect to antiinflammatory effect?

So the other side of the question is, it is clear here that the antifungal, assuming it beats placebo, would be indicated for all types of tinea. It is clear to me that it would be. But is the flip side if someone gives you agent A, that antifungal, and B, the corticosteroid and this combination, these are the results of these trials the you say, "Sure, A is fine for all types of tinea but we are not going to approve the combination of A and B because you already have something that is, in fact, better in one metric and equal in the other metric, so no combination agent."

DR. WILKIN: Yes; that is exactly what is intended by this. That is what is intended by that decision.

DR. STERN: I think you should say then only the

AF would be approved because it doesn't say, "And we would reject the AF/CS combination."

DR. WILKIN: Yes. It does say, "Then approve AF alone, the antifungal alone." That is what the intent of that was. But you are right; we could have added in there, "And reject the combination."

DR. DRAKE: I see some hands. Dr. Rosenberg?

DR. ROSENBERG: At the risk of wandering a little bit, I feel I really want to make a few remarks about the one particular antifungal/corticosteroid combination, the Lotrisone, which is--

DR. DRAKE: Bill, can I wait until we get to the section?

DR. ROSENBERG: Well, no; I want to talk in general. It relates to the product we have seen.

DR. DRAKE: If you comment on general policy for any product--

DR. ROSENBERG: Yes; general policy.

DR. DRAKE: This, right now, is general policy on any product that might come before the FDA.

DR. ROSENBERG: Exactly; this is general policy.

DR. DRAKE: Please.

DR. ROSENBERG: When the first of these products--and I wanted to commend Dr. Wilkin and the agency for the format of this in which we look at the whole issue of

corticosteroid/antifungal combinations.

DR. DRAKE: I think that is very proper.

DR. ROSENBERG: I think it is necessary that we do that. I recall when the first of these products was being developed and when it was being reviewed and so forth, different people were here at that time. It had to meet very specific criteria. It had a very active, good antifungal, clotrimazole, and to add a corticosteroid to it and meet the combination product requirements, it had to add a dimension.

The dimension that was required was that the inflammation--the clotrimazole was going to cure the fungal infection at a high rate, so why add something to it. What was added was a high-potency corticosteroid in order to give more rapid symptomatic relief than could be achieved with the clotrimazole alone.

Now, the plain clotrimazole is quite good at providing symptomatic relief.

DR. DRAKE: Bill, can I get you off the product and get you back into generics?

DR. ROSENBERG: Okay; we will talk generically.

DR. DRAKE: Yes, please.

DR. ROSENBERG: The antifungals we now have are quite good and people get better quite quickly and their symptoms go away quite quickly. If you are going to

demonstrate that putting a corticosteroid into the product adds to it, you need a very good corticosteroid. You need a very good corticosteroid to make it go that much more quickly.

So that is why we have very high-potency corticosteroids added to antifungals, because if you had a lesser potency corticosteroid, it would be hard to catch up with the good antiinflammatory of curing the fungus infection.

I submit that that may not be the right question. I think more to the point is that is there a really a clinical need for such rapid relief of symptoms that we need to add a corticosteroid to a good antifungal. I would submit that, no, there is not, really. But I think there is a major and very important need for a reasonable treatment for red, scaly spots that might be fungus and might not be fungus.

In the real world, in managed care, where we have primary-care doctors, there is public policy towards OTC where possible, where even specialists who are on time categories of patient visits and laboratory fees, et cetera, are trying to hold down costs, that there is a real place for something that would be a very good treatment for something that might be fungal but not necessarily so, in the hands of whatever person is treating it.

In fact, I submit that the product which is now there, the combination product, succeeds as it does not because it provides more rapid symptomatic relief for bona fide fungal tinea pedis but because it fills that need for a combination corticosteroid/antifungal.

I submit that a better performance for that purpose, the combination, would be one with an antifungal with a less strong corticosteroid, one that is suitable for use in something that doesn't require a very powerful one, hydrocortisone, for instance.

In fact, the old CIBA Viaform, if I may mention it, hydrocortisone product which left because it couldn't meet the antifungal requirements--I remember the hearing. I was involved in that. The plain Viaform wasn't all that good for antifungal but it was a very good product. Of course, it might have been fungal, it might have been nummular, it might have been bacterial and it just might have been dermatitis. In fact, I see it is back.

So, we have, now, a public policy where most medical problems of this magnitude are being handled by primary-care physicians and many of them, again with public policy in yesterday's New York Times at the OTC level where patients see that there is something round and itchy and they would like to buy something that would be helpful for it, and should be allowed to have something over the

counter.

So this is a whole different set of questions. I think the present combination products are not being used for--I think we are telling ourselves a story if we are going to characterize these things on how rapidly they relieve symptoms without interfering with the antifungal properties and if there are any side effects and so forth.

I think we have backed ourselves into a very useful product that could be made better by making the regulatory aspect of it somewhat different.

Thank you.

DR. ROSEN: Lynn, can I make a comment?

DR. DRAKE: Please.

DR. ROSEN: I think more specifically to the question that is being asked right now, at least one of the questions that is posed to the panel, is whether you want some approval from us or the panel whether to go from a four-arm to a three-arm in terms of how to determine the efficacy of antifungal, antifungal combination drugs.

The one thing you are dropping out is the corticosteroid-only arm. I think that is a major question that you are asking. While I think that that was not of significance, and I am going to address this later in my presentation so I won't elaborate, it wasn't of significance for some of the antifungal agents because there is actually

a hierarchy of inherent antiinflammatory activity for the antifungal drugs as stand alone.

It is really not an issue for the current one that is going to be discussed later but there may be an issue for some of the other antifungals which have come along subsequently which have more inherent antiinflammatory properties.

The thing is a manufacturers probably will not attempt to claim antiinflammatory activity equal to corticosteroid because the only way to verify that would be to continue with a corticosteroid-only arm. But I don't think the manufacturers are really going to go after that claim. That is the first thing.

The second thing is from a purely pragmatic standpoint, if you include the corticosteroid-only arm, then what you are doing is deliberately subjecting some number of patients in a clinical study to application of corticosteroid to a fungal infection. I seriously doubt that any clinician in the room would really want to do that to their patients.

Now, intellectually, it might be nice to compare corticosteroid-only to antifungal-only and that would allow the claim of the antifungal if, in fact, it were equal or better. It would allow the claim of the antifungal to possess antiinflammatory properties equal to or better than

the corticosteroid.

But I think nobody really would want to do that, as a clinical investigator, to put corticosteroid-only on known fungal infections because you have excluded negative KOH and negative culture. You are not putting it on question-mark diagnoses. You are putting it on patients who have a known fungal infection.

So I would be in favor, although it would be intellectually interesting to compare corticosteroid and antifungal, I would be in favor of leaving your three-arm as you propose and dropping out the corticosteroid-only arm unless or until some sponsor said, "I want to claim that my antifungal is as good as a steroid," and I don't think you will have many takers on that.

Even though it may be true, that study could pose risks for the participants. So I think your three-arm for virtually everything you might get would be appropriate rather than the four-arm. And that is your specific question and that would be my suggestion.

DR. DRAKE: I have three hands that I have noted; Bob Jordan, Wilma Bergfeld and John DiGiovanna, in that order, please.

DR. JORDAN: I guess I come back to my comment earlier about the exclusion of patients who are KOH-negative. The main reason, I think the way these products

are being used now, those are the very patients that are being subjected to these kinds of treatments.

As I mentioned before, very oftentimes, with very inflammatory tinea, you may have a negative KOH. You may have a positive culture, but, again, it is this group of patients that probably are being treated with this combination more than just the antifungal alone. So I still have a problem with that.

DR. DRAKE: Bob, I just want to elucidate a little bit. I want you to elucidate a little bit because everybody in the audience may not know exactly what you are referring to about the inflammatory nature of an early patient and the enrollment criteria for study, and they may never get in one of these.

Would you please comment on that for the benefit of the total audience?

DR. JORDAN: Very oftentimes, in tinea, when it is very inflammatory, the KOH will be negative. The culture may be negative for that matter because of other superimposed factors that are involved with the tinea. I think by excluding that group of patients, those are the very patients that are going to be treated with this combination anyway, it seems to me we are losing something in terms of the benefit, if there is a benefit, to these combination products.

DR. DRAKE: Thank you.

Dr. Bergfeld.

DR. BERGFELD: I think there are many questions that have been put upon the table but I would like to address a couple of things that have been said. First of all, Dr. Rosen, I disagree with you that you don't need a corticosteroid arm because, if you heard from the FDA, they stated that this was a tinea pedis, interdigital type. There is very, very little risk to the patient if you were to do a corticosteroid arm in that particular group.

I am sort of interested in the fact that tinea pedis is sort of the gold standard for the site to be treated yet the application will be to the groin and to the trunk and maybe a small spot, or a very large area, which adds a dimension of risk. But, as far as treating tinea pedis, there is very minimal risk to using a corticosteroid arm.

The other thing that I was interested in in the study design was if you are going to have a response to corticosteroids, and it was very nicely demonstrated that the response was in the first five days, and that the tinea response, the fungal response and the fact the culture-negative was seen at the end of the treatment period which was stated to be 30-plus days.

In the design, and I didn't see this but I suspect

it was done, was there a notation on clinical symptomatology in the first five days rather than the global which was, I gathered, what was presented at the 30-day marker, because the symptom response for corticosteroids, as stated by everyone, is acute within the first week. If the was significantly improved, that would be a significant feature.

DR. WILKIN: The actual time of when the antiinflammatory effects are assessed is somewhat up to the sponsor to suggest. What we don't like to see in phase III trials is where they will look at inflammatory signs and symptoms over several days and then come in and tell us, "Well, the greatest difference was on Day 3 or 4 or 5," sort of after the fact and that was where the statistical difference is.

So it is always nice if they have looked in a phase II kind of study where they have figured out when they are going to see that difference and that they will, then, do the study in phase III where they will assess at the time that they anticipate the greatest delta between the corticosteroid-containing arms and the non-corticosteroid-containing arms for the inflammatory signs and symptoms.

DR. DRAKE: John?

DR. DiGIOVANNA: I think a part of my comment has already been iterated, but I would just like to rephrase it a bit in that I think that this is labeled as a policy

document. I think that a main issue that I see is if one were to appropriately look at when a wise use of these compounds, this combination would be, it would be mostly for individuals who have been excluded by the entry criteria that you have listed.

Most dermatologists who get a positive KOH, or most dermatologists would do a KOH, in a suspected tinea if it was inflammatory. But I think there is enough documentation to know that there are many of those, if not most of those, that would have a negative KOH and a negative culture.

Therefore, if you exclude those patients who are most inflammatory and most likely to be the ones to benefit from this, you have already set up a situation where the rest of the very nice logistic paradigm falls through.

So what I would like to suggest is whether or not there is a role for a redefinition of what the clinical circumstances, what the appropriate indication might be, for, as Dr. Rosenberg said, a red, scaly spot that is suspected of being a tinea.

DR. DRAKE: Dr. Wilkin?

DR. WILKIN: Yes; if I could get some--it sounds like there is actually some convergence in Dr. Jordan, Dr. DiGiovanna and Dr. Rosenberg. They are going into, I think, a very helpful area for us at the FDA to hear.

There is this group that really has not been identified in our previous studies that come to us that may have some benefit from this kind of a product. My question back to the whole committee, but especially the three of you, is do you envision that ultimately in the population that will be analyzed statistically for outcomes that, at some time during the treatment, there will be a positive KOH or a positive culture, or are you suggesting that really we should have more of a reductive kind of approach to the indication and the indication should be "red and scaly?"

DR. ROSENBERG: If I could answer, I would say absolutely. I think there is a place for studies of red scaly things that might or might not be fungus, which comes up all the time in many, many offices and many, many households.

I think the appropriate study would be to enlist those kinds of people, just as they are, to do KOHs and do cultures to see how things turned out, but to treat them with these different arms and see, in fact, how the combination product versus the different single products did for the whole mass of them, those who turned out to have it and those who turned out not to have it.

One of the things we would be looking for would be if the combination did no harm and it got a few that wouldn't have been picked up by the other, then why not a

combination. Certainly, the over-the-counter area of medicine includes such cough-cold--if we backed up and went after the symptoms of redness and scaliness, then such a product would make all kinds of sense, or similar products, a nystatin, a hydrocortisone cream, a Viaform--back to Mycolog 1.

Those are things, though, that enjoyed great popularity in a profession of doctors who are getting up every day and trying to do the right thing for their patients. I think, by being so rigid in terms of how we define these products, we have backed ourselves into the same sort of a thing, but not the way we have intended.

DR. DRAKE: Jon?

DR. WILKIN: If I could just respond to that, not to the part about rigid but, actually, to the part about--what I think the evidence has come in in the past and what we have asked for on these kinds of products would allow us to say, yes; there is an antifungal contribution. We have documented that, and also there is an antiinflammatory contribution and then taking that information that both of those have been demonstrated, then I could actually see a translation into the clinical setting of reduction where, then, it is a reductive approach to the clinical problem but it is based on a fairly substantial database that says if it is fungus, it is going to be okay. We have good outcomes

with this product. And, if it is not, you are treating the inflammation anyway.

DR. DRAKE: Rob?

DR. STERN: As we are coming to convergence, I hate to throw a random thought out there, but when we have looked at these data, it seems that the antiinflammatory component from corticosteroids, if there is a benefit, is early on, usually in the first five or seven days of what is typically two- or three- or even four-week courses of therapy.

So we have coupled two agents, one of which you need to use for a number of weeks if there is fungus there for clearing and nonreoccurrance with an agent that you only want there for the first five or seven days because there is little or any evidence of additional benefit either practically or theoretically once you have gotten beyond that point for these red, scaly, itchy things.

So I guess my question, from a health perspective, given the wide variety of these very efficacious antifungals, why have these agents at all when you have unnecessary therapy for sometimes as much as 80 percent an extra agent there. You only need it for the first 20 percent.

It is not so difficult to have recommendations, in fact, that you use in certain situations, two agents when

there is ambiguity. That is certainly something I do. You use the appropriate antiinflammatory corticosteroid, depending on its degree and the site, the appropriate one, for three, five, seven or ten days and then, since you think there might have been fungus there, you use the appropriate antifungal agent for two, three or four weeks, depending on the site of the agent and the data for that.

So I guess I would like to go back and sort of maybe take the radical position, are we missing the main boat about whether these agents are, in fact, useful enough in clinical practice, given the widely available, over-the-counter antifungal agents that are highly efficacious for yeast and fungus and very inexpensive.

Are we doing bad things rather than good things even considering them for approval because, in fact, their net clinical benefit, in terms of risk/benefit, is likely to be small. So maybe we should make one step back before we make rules.

DR. DRAKE: I want to apologize to the committee for kind of taking the prerogative here, but time is a little bit tight here. I think this discussion has really demonstrated how important something new in the last few years that the agency is doing, and that is addressing the policy issues.

I saw them do policy with respect to

onychomycosis. I saw you do policy with respect to psoriasis. I think this is another major step in trying to prospectively define the policy which is a benefit to industry, a benefit to us and a benefit to everyone.

However, any time you get into policy, the discussions become quite interesting and wonderful. First of all, I want to compliment you for it and I want to apologize to the agency for us kind of having a packed agenda here and, as chairman, I want to get us done on time. But we would come back to it.

Having said that, in the interest of time, what I would like to do is kind of get a sense of the committee on your specific questions that you have asked us so we can go on to the invited presentations. Time permitting, we may, then, revisit this later in the day. Would that be acceptable?

I still don't understand Question 1, so I am going to skip it and come back to it. But I think we do have a lot of understanding about Question 2b. I am going to start there, and I am going to read it. "Is the knowledge and corresponding labeling that allows the claim that antifungals alone provide the antiinflammatory activity comparable to a corticosteroid a sufficient advance in public health to warrant a corticosteroid-only arm?"

I don't know that we want to have a vote. Do you

want just the sense of the committee, or do you want a vote on this? How much information do you guys want? Do you want a sense so that you can have leeway to continue to contemplate this or do you want to vote?

DR. WILKIN: We would be pleased to have a vote on this, but I should say that we always listen very carefully to all of the discussion leading up to the vote, so it is not just the vote that we rely on.

DR. DRAKE: I think it is clear that there are a lot of parameters that this committee has put on the table that are not being addressed, perhaps, in the traditional way we do the studies. We may be missing a big cohort of patients that would benefit from such a product.

I wanted to ask Dr. Rosenberg a very quick question before we vote. When you said red, scaly spots, did you mean that we would still try to identify a causative agent such as mycology or would you just throw that out and base it totally on just red, scaly spots?

DR. ROSENBERG: Otherwise undiagnosed. I think the study should be done at a primary-care level or a walk-in-clinic level.

DR. DRAKE: I think that is a very important notion.

DR. ROSENBERG: That is where the people are, and that is where the prescriptions are written.

DR. DRAKE: As a lot of things move to OTC, this becomes a more important notion because not everybody has the expertise to do the KOHs or to interpret them properly. So I think that is an important notion for FDA to please think about when you work with industry and for industry who is in the audience, I would strongly suggest that one of you perhaps capture this opportunity to answer some of these questions which are clearly important to the committee members.

Now, back to Question 2b. Yes? Jim? I knew I couldn't get straight to it.

DR. KILPATRICK: I would like to ask the agency about "comparable to." That speaks to equivalence which is difficult to establish, or do we simply mean not statistically different from which is a question of how large the sample is. Jon?

DR. WILKIN: We don't mean just simply not significantly different from, which always allows the type-2 error. No; we are interested in actually a formal analysis of equivalence. Noninferiority is what we are looking for.

DR. DRAKE: So what we are talking about is how many of us think that--does everybody understand the question on 2b? I would like to ask for how many are in agreement with this Question 2b. If you are voting yes, please raise your hand. If you want a corticosteroid arm,

raise your hand, please.

[Show of hands.]

DR. DRAKE: Ten. I think it is a unanimous vote.

DR. MINDEL: I have a question. How long is the corticosteroid arm?

DR. DRAKE: I think what we have seen, in this study, at least, was about eight days. Jon, would you like to address that?

DR. WILKIN: I think Dr. Mindel has an important question. One can build into protocols an ethical safety escape clause, if you will, that if these patients are followed very closely and if it looks like there is deterioration, while one will not know which arm of the study they have gone into, that patient can be taken out of the study immediately and given standard therapy.

DR. DRAKE: Wilma?

DR. BERGFELD: I am trying to grapple with all this as many of the panel members are, but I am looking at the reverse side of that and that is called the risk side. If, for instance, you were to apply this to a rash, clinically suspected to being tinea and it wasn't, what harm would be done?

Well, in reality, none, with how we give it. If this was applied, this topical combination was applied, to something that was tinea and it also has a limitation of

duration of therapy, what harm would be done?

The worst scenario I can see, and I did read some of the information sent here, was that you might have some thinning of the skin. But, again, you have limitations of time. It is not a forever application. It is two weeks, four weeks, max, usually.

So when we are talking about risk assessment, which I know we will speak about later, no matter which way you go with either product, the harm is rather minimal.

DR. DRAKE: One other thing they suggested in the data they presented us is that--I agree with you. I think the harm is rather minimal. Besides the thinning skin, one other thing that was pointed out was that the corticosteroids may--by suppressing the inflammatory response, if it is tinea that is present, then there may be--it may work less fast. That is not good English, but it may work not quite as quickly if it is on the tinea because you are getting a suppression of the host response from the corticosteroids.

DR. BERGFELD: But your studies would reflect that.

DR. DRAKE: I think if the studies are designed properly, they would. I think that is the issue. That is the question they are asking us on policy that we need to make sure that these prospective studies are designed with

that information.

Question 2c, I am going to go to next. "Is it sufficient that the corticosteroid does not reduce the antifungal activity of the combination to label the product for all tinea or should combination products containing corticosteroids be labeled only for the more inflammatory tinea warranting antiinflammatory treatment?"

I think this is a key question and I think one of the things they have asked to address, according to Dr. Wilkin's introductory statement. It is not a question of whether this at least one upcoming product and, potentially future products are approved, but do we want to tinker with labeling or do we want to make recommendations about labeling.

Am I correct on that, Dr. Wilkin? Please clarify.

DR. WILKIN: Yes, Dr. Drake, you are. And 2a actually helps this question in that we are asking about this, perhaps somewhat inelegant phrase, of "sufficiently inflamed tinea warranting a corticosteroid component," which is, then, captured again in 2c.

We were hoping that you might first address this.

DR. DRAKE: I would be happy to do so.

DR. WILKIN: Come up with maybe something better to put in labeling if you think this is an important consideration in the Indications Section of the labeling.

DR. DRAKE: May we go to 2a instead. I think that is a better order. I am still avoiding 1 for the moment. I want you to know that.

Question 2a; "Can a distinction be made in labeling between minimally inflamed tinea not requiring a corticosteroid component and sufficiently inflamed tinea warranting a corticosteroid component and, if so, suggest wording."

So the first question I would like to pose to the committee is can a distinction be made between minimally inflamed and sufficiently inflamed warranting a corticosteroid. First of all, I want to ask you to vote, can a distinction be made between that or do you want a little discussion beforehand because we have not discussed that at all.

Dr. Bergfeld?

DR. BERGFELD: We have never had great success in defining minimal to severe in any disease. My preference would be inflamed versus noninflamed.

DR. DRAKE: Other comments? All right; then let's vote. Would the committee vote, please. I want to vote on the question, not on Wilma's comment. I agree with your comment, actually, but I think we should do this.

DR. STERN: Are we interested in the presence of inflammation or are we interested in the presence of

inflammation and symptoms associated with inflammation, particular pruritus, in most cases, because most of the tinea I see--I see a lot of tinea that is completely asymptomatic but it is still pink and, therefore, inflammatory but it doesn't need a corticosteroid because they are not itchy.

So I wonder if it should be a distinction between inflammatory and symptomatic as the criteria versus not meeting both of those criteria.

DR. DRAKE: I see a lot of heads nodding. I would like just a sense. This is not a vote. I would like just a sense of the committee about recommending linking inflammatory and symptomatic together versus inflammatory alone.

How many would like to see the two words linked?

[Show of hands.]

DR. DRAKE: For the FDA, I think you see a sense of the committee that just pink doesn't cut it, that you need pink and itchy, or whatever.

Now then, back to Question 2a. That is a suggested labeling. Now, with respect to Question 2a, and I am going to try to help the committee get this simmered down, would the FDA be willing to accept inflammatory versus non-inflammatory? Do you want me to address the issue just as the question says, "minimally versus more than minimal?"

Hearing no answer, what we are going to do is we are going to do it just the way the FDA did it. I want a sense of the committee. First of all, can we distinguish, do you think, and should the labeling distinguish, between minimally inflamed and sufficiently inflamed? Can we make that distinction?

All those who think we can make that distinction, please raise your hand.

[One hand raised.]

DR. DRAKE: All those who think we cannot make that distinction, raise your hand.

[Show of hands.]

DR. DRAKE: John, comment?

DR. DiGIOVANNA: I think we can do it by the way Rob said we can do it.

DR. STERN: But not by that word alone.

DR. DiGIOVANNA: By the presence of symptoms.

DR. DRAKE: I understand that, but we sort of backed into it. I wanted the sense of the committee. Now, I would entertain a suggestion from the committee, having done those two steps. I would entertain, then, a motion so that we can vote on it to provide some information to the committee regarding how we ought to phrase it.

Rob?

DR. STERN: I would suggest that the labeling

should be distinguished between those agents which are just to treat tinea pedis and those agents which might be tested for treating tinea pedis which has associated symptoms since I think it is hard to have much tinea pedis without any inflammation and recognize it except by culture and random sampling.

So I would say it is plain tinea pedis and tinea pedis with associated symptoms as opposed to signs or laboratory tests--associated inflammation, rather than symptoms.

DR. DRAKE: Symptomatic inflamed tinea? Would you accept that?

DR. MILLER: Symptomatology can be very varied also. With some tinea pedis, you can have fissures and it is very painful and perhaps the corticosteroids are not going to play a role there. So there might be some obfuscation with just symptomatology.

DR. STERN: Can we think of anything but pruritus, I guess would be my question, that would be an indication for--probably pruritus is really the only one. I don't think burning or pain, as you rightly suggest, are likely to be corticosteroid-responsive aspects of--

DR. DRAKE: So would you like to change the wording of your motion to read--to use the word "pruritus" instead of symptoms?

DR. STERN: Can you think of other symptoms beyond pruritus that we are really thinking about with this that would be reasons for using a corticosteroid?

DR. ROSENBERG: I don't want to go over and over again. I think the reason for using a corticosteroid is maybe it is just a patch of eczema and not fungus at all. That is the reason for putting the corticosteroid on.

DR. DRAKE: And it might not itch. A patch of eczema might not itch.

DR. ROSENBERG: It doesn't have to itch. If you don't know what it is, that is what you do.

DR. DRAKE: Then let's leave some leeway.

DR. ROSENBERG: If you will put in, "For use on rashes of unknown--dermatitis of unknown cause," then undiagnosed. If you want to have a product for undiagnosed skin disease, it would fill a major societal need.

DR. DRAKE: We will come back to that. I want to stay on my questions.

DR. ROSENBERG: This would be a start.

DR. DRAKE: We will come back to that.

Wilma?

DR. BERGFELD: I would like to revisit the terms. I still think that symptomatic and inflamed might be the best term. I disagree with my colleagues who say that it doesn't help when it is painful. I think that pain is

related to inflammation and swelling and it does help that. And it may even help fissures because they are involved with swelling and inflammation.

DR. DRAKE: Pain and itch are often very hard to separate because those fibers run right next to each other and they have shown the synapses jump. So I think there is a legitimate argument probably not to separate them.

Fred, you had a comment?

DR. MILLER: I guess I do. I was just going to comment on Bill's comment about using this on red, scaly areas undiagnosed. We are certainly going to have to change the entire way we have been taught and we think about diagnosis and using combination therapy.

When we look at these particular products--indeed, I don't know dermatologists that really are using them; it is mainly the non-dermatologists who are using the combinations.

DR. ROSENBERG: I would just interject that the good non-dermatologists are using these. The bad ones are giving them dose packs. Let's put this all in perspective.

DR. DRAKE: Bill, as usual, you are about six years ahead of the rest of us. In the interest of time, I really do want to try to--Rob, can we say symptomatic?

DR. STERN: Yes.

DR. DRAKE: All in favor of that motion, please

raise your hand.

[Show of hands.]

DR. DRAKE: All opposed.

[No response.]

DR. DRAKE: It passes. I have done 2a. Now, I am going to go to 2c, please. That is the one we read a minute ago. "Is it sufficient that the corticosteroid does not reduce the antifungal activity of the combination to label the product for all tinea or should combination products containing corticosteroids be labeled only for the more inflammatory tinea warranting antiinflammatory treatment?"

It seems like we just answered that. But we can vote on it. Any comments on this motion?

DR. BERGFELD: I am going to bring back the issue of "no harm." What harm would be if it was incorporated into the--a combination was used, a noninflammatory? Whether there is a need or not, what harm would there be?

DR. STERN: Wilma, would you be in favor of having class 2 steroids be over the counter? I think if you are not in favor of that, then there is some potential for harm in these agents because, if there is no harm with their potential use, a class 2 steroid as we are discussing here, then that would be grounds for it.

I certainly think there is potential for harm with these agents used when they don't add additional benefit.

That is why I think the labeling should be restrictive to cases where there is, in fact, also some additional potential benefit and, therefore, since it is hard for me to believe, nor have I seen demonstration of additional benefit of corticosteroids with an antifungal in the absence of symptoms related to inflammation, I would say that we would take the more restrictive approach.

DR. BERGFELD: I would agree with you in the fact that it seems logical not to include an extra chemical when you don't need it. The fact is this is still a prescription item and the fact is that the prescribed use is two to four weeks, max six weeks. That is the labeling.

Now, one could approach the "no harm" part of it by the labeling if one desired.

DR. DRAKE: I think, though, that all of us have seen six weeks--I mean, if every doctor in the world stuck strictly to the labeling religiously, it might be a different world. But, in fact, I think we have to really seriously consider whether we want combinations used just willy-nilly, or whether we want to have some restricting labeling on it and try to encourage doctors to use it appropriately instead of using it inappropriately.

I think that is the issue, is that nobody is trying to deny access to this drug. What we are trying to do is help the agency look at the labeling to try to

encourage better behavior and better compliance with the labeling.

So your choice with this motion, or with this question, is whether you want to endorse the first half or the second half. The second half really calls for a little more restrictive where it says you really shouldn't use corticosteroids. The labeling will outline corticosteroids for inflammatory, and not just tinea across the board, which is the first half.

So I am going to ask you to choose between the first and the second half of this question. Everybody in favor of the first half where you would just--all products for all tinea, please raise your hand.

[No response.]

DR. DRAKE: All in favor of having the label--any product containing corticosteroids be labeled only for the more inflammatory tinea warranting antiinflammatory treatment. Please raise your hand.

[Show of hands.]

DR. DRAKE: Once again, it is unanimous.

So now we have answered every question except 1. We are back to my 1. Maybe since we have had all this discussion, we can understand this a little better. I think what we have just decided maybe is what this question is all about, wouldn't you say? I think we have answered this

question because we have given you--by answering 2, we have actually answered 1. Is everybody in agreement? Does anybody on the committee have a different opinion?

Bingo. We are on time. Wilma?

DR. BERGFELD: I'm sorry. I think that one important statement has to be made and that is the fact that, for patient compliance, the need to get the patient the information is probably the most important factor. So patient handouts regarding use need to accompany these kinds of products.

DR. DRAKE: That is a positive suggestion. Another positive suggestion I would like to make is I think this whole notion of the FDA addressing the policy issues--I said it earlier. I can't tell you how important I think it is. I think the things that Bill Rosenberg and others here today have put on the table--just like Eduardo and John and Bob putting this business of improper enrollment or maybe improper exclusion in the inclusion criteria.

I think Joe's question--well, you have asked questions earlier about other things, anyway. I just think all the questions--I told you I would be the first one to do it--I think all the questions that have come about here really are important and may warrant a longer session with more in-depth discussion and contemplation.

I think getting the policy set prospectively is

really to everybody's benefit and I want to congratulate you for it.

Joel?

DR. MINDEL: I would like to throw one other question, whether all these steroid antifungal agents should be limited to a five-day maximum use, because whether it is a fungus or not, it seems like that is the limit. If it is not a fungus, five days is enough. If it is a fungus, then you should switch, at that point, to an antifungal agent alone.

The problem you get with a combination, the worst pharmacologic, or one of the two worst pharmacologic reasons, for giving a combination, the first worst argument--there are three. But one of them is that you continue one of the drugs when you don't need it.

I showed this to Jonathan and he said would I bring it up, but the U.S. Pharmacopoeia, in talking about the clotrimazole and betamethasone topical combinations makes the recommendation in the U.S Pharmacopoeia's publication--it says, "During the first few days of treatment," they are recommending this, "or as along as inflammation persists, after this time U.S.P. medical experts recommend the use of plain clotrimazole or other topical antifungal agents," and their experts also recommend a maximum of five days."

That seems to me a reasonable length of time. It would cut out, I think, actually a lot of the considerations that we have today. If it came in a tube that was just a five-day supply.

DR. DRAKE: A dosing tube of five days. Interesting.

Bob?

DR. JORDAN: I guess this is a paradox that I think all of us are kind of wrestling with, at least I am, as a physician when I see patients like this. Again, the way the studies were designed, with a positive KOH and culture, my likelihood of using one of these agents, if I have got a positive KOH and culture, is pretty small. It is actually the patients that Bill Rosenberg has been talking about where there is a confusion between an eczema versus a tinea where they might have some benefit for the patient.

There may be a need to treat for longer than five days, but maybe Bill could comment on it. Personally, though, if I have got a patient that I have seen and I have got a positive KOH and culture, I doubt that I would ever use an agent like this.

DR. DRAKE: Bill?

DR. ROSENBERG: I think that is right. To move up a notch from something on the skin, I don't know what it is, to--maybe it is nummular dermatitis, round, patchy

dermatitis, that can be confused with fungus frequently and can be hard to treat and which--the older books, the British books, still, the new Rooks textbook still comes out for Viaform corticosteroid combinations--require actually persisting treatment.

So to the degree that we were going to have a product that was good for a fungus and good for nummular eczema, and really no criticism of the person who couldn't tell which it was, then I think the limitation on days starts to fall down.

Rather, I think we should think about a product--there is no harm in using any of these antifungals forever. They really don't do any harm. I think the time limitation has to do with the corticosteroid and that relates to its category, whether it is a very strong one or a weaker one.

A lovely product would be a hydrocortisone combination with some appropriate antimicrobial. The problem with that is if you are trying to make that product go through the hoop of bringing more rapid statistically significant relief of symptoms than the antimicrobial alone in a defined fungus infection, you are not going to get it.

So to get from here to there, we have to--you can't get from here to there the way the rules are now written.

DR. DRAKE: Joe. That is the last comment before

we go on to the next section.

DR. McGUIRE: Okay; this is the last word.

DR. DRAKE: You betcha. From the expert. It is your final answer; right?

DR. McGUIRE: I just wanted to point out that we are shooting at two different products. Bill wants something that is safe, that is going to be used in a shotgun way by lots and lots of practitioners. Our other goal is to somehow limit and make this product safer in the market.

Everyone sitting around the table realizes that the use of these combination drugs is far more related to the practitioner than whether the KOH is positive. Some people use the drugs. Others, like Bob Jordan, rarely use the drug. So we are marching off in two different directions.

DR. DRAKE: We are, and we are going to march right back down the road here to where we need to be. What I want to do is I would like to take this opportunity to welcome two additional experts who have come in late. I suspect planes were late, if I had to guess; Dr. Merve Elgart and Dr. Mary Spraker. I would like you to identify yourselves, which I have just done, but give us your affiliation, please, for the record.

DR. ELGART: I am Dr. Elgart. I am in private

practice. I am Clinical Professor of Dermatology at George Washington University and my plane flew in from Alexandria. I couldn't find a place to park.

DR. DRAKE: Then I have a real question about your watch.

DR. SPRAKER: I am Dr. Mary Spraker. I am a pediatric dermatologist on the faculty of Emory University in Atlanta. I came a day early because I wanted to be here for the Lotrisone discussion because it is of interest to all of us in pediatric dermatology.

DR. DRAKE: Good. Now then, we have three presentations between now and the noon hour. I don't know how much time each of you were given, but I know it wasn't more than fifteen minutes. However, if you can do it in twelve minutes or so, that would be wonderful. If you can't, that's fine. We will run late.

Yes, Jon?

DR. WILKIN: Excuse me, Dr. Drake. We still have Dr. Luke and Dr. LaGrenade to give the Lotrisone--

DR. DRAKE: I can't believe I just did that. Do you want to fire me?

DR. WILKIN: No.

DR. DRAKE: I can be fired, you know.

DR. WILKIN: We're doing fine.

DR. DRAKE: We are not on time and that is why you

were trying to get my attention a minute ago. Now we are in big trouble, you guys, time-wise. That's okay. It's worth it. Dr. Luke, would you please give us your presentation in the manner in which you see fit.

NDA 20-010 Lotrisone Lotion

DR. LUKE: Hi. Good morning. I would like to discuss NDA 20-010, Lotrisone, betamethasone and clotrimazole, Lotion.

[Slide.]

Part of the evidence for effect of Lotrisone Lotion, NDA 20-010, is based on the effectiveness of the combination of the two active components in Lotrisone Cream, a different NDA, NDA 18-827, submitted on December 23, 1982 and approved in 1984.

Lotrisone Lotion has the same active ingredients in the same concentrations and the same indication and dosing regimen as Lotrisone Cream.

[Slide.]

The development program for Lotrisone Lotion, NDA 20-010, formulation, the same concentration, again, is as follows: one parallel group comparison of active lotion and vehicle in tinea pedis. The tinea pedis is considered to be the higher efficacy hurdle, as Dr. Wilkin had stated earlier.

A parallel group comparison of active lotion and

vehicle in tinea cruris. Tinea cruris is the most sensitive for adverse drug reactions, as was previously stated. Together, the two trials would allow interpolation for tinea corporis, a separate indication.

In addition, a vasoconstrictor assay to compare cream and lotion and confirm availability of corticosteroid was performed.

[Slide.]

NDA 20-101 for Lotrisone Lotion was originally submitted to FDA on August 31, 1989. I would like to have you keep in mind that the studies were done over a decade ago.

[Slide.]

Study No. 1 was conducted with Lotrisone Lotion versus vehicle. This is a two-armed study for Lotrisone Lotion. 119 patients were included for safety. 93 of those patients were included for efficacy. The age group of the patients was ages 12 to 80. Lotrisone Lotion was found more effective than vehicle in treatment of tinea pedis.

[Slide.]

Study No. 2 was a study on Lotrisone Lotion versus vehicle in tinea cruris. This, again, was a two-armed study for Lotrisone Lotion. 126 patients were included for safety, 120 patients included for efficacy. The age group was 16 to 88. Lotrisone Lotion was found more effective

than vehicle in the treatment of tinea cruris.

[Slide.]

Again, from Study 2, 7 of the 63 subjects using Lotrisone Lotion failed to complete the study all due to lack of efficacy. 15 of 63 of the vehicle patients failed to complete the study, again, all due to lack of efficacy. Two patients in the Lotrisone group and one patient in the vehicle group experienced dry skin during the study and that was the major local side effect of the drug.

[Slide.]

A vasoconstrictor assay was submitted. The date was 1990. The Lotrisone Lotion, the to-be-marketed product, from this data, appears to have comparable or lower blanching scores compared to Lotrisone Cream. No confidence intervals were provided and no bracketing was done in this study with the lower strength topical corticosteroid; hence, the submission of additional vasoconstrictor assay data by the sponsor.

[Slide.]

Two additional studies were performed and a different manner of presentation of the study was given using a categorization of the subjects upon where they would fall, whether they would favor Lotrisone Cream, whether no difference was detected or whether they would favor Lotrisone Lotion. The nonsignificant McNemar's test exact

p-values were shown.

[Slide.]

To summarize, the combination antifungal/corticosteroid was shown to be superior to vehicle for antifungal effect. Vasoconstrictor assays showed that Lotrisone Lotion was comparable to Lotrisone Cream for corticosteroid effect. The safety profile was adequate to allow labeling for the population study.

A side note; this was the last NDA for which vasoconstrictor assays were used to determine inflammatory effect.

[Slide.]

Based on information submitted, the agency determined that Lotrisone Lotion was approvable. An approvable letter was sent to the Schering Corporation on July 31, 1991. The issues for response were CFC issues and a labeling update.

[Slide.]

On October 7, 1999, Schering Corporation submitted a response to the approval letter of July 31, 1991. This and subsequent submissions responded adequately to the issues brought forth in the 1991 letter.

[Slide.]

During the interim between 1991 and 1999, additional information regarding the Lotrisone drug product

emerged.

[Slide.]

The first of these, I would like to propose, is the Rosen and Elewski paper from 1995 in JAAD which proposed the failure of clotrimazole betamethasone diproprionate cream in treatment of Microsporum canis infections.

[Slide.]

In 1996, there was a paper by Dr. Elgart which appeared in Dermatologic Clinics describing the use of topical corticosteroids in the treatment of unrecognized dermatophyte infection, tinea incognito, which may lead to non-cure. Additionally, he discussed the use of combination antifungal corticosteroid drugs.

[Slide.]

In 1999, Fleischer and Feldman described a prescription of high-potency corticosteroid agents and clotrimazole betamethasone diproprionate by pediatricians.

At this point, I would like to introduce Dr. Lois LeGrenade from the Office of Postmarketing Drug Risk Assessment, or OPDRA for short. She will describe a review of Lotrisone adverse events as has been reported.

Review of Lotrisone Adverse Events: 1984-1999

DR. LeGRENADE: Good morning.

[Slide.]

I am going to summarize for you the results of a

review of Lotrisone adverse events reported to the agency from the time of approval to 1999.

[Slide.]

First a little background. Lotrisone Cream was approved in July of 1984. It is a combination product consisting of clotrimazole, which is a synthetic antifungal agent and betamethasone diproprionate which is a high-potency topical steroid.

It is labeled for twice-daily use for two weeks duration for tinea cruris and tinea corporis and twice daily use for four weeks duration for tinea pedis.

[Slide.]

The original 1984 label indicated that it was not to be used in children under the age of 12. The Precaution Section of the label, Pediatric Use, contained the statement that "Safety and efficacy have not been established in children under 12."

In 1991, the label was strengthened with the addition of the words in the same section, "The use of Lotrisone in diaper dermatitis is not recommended."

[Slide.]

The objective of our review was to compile a list of all the adverse events reported to the agency from the time of marketing to 1999. Specifically, we were asked to focus on the following questions; were the adverse events

reported associated with the duration of treatment longer than indicated by the label and were adverse events reported in the under-12 age group.

[Slide.]

In order to compile this review, we searched the agency's Adverse Event Reporting System, AERS for short, for all adverse events reported to Lotrisone Cream in the time period under review. We also used commercially available databases IMS Health and we used two of their databases which are available to the agency, NPA, National Prescription Audit. We used this to estimate the total numbers of prescriptions for Lotrisone over the period, and NDTI, National Disease and Therapeutic Index, to get the demographics of the patients for whom these prescriptions were written and the indications for use.

[Slide.]

Just the next few slides, I will tell you a little bit about the databases that we used. AERS is a computerized passive surveillance system into which all our adverse events reported to any drugs in the agency are entered. It is a spontaneous system and that means that the agency does not go out and solicit, actively solicit, adverse-event reports, but we rely on health-care practitioners, physicians, nurses, pharmacists and consumers, themselves, to report adverse events to us in the

agency either directly or though the company responsible for the drug. It contains all adverse events reported from 1969 until the present time.

[Slide.]

The strengths of AERS is that it is a cost-effective method of detecting rare adverse events. Its limitations are that it is not comprehensive. There is substantial underreporting and it varies depending on the type of adverse event, the seriousness of the adverse event, and whether it is a labeled or unlabeled adverse event.

[Slide.]

It also has limitations in the fact that individual case reports are not always complete. For example, we may lack information in the age of the case or on the gender of the case and other information may be missing from each report.

[Slide.]

The IMS data that we have available or that we used for this review, National Disease and Therapeutic Index, or NDTI. It is an ongoing survey of treatment practices and diseases at patient visits to office-based medical practices in the Continental United States. From that we got the demographics of the cases and indications for use.

The National Prescription Audit, or NPA, provides

estimates of the total numbers of prescriptions written for drugs in the United States. Its basis is an audit of retail pharmacies including chain, independent, food stores and mail-order pharmacies.

[Slide.]

Now to the results. The total number of adverse events reported to the agency in association with Lotrisone Cream use was 786. The total number of cases was 330. The reason why the number of events exceeds the number of cases is because it is possible, and, indeed, it often happens, that a case may have more than one adverse event reported.

For those cases for whom we had information on gender, there were 151 females and 126 males. This slide shows the number of Lotrisone adverse events reported by year. You can see that there is a gradual rise from the time of marketing until the present time, then a decline until the present time, with a peak in 1991 and again in 1994.

[Slide.]

This slide shows the top ten adverse events reported with Lotrisone. The first three are more or less common to nearly all topical drugs reported to the agency. What I want you to focus on are that skin atrophy and skin striae are both in the top ten, and these are permanent conditions once they develop.

[Slide.]

This slide shows the distribution of cases by age, gender and duration of treatment. But first I want to explain how we defined our age categories. For example, in the first category, 0 to 1, 1 includes all cases who have not reached their second birthday and is similarly applied down the categories.

We see that, in the first three categories, in the 0 to 1 age group, there were twelve cases of adverse events: 2 to 6, 13; 7 to 12, 19; and, in all, in the 0 to 12 age group, there were 25 percent of all adverse events reported to the agency for Lotrisone Cream.

Additionally, we see on the far-right column that 58 percent of patients in the 0 to 1 age group were treated for longer than two weeks, 38 percent in the 2 to 6, and 32 percent in the 7 to 12 age group.

[Slide.]

Looking at the pediatric adverse events by age group, in the 0 to 1 age group, there were nine patients treated for diaper dermatitis, nine of the twelve, making 75 percent. 16.5 weeks was the mean duration of therapy. The median was six weeks and the range was 1 to 80 weeks. Seven of the nine cases of diaper dermatitis had a duration of therapy in excess of 2 weeks.

[Slide.]

Also in the 0 to 1 age group, we had one case of growth retardation. A male infant, aged 1 year and 4 months. The indication for the prescription was diaper dermatitis and he was treated for 27 weeks.

[Slide.]

There were three cases of skin atrophy in the 0 to 1 age group as well. Two of them were female. All had, as the indication for prescription, diaper dermatitis and all were treated for longer than 2 weeks and one extreme case, 80 weeks.

[Slide.]

There was also one case of benign intracranial hypertension in this age group, a five-month-old infant, for whom other information was not forthcoming.

[Slide.]

In the 2 to 12 age group, there were 32 cases with an equal gender distribution. 61 percent of these patients were treated for longer than two weeks with a mean of 26 weeks, a median of 6 weeks and a range from 1 day to 156 weeks.

[Slide.]

The indications for treatment in this age group, the top three were tinea facei, tinea corporis and diaper dermatitis.

[Slide.]

In the 2 to 12 age group, the most frequent adverse events were similar to that for the overall group. We also see that there were three cases of atrophy of the skin, two in patients who had tinea facei and, in both of these patients, the duration of treatment was longer than two weeks being 4 and 13 weeks respectively.

[Slide.]

We also had clinically serious adverse events in adults. We had three patients with Cushing's syndrome. We only had clinical information on one patient who was a 38-year-old female who was prescribed Lotrisone for a yeast infection and whose duration of therapy was 5 years.

[Slide.]

Now we turn to the usage patterns which we got from IMS Health Data. I must say, at this point, that we are using this at this presentation with permission from IMS Health.

[Slide.]

The computerized NPA records only go back as far as 1993. We can see that between the years 1993 and 1999, the estimated total number of prescriptions for Lotrisone Cream rose from 4.3 million gradually to 5.1 million in 1999.

DR. DRAKE: May I interrupt you for just one moment. What is IMS Health?

DR. LeGRENADE: IMS Health is a data vendor. It used to stand for something but it no longer--the name is now IMS Health.

DR. DRAKE: Okay; so it is just a data bank.

DR. LeGRENADE: Yes; it is just a data vendor.

DR. DRAKE: Thank you.

[Slide.]

DR. LeGRENADE: This slide shows the total Lotrisone prescriptions by age. This we got from the NPA data. We can see that 6.5 percent of all prescriptions written in the time period were for patients in the 0 to 1 age group, 6.8 in the 2 to 6 and 6.4 in the 7 to 12 age group--

[Slide.]

--making for a total of nearly 20 percent of all prescriptions written in the time period in the United States being written for children under the age of 12.

[Slide.]

This slide and the next few will show the top five diagnoses for which prescriptions of Lotrisone Cream were written. For the non-physicians present, ICD-9 stands for the ninth revision of the International Classification of Diseases which is a numerical coding system which facilitates the tracking of morbidity and morality data over time and worldwide.

We cans see from this data that prescriptions were written in the 0 to 1 age group for candidiasis and diaper dermatitis in the top five in the 0 to 1 age group.

[Slide.]

In the 2 to 6 age group, the top five prescriptions also included diaper dermatitis.

[Slide.]

In the 7 to 12 age group, these are the top five conditions. They include non-fungal infections of alopecia and pityriasis rosea.

[Slide.]

So we concluded from this review that Lotrisone Cream is widely used off-label. It is used in children younger than 12 years old. It is used for diaper dermatitis. And it used for longer than two weeks. Serious adverse events have been reported in association with this off-label use and I must point out here that the actual numbers of events are likely to be much higher because of the substantial underreporting that I mentioned earlier.

Thank you.

DR. DRAKE: Very nice.

Markham, do you have more?

Recap

DR. LUKE: That would start on Slide 17.

[Slide.]

I would like to recall what the agency has discussed. Our indication for Lotrisone Lotion needs clarification. We would like the committee to discuss what would be an appropriate indication for this NDA. We have put on the table inflamed tinea versus all tinea.

Additionally, we would like to address the issue of Microsporum canis indication which the sponsor has proposed and I understand will be discussed. Additionally, we would like to discuss means for addressing off-label use of the Lotrisone Lotion and, perhaps, the Lotrisone Cream product as Dr. LeGrenade has discussed.

Specifically, we would like to discuss pediatric use, diaper dermatitis and duration of use.

[Slide.]

I would like to show you what the applicant has proposed as a Pediatric Use Section for Lotrisone Lotion, NDA 20-010. Pediatric use: Lotrisone Lotion is not recommended for use in children under 12 years of age as the safety and effectiveness have not been established in well-controlled clinical studies in pediatric patients under 12 years; it is not to be used for diaper dermatitis. It is not to be used under the age of 12 and not to be used in diaper dermatitis.

I understand we have guest speakers.

DR. DRAKE: Let me make sure I have my agenda

correct. We will go through the whole presentation and we will do the questions last. Is that satisfactory? Fine.

I think we have time to at least start on our invited presentations. We are actually fine on time. We are okay because there is some time this afternoon which is not committed that we can commit. But I do believe we have time to at least do one of the presentations before lunch.

Dr. Rosen, about how long is your presentation?

DR. ROSEN: It is an hour but, for you, I will do it in fifteen minute.

DR. DRAKE: You are a wonderful human being. How would you like to go right now

DR. ROSEN: Let's do it.

Presentations - Invited Experts

Perspectives on Topical Antifungal Therapy

DR. ROSEN: Good morning.

[Slide.]

Dr. Wilkin asked me to give an academician-clinician view of the perspective of combination antifungal agents. I want to make a few key points. I have to lay some predicates for that. I will try and do this very quickly. I have already told you where I am from.

[Slide.]

Of course, we are talking about superficial infections. We are not talking about anything other than

that. And we are primarily talking about dermatophytosis because that is what the indication is. While I agree with Dr. Rosenberg's comments that there may be some ambivalent, ambiguous cases and we might need a nice, safe drug for those cases, in fact, what we are talking about is a drug that is approved and indicated for dermatophytosis.

[Slide.]

I do want to point out that there are different dermatophytes. There are those that primarily affect humans, anthropophilic, those that primarily affect animals, zoophilic, and some that primarily are found in plants and soil, the geophilic. They are not all equivalent. Just like spokes in a bicycle, they are not the same.

[Slide.]

I also want to point out that we are talking about different tineas. When we were talking about the studies where tinea pedis is sort of the gold standard, and I thank Dr. Bergfeld for disagreeing with me and pointing out that the risk may be low on the feet, in point of fact, we are also talking about an agent that is approved for tinea elsewhere. That includes in the groin and on the body.

I would like to further point out that some of these are quite chronic, in fact. Tinea cruris may be recurrent over many years or even an entire lifetime and that chronicity and that recurrence leads to the inescapable

possibility of repetitive clinical use despite the labeling being for short-term use as in two weeks.

If the patient has a tube and they have recurrence of tinea cruris, crotch rot for those who are not dermatologist or physicians, they will see fit, I am certain, to use the drug over and over again. So we are talking about apples and oranges. Tinea pedis is not the same thing, athlete's foot, as fungal infections elsewhere.

[Slide.]

And then we have talked a little bit about finding fungi. And for everything that is fungal, there is something that looks an awful lot like it that isn't fungus. I am of the opinion that people should try and find fungus and that there are ways to find fungus.

[Slide.]

I am also of the opinion that most clinicians who are adequately trained can find fungus, whether it is by KOH or culture or other methodology. There are some cases, and this has already been discussed by the panel, and probably deserves additional discussion and maybe an entire other session, where one, despite repeated efforts and diligent and proper efforts, cannot find fungus.

By the same token, the fact that a drug may be used, not approved but used, in a "shotgun" fashion then sends a message that, perhaps, these endeavors are not

worthwhile at all to which I disagree. I think the proposition should be that individuals, regardless of their specialty and that includes primary care, should be trained to adequately use the appropriate one of these techniques to find fungi and to know what they are treating.

[Slide.]

Granted, there are some that we can't find but I think an effort should be made in every case and that using a "shotgun" method of therapy really discourages appropriate investigation.

Now, granted, if something is fungal and that is what we are talking about, a drug that is approved for fungal infection, one has to make a choice of therapy. There are various factors that enter into that including the site of infection, the likely pathogen which we will get back to, what are the risks, the age and health of the patient.

[Slide.]

There are two basic possibilities in algorithmic approach, either a topical or a systemic drug.

[Slide.]

For some conditions, a systemic drug really is the drug of choice for most nail infections, for tinea capitis, for, of course, the deep or systemic fungal infections that involve the viscera and, possibly, for extremely extensive

superficial fungal infections. What is extensive enough to warrant systemic therapy versus topical therapy I think could be defined by the physician. And then, for most localized infections, topical therapy is certainly an adequate form of treatment.

[Slide.]

It would be nice to avoid the potential for side effects, which I think are greater with oral medications, if topical medication is used. And so you avoid the potential for drug-drug interactions and serious adverse reactions such as hepatotoxicity, hematologic toxicity, taste disturbance, skin rashes and so forth with systemic agents.

[Slide.]

I think it is important that we understand that antifungal agents--just as diseases are not the same, antifungal agents are not the same--and that clotrimazole is not the same thing as econazole which is not the same thing as naftafine or butenafine or cyclic peroxolamine.

They are different based on pharmacokinetics and pharmacodynamics. Basically, what happens when you rub that cream on, where does it go, how long does it bind, how is it ultimately metabolized and excreted and what does it best work for, what is the spectrum of antifungal activity. These do impact upon even topical agents.

[Slide.]

I have listed all of these different aspects of topical antifungal mechanisms. Each one of them has some bearing on the use and the efficacy of the drug. I am going to go through them very quickly, but I am going to come back to them at the very end.

For example, the various agents that we now have available, and I do think we need to keep in mind that 1984, when the drug Lotrisone was first approved, is not 2000. We now have a large number of classes of drugs. In 1984, all we had were the azole, the imidazole agents. We now have allylamine, benzylamine, hydroxyperidone and there are several other entirely new classes of antifungal drugs that are being worked on.

They all have a different mechanism of action. While the end result resolution of the fungal disease is the same, the different mechanisms of action impact upon other properties of these drugs and impact on which organisms the various classifications of drugs work best upon.

Also, the impact on a laboratory granted property of the drugs whether they are fungistatic or fungicidal and without going into great length as to how that is determined, it is a laboratory technique.

[Slide.]

Ultimately, the difference between fungistatic and fungicidal may not alter the ultimate results but, in fact,

fungicidal activity, those that have been demonstrated in vitro in a test tube to be fungicidal are generally associated with more rapid resolution.

[Slide.]

Some drugs, antifungal drugs, bind to keratin, the outermost dead portion of the skin, more than others do, and is that important? Again, keratin biding, like fungistatic or fungicidal, does not materially alter the ultimate result that can be obtained but it is associated with reduced frequency of application in a shorter duration of therapy.

As you notice, Lotrisone is approved for four weeks for tinea pedis where some of the newer agents can be used for as short a duration as one week based, in part, because they bind to the site and can be used for shorter periods of time. Ultimately, the resolution may be the same but there is a difference.

[Slide.]

In vitro assays are very difficult to compare because there are varying techniques, varying methodologies, various parameters that are set up but basically, within any given technique, all the publications pretty much agree that for the dermatophytes, the subject of this discussion, butenafine, terbinafine and naftifine generally have lower minimal inhibitory concentrations than the azoles.

Does that mean that the azoles won't work? Of

course, it does not. But what it does mean is that, in some situations, this may be a disadvantage. Again, we will get back to that.

[Slide.]

To show you some quantitative data derived from a variety of publications, and there is a degree of variation, again based upon the technique that was used to determine in vitro minimal inhibitory concentrations which do not always correlate with clinical use, but you can clearly see that the minimal inhibitory concentration for virtually all the imidazoles are higher than some of the newer agents when it comes to dermatophytes.

[Slide.]

The opposite is true when it comes to Candida albicans.

[Slide.]

Again, a lower MIC does not improve the achievable ultimate results but those agents for which a given organism is used that have a lower minimal inhibitory concentration generally will have more rapid symptomatic relief and shorter overall courses of therapy. These are based on comparison studies, head-to-head comparison studies where the azoles have been compared to some of the more new agents.

Also, the lower MIC does become important not so

much for the anthropophilic fungi like Trichophyton rubrum or even many cases of Trichophyton mentagrophytes, but it does become important for those organisms where the MIC is at the absolute upper end of those MICs that have been measured, mostly zoophilic and geophilic fungi, particularly zoophilic, those that are acquired from animals.

[Slide.]

So this brings me, with that predicate, to steroid antifungal combination. I think the rationales for use would be to treat both fungal infection and some form of eczema or red scaling spots, as some of you have called this, when the diagnosis is uncertain.

The steroid component, in theory, should aid in symptomatic resolution even if the disease is known to be fungal in nature. These would be the two rationales for use of a steroid antifungal combination understanding that the first rationale listed is not the one for which the drug under discussion is indicated nor approved.

There is no indication nor approval for use of a combination agent for red scaly spots whose etiology is unknown. I think that is a very good issue that has been brought up and really warrants an entirely separate discussion and, perhaps, a charge to the sponsor if they should choose to seek that sort of indication.

But, really, what we are talking about is the

second one where the steroid should aid in the symptomatic resolution when a disorder is known to be fungal.

[Slide.]

I have already said my prejudice, and I admit it, that using this, in fact, to me discourages very careful medical care because it says, "Use a combination. It doesn't matter what it is; it should take care of it." I am of the opinion that our primary-care physicians as well as dermatologists should be capable of looking for fungi and knowing what they are treating.

There are potential side effects. Those have already been mentioned. I will show, I think, one more slide along those lines. But the other important point I want to make, based upon MICs, based upon fungistatic versus fungicidal activity based upon keratin binding and mechanism of action, all of those properties, at least the steroid antifungal combination agent under discussion today, which may or may not apply to other agents with different antifungals because they are not all the same, may not work in those infections acquired from animals.

[Slide.]

We have already been told about some of the potential for steroid-related adverse events. Again, I agree that the likelihood on the foot is small, but do bear in mind the chronicity of use for recurrences if patients

have fungal infection involving the groin which may actually originate from the foot and even from the nails. The patient who has an agent that has worked once will use it again without their physician's supervision.

That is a proviso. It is a given. It is common sense and it happens. So one has to be concerned about things like atrophy and striae in the groin. That is in adults and perhaps even more so in children.

I agree, again, a very elegant discussion about adverse events seriously underestimate the number of adverse events because this is a voluntary reporting system and not everybody is going to report every adverse event.

[Slide.]

I also would like to point this out, that in the Year 2000, it is not the same as 1984, that some of the current antifungal agents have inherent antiinflammatory properties.

[Slide.]

Without, again going into detail, and for time, suffice it to say that we have investigated this in an in vivo system in human beings--

[Slide.]

--based upon the similarity of inflammatory mediators induced by ultraviolet exposure and fungal infection.

[Slide.]

This is just an example. You can see some red dots and some minor red dots and no red dots.

[Slide.]

It is one of the patients in our studies which showed that, of the antifungal agents as they are currently available for prescription--i.e., out of the tube, the entire preparation--that, based upon measuring reduction in erythema and inflammation, some of the newer agents are actually quite inflammatory in this in vivo system in human beings.

There have also been in vitro investigations and in vivo investigations in animals that support this data in human beings. They are all very parallel. My point in showing this is that if one of the predicates for using a steroid antifungal combination is that the steroid component is important for reducing the inflammatory portion of a fungal infection, that, in point of fact, some of the currently available antifungals are quite good at reducing at inflammation by themselves.

You have a protocol which you agreed to, at least in theory, that may allow a sponsor to claim that inflammatory property, but it has already been shown in an informal, small study on human beings.

[Slide.]

There are the references for that particular work.

[Slide.]

Here is the bottom line and towards the end of my discussion. Because the current steroid antifungal product under discussion utilizes an antifungal agent that has a high MIC for some organisms, particularly the zoophilic ones, has a low keratin binding, is fungistatic rather than fungicidal, there is a theoretical risk. That is why there may be some failures or some worsening of infection.

You have been shown data to the effect that that can happen on occasion. The reality is that most of the time, this is not a clinical issue but it is an issue when certain organisms are involved.

[Slide.]

That relates to some of the patients that we reported in the paper that you have been given in advance. An individual who was diligently applying a steroid antifungal combination to tinea of her hand acquired from her new kitten. By the way, I am not anti-kitten. I have two cats, so I like them. But this is what she was applying diligently, twice daily and her disorder getting worse instead of better.

[Slide.]

In one week of applying a different antifungal agent which is keratin-binding, inflammatory and a lower MIC

for Microsporum canis, which is what she cultured, she was clear.

[Slide.]

Another patient who was diligently applying the steroid antifungal combination in consideration today who acquired Microsporum canis infection from a kitten that his wife had purchased who slept in the bed with them mostly on him. He cleared when this combination agent was stopped.

There are several other cases in the paper that you have.

[Slide.]

The question might be put, well, why should this happen at all, because if you do in vitro testing, while there is a high MIC for Microsporum canis with clotrimazole, in point of fact, it is still within achievable ranges. My suggestion is that it may be either. It is at the upper limits and, therefore, this is a marginally effective antifungal for this kind of organism, or the steroid component suppresses several of the five or six innate defense mechanisms that we use against fungal infection and that may impair the person's own contribution to clearing the infection or some as yet undetermined combination of both of those events leading to failure with Microsporum canis infections, which I have reported and have seen more than just the cases reported.

But it is of some concern to me and I think it is based on the pharmacokinetics and pharmacodynamics of the antifungal agent in this combination plus the steroid.

[Slide.]

We also know that steroid alone--you have mentioned using a steroid-alone arm and chosen or recommended that that should be used. Just keep in mind that if you have a patient who has a known fungal infection for which they are applying steroid alone, that that may be responsible for exacerbation of their disease.

[Slide.]

While that may not be a serious problem on the foot, it may, certainly, be in the face, in the groin or in the trunk--

[Slide.]

--as this patient who was diligently applying a steroid given her for the diagnosis of eczema and her fungal infection was ever increasing.

So we know that steroids, by themselves, while they may relieve some symptoms, ultimately may exacerbate the disorder. You will hear more about that from one of the other speakers.

We know that if you combine a high-potency steroid with what I would consider to be a lower-potency antifungal agent under certain conditions, like with zoophilic fungi,

there are some potential problems.

[Slide.]

Of course, everybody is concerned about cost. The highest cost of a drug is one that either doesn't work for what it is given for or given for the wrong diagnosis. I am particularly concerned about failure to achieve the goal of therapy with a steroid antifungal combination when the fungal infection is with an organism where there may be problems with that agent.

[Slide.]

So, in conclusion, I think that there are potential for adverse events. There is clearly use beyond the label, both for age and indication. Whether that is justifiable for indication is an entirely different discussion.

There are cases which have exacerbated. There are cases which have failed to achieve the goal for which the drug was given which have been summarized for you from the agency and for which I have shown you several examples and published additional ones.

I think that information should be considered when you take up the issue of labeling for this extension of the product line.

I apologize for the fact that my presentation is not before you. I tried six different ways to send it.

Maybe that is another federal hearing. It kept bouncing back from the FDA, "user unknown." I tried to send it to Mr. Henriquez.

But thank you very much for your kind attention. I hope those remarks will be helpful.

DR. DRAKE: Ted, those were very helpful.

It is past the lunch hour, significant so. So I think we will recess. We will reconvene promptly at 1 o'clock. See you then.

[Whereupon, at 12:15 p.m., the proceedings were recessed to be resumed at 1 o'clock p.m.]

AFTERNOON PROCEEDINGS

[1:05 p.m.]

DR. DRAKE: I am going to reconvene our meeting. The same rules as outlined earlier are in place.

I want to do one thing before we have our next two presentations. Posted in the agenda at 1 o'clock was the Open Public Hearing section of this meeting.

Open Public Hearing

DR. DRAKE: We had no requests in advance for time at the mike. But I do want to make that opportunity available if anyone has a comment that they would like to make at the mike from the audience.

Seeing none, then I think we shall proceed, then, with our presentations. We have two; Dr. Elgart and Dr. Feldman. Dr. Elgart, would you please proceed?

Presentations - Invited Experts (Continued)

Tinea Incognito and Strong Topical Steroids

DR. ELGART: Hi. I am Dr. Elgart.

[Slide.]

I am going to review a little bit a paper which, I think, has now been placed in front of most of you that I wrote on tinea incognito. At the time I wrote it, I was at George Washington University. I am now in private practice.

[Slide.]

The paper talks a lot about Majocchi's granuloma.

Majocchi's granuloma is really an infection by a dermatophyte; in other words, a fungus that is a superficial type of fungus which loses its way and gets down deeper into the skin. Most of the dermatophyte infections are within the keratin portion of the epidermis, but, in these instances, the fungi get down, usually down a hair follicle, then rupture the hair follicle and produce an inflammatory response down in the deeper epidermis and, indeed, in the dermis.

It usually produces a granulomatous response. By this definition, I guess you would have to include not only the dermatophyte infections but, also, Pityrosporum folliculitis you might consider a form of this disease.

[Slide.]

Dominico Majocchi was the first great Italian dermatologist. In 1883, he described a strange kind of fungus infection in the groin. This was in the groin of fairly large Italian men built something like me who had a large panniculus and the panniculus folded over the groin, to some extent.

So, when they would get a dermatophyte in that area, there was no time at which that dermatophyte was exposed to the air because they were sitting and it was always macerated. Because of this, the fungus was able to grow down into the follicles and produce a more inflammatory

disease.

This was a curiosity until 1954. J. Walter Wilson, who wrote a wonderful textbook of mycology, gave a paper when he was initiated into the ADA on Majocchi's granuloma. It turned out that the Majocchi's granuloma that he was seeing was in young women who were shaving their legs. They would start with the razor at their ankles and work their way up.

Those who had fungus infections on their feet would pick up bits of fungus on the razor and then plant them along the way, producing a fungal folliculitis because of the trauma produced by the razor.

[Slide.]

Here are some photographs of that type of disease. You can see small papular lesions--

[Slide.]

--and, in one instance here, pustular lesions from what had been a fungus infection that was on the surface and showed only the scaly lesions and now is developing more pustular problems.

[Slide.]

Here is a biopsy of one of those to show a follicle in the center with this epidermis and dermis there--a follicle in the center and then inflammatory reaction around it.

[Slide.]

When you get down a little deeper, you can find inflammatory responses, not a granuloma but there is a fungal element in the center and there are polys around the edge.

[Slide.]

The fungus, in this instance, was Trichophyton rubrum. There are a fluffy top--

[Slide.]

--and the red backing and the birds-on-a-wire microconidia that one sees in Trichophyton rubrum. But you can get this from any of the dermatophyte infections given the right sequence of events.

[Slide.]

Okay; we know that in Italy, in the late 19th Century, this could be caused by occlusion and in America, in the mid 20th Century, this could be caused by trauma and shaving. What causes Majocchi's granuloma in the Year 2000?

There are two things, immunocompromised patients, particularly, and in immunocompromised patients, they can have AIDs, they can have transplants, they can be immunocompromised because of medications, cancer chemotherapy, oral steroids, azathioprine. These are all patients who, before, say, 1980 probably would have died because we didn't have the ability to keep them alive.

But now we have people whose immune response to this organism is not the same and, therefore, the organism is able to penetrate down deeper and cause some problems.

But the other cause that I see of Majocchi's granuloma is topical steroids. Class 1 and Class 2 topical steroids place on dermatophyte infections can induce the penetration of the fungus down into the follicle to produce this disease.

[Slide.]

Here is just such a case. There was an annular lesion. You can just see the outlines of the pigmentation. The Lotrisone was used. The lesion disappeared and then it keeps coming back in this one place. They keep putting the Lotrisone on. The surface disappears. In other words, the scaling on the surface, or, really, the dermatophyte on the surface disappears, but there is still dermatophyte down deep where the clotrimazole, the Lotrisone, can't penetrate and so it keeps coming back because it can't be reached.

[Slide.]

Majocchi's granuloma, you also have to Pityrosporum folliculitis, is probably part of this same picture. Pityrosporum has gotten more complicated because there has been work to separate the Pityrosporum that we used to think of as two organisms into, now, seven organisms. It is uncertain whether one species is

responsible for more of this than the others.

[Slide.]

But Pityrosporum folliculitis is certainly seen, particular in AIDs patients, and it shows up as usually noninflammatory follicular prominence lesions that look like this.

[Slide.]

Microscopically, one can see the Pityrosporum yeast--these are yeast and not filamentous fungi--you can see the Gram-positive budding yeast within the follicle. Sometimes they rupture and sometimes they can cause inflammation.

[Slide.]

Ofuji's syndrome is called eosinophilic folliculitis and it is another kind of folliculitis associated with immune-compromised patients. In most instances, the etiology of Ofuji's syndrome is unknown, but occasionally in Ofuji's syndrome, a fungus has occasionally been demonstrated.

[Slide.]

Indeed, some--this is a Gomori methenamine silver stain showing fungal elements in one of those patients. Of course, these patients do respond to systemic antifungals.

[Slide.]

Getting back to the Majocchi's granuloma that I am