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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

IN JOINT SESSION WITH THE DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

Thursday, May 6, 2004

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Advisors and Consultants Staff Conference Room
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

Louis R. Cantilena, Jr., M.D., Ph.D., Chair
LCDR Dornette Spell-LeSane, MHA, NP-C, Executive Secretary

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE MEMBERS

Roselyn E. Epps, M.D.
Robert Katz, M.D.
Paula Knudson (Consumer Rep)
Peter A. Kresel, M.B.A. (Industry Rep)
Sharon S. Raimer, M.D.
Eileen W. Ringel, M.D.
Jimmy D. Schmidt, M.D.
Thomas R. Ten Have, Ph.D.
Elizabeth S. Whitmore, M.D.
Michael G. Wilkerson, M.D.

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEMBERS

Michael C. Alfano, D.M.D., Ph.D.
(Industry Rep)
Neal L. Benowitz, M.D.
Leslie Clapp, M.D.
Frank F. Davidoff, M.D.
Jack E. Fincham, Ph.D.
Y.W. Francis Lam, Pharm.D.
Sonia Patten, Ph.D. (Consumer Rep)
Alastair Wood, M.D.

CONSULTANTS (VOTING)

Alan Bisno, M.D.
Mahmoud Ghannoum, M.Sc., Ph.D.

FDA

Jonca Bull, M.D.
Charles Ganley, M.D.
Jonathan Wilkin, M.D.

C O N T E N T S

PAGE

Call to Order and Introductions:
Louis R. Cantilena, Jr., M.D., Ph.D. 5
Conflict of Interest Statement:
LCDR Dornette Spell-LeSane, MHA, NP-C 8

Welcome and Introductory Remarks:
Charles Ganley, M.D. 11

Efficacy and Labeling Issues
for the Over-the-Counter Drug Products
Used in Treatment of tinea pedis
in Patients 12 years of Age and Over

FDA Presentation

Natural History of tinea pedis and Dermatophyte Infections:
Joseph Porres, M.D., Ph.D. 12

Study Design and Efficacy Results for tinea pedis Clinical Trials (Rx and OTC):
Kathleen Fritsch, Ph.D. 44

History and Overview of OTC Topical Antifungal Drug Products Monograph:
Houda Mahayni, Ph.D. 67

Topical Antifungal Drug Product Labeling:
Daiva Shetty, M.D. 94

Infectious Disease Complications of tinea pedis:
Alan Bisno, M.D. 127

Microbiology and Dermatophyte Resistance Related to the Treatment of tinea pedis:
Mahmoud Ghannoum, M.Sc., Ph.D. 154

Committee Discussion 178

C O N T E N T S (Continued)

Open Public Hearing

Consumer Healthcare Products Association:
Doug Bierer, Ph.D. 193
Boni E. Elewski, M.D. 194
Doug Bierer, Ph.D. 214

Schering-Plough:
John Clayton, M.D. 220

Novartis:
Helmut H. Albrecht, M.D., M.S., FFPM 231

Committee Discussion 299

P R O C E E D I N G S

Call to Order and Introductions

DR. CANTILENA: Good morning. I am Louis Cantilena. I am Director of the Division of Clinical Pharmacology and Medical Toxicology at the Uniformed Services University of the Health Sciences in Bethesda, Maryland. I am going to be chairing this joint session of the Nonprescription Drugs Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee held here in Rockville.

Before we get started with the agenda and the conflict of interest statement, I would like to go around the room and have everyone introduce themselves and state their affiliation. We can start to my right since there are more filled seats to the right than left.

DR. RINGEL: I am Dr. Eileen Ringel. I am a dermatologist in Waterville, Maine and loosely affiliated with Mary Hitchcock Medical Center.

DR. LAM: Francis Lam from the University of Texas of Texas Health Science Center at San

Antonio, a member of NDAC.

DR. PATTEN: Sonia Patten. I am consumer representative on NDAC. I am an anthropologist on faculty at Macalester College in St. Paul, Minnesota.

DR. WILKERSON: Michael Wilkerson, Tulsa, Oklahoma, Hillcrest Healthcare Systems.

DR. RAIMER: Sharon Raimer, dermatologist, University of Texas in Galveston.

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

DR. BENOWITZ: I am Neal Benowitz from U.C., San Francisco, internal medicine, clinical pharmacology, medical toxicology, and on the Nonprescription Drug Committee.

MS. KNUDSON: Paula Knudson on the Dermatology Committee as the community representative. I am an IRB administrator.

MR. KRESEL: I am Peter A. Kresel, Senior Vice President of Global Regulatory Affairs with Allergan in Irvine, California. I am the industry

representative for the Dermatologic and Ophthalmic Drugs Advisory Committee.

DR. ALFANO: I am Michael C. Alfano, Dean, College of Dentistry at New York University.

DR. TEN HAVE: Tom Ten Have, biostatistics and epidemiology at the University of Pennsylvania.

DR. WOOD: I am Alastair Wood from Vanderbilt.

DR. GANLEY: I am Charlie Ganley, Director of Over-the-Counter Drugs at FDA.

DR. WILKIN: I am Jonathan Wilkin, Director of the Division of Dermatologic and Dental Drug Products, FDA.

DR. KATZ: I am Robert Katz, dermatologist, Rockville, Maryland and Clinical Assistant Professor of Medicine at Georgetown. I am part of the FDA Advisory Committee.

DR. SCHMIDT: I am Jimmy Schmidt from Houston, Texas.

DR. DAVIDOFF: I am Frank Davidoff. I am on NDAC. I am an internist and Editor Emeritus of the Annals of Internal Medicine.

DR. WHITMORE: Beth Whitmore. I am a dermatologist in private practice, Wheaton, Illinois.

LCDR SPELL-LeSANE: Dornette Spell-Lesane, Acting Executive Secretary for NDAC.

DR. CANTILENA: Did we miss anyone?

Go ahead, Dr. Bisno.

DR. BISNO: I am Alan Bisno, Professor Emeritus of Internal Medicine, University of Miami, School of Medicine.

DR. CANTILENA: Thank you.

Dornette will read the conflict of interest statement for this meeting.

Conflict of Interest Statement

LCDR SPELL-LeSANE: Good morning. The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the agenda, it has been determined that the topics of today's meeting are issues of broad applicability and there are no

products being approved at this meeting. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

All Special Government Employees have been screened for their financial interests as they may apply to the general topics at hand. To determine if any conflict of interest existed, the Agency has reviewed the agenda and all relevant financial interests reported by the meeting participants.

The Food and Drug Administration has granted general matters waivers to the Special Government Employees participating in this meeting who require a waiver under Title 18, United States Code, Section 208.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Because general topics impact so many entities, it is not prudent to recite all potential

conflicts of interest as they apply to each member, consultant, and guest speaker.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

With respect to FDA's invited industry representatives, we would like to disclose that Mr. Peter Kresel and Dr. Michael Alfano are participating in this meeting as industry representatives acting on behalf of regulated industry. Mr. Kresel is employed by Allergan, Dr. Alfano is the Dean of College of Dentistry at New York University.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' 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 involvement with

any firm whose product they may wish to comment upon.

Thank you.

DR. CANTILENA: Thank you, Dornette.

Now we will have our kickoff from Dr. Charlie Ganley of FDA.

Welcome and Introductory Comments

DR. GANLEY: Thank you. I am just going to say a few words.

First, I wanted to thank the members of the Nonprescription Drugs Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee for participating in this discussion.

Today, we are going to talk about tinea pedis. It is not a high profile disease, but it does affect millions of people in the United States each year, and it is important to those individuals who have the disease.

So, we are looking forward to the discussion today. I think the executive summary and the questions provide you with some of the concerns we have, the current products, and the

current development programs that are going on right now.

I think John Wilkin is going to talk a little later, prior to answering the questions about some of the issues, so I think we ought to just start with the FDA presentations.

DR. CANTILENA: Thank you, Dr. Ganley. For the members of the committee, your blue folder in front of you has slides for all FDA speakers except for the last person, so as soon as we get those, we will hand those out to you.

We would like to then start. Dr. Porres from FDA will be the first FDA speaker, and he will then be followed by four other speakers.

FDA Presentation

Natural History of Tinea Pedis and Dermatophyte Infections

DR. PORRES: I am Joseph Porres, a medical officer in the Division of Dermatological and Dental Drug Products. I don't suppose that is a conflict of interest for this presentation.

[Slide.]

I would like to start by sharing with you a few points about the natural history of tinea pedis. Later on, I would also like to share some points with you about clinical trials for tinea pedis, just to set the tone.

In the first part, we talk about natural history, and I will cover the types of clinical presentations for tinea pedis, dermatophyte species, which most often cause this infection, the so-called dermatomycosis syndrome, some of the factors which may predispose someone to develop tinea pedis, factors that complicate tinea pedis and complications that may develop from tinea pedis.

I will try to give you a brief outlook of epidemiology, and will talk about recurrence, some people who have been treated. We talk about diagnosis of tinea pedis and a little bit about treatment.

[Slide.]

There are two main anatomic subtypes of tinea pedis - interdigital, which some people refer

to as intertriginous, in between the toes, and plantar.

Within the plantar, there are two distinct types - moccasin and vesicobullous.

Let's talk a little bit more about each one of these.

The interdigital often comes with pruritus, erythema, some scaling, occasionally fissure and maceration particularly if there has been overgrowth with some bacterial or candida species.

The moccasin type, which is the one affecting the sides of the foot, tends to be dry-looking and scaling, sometimes there may be pruritus, sometimes there may be some erythema.

The vesicobullous usually affects the plantar of the foot or the arch of the foot, and the vesicles is the main component. Oftentimes, there may be itching, scaling, and erythema.

Most patients seem to present with a combination of some of these features. It is rare to find someone who has just one pure type.

Then, we have the term "athlete's foot," which is sort of a generic term that the layman uses when they refer to just about any type of fungus infection on the foot. It is a loose term, it is hard to define. It is not really a medical term.

[Slide.]

Now, about the organisms that tend to cause these infections. The most common is Trichophyton rubrum, which is the predominant organism in this country since World War II, and it tends to account for about anywhere from 60 to 80 percent of cases of tinea pedis, mainly tends to cause the plantar, moccasin type.

Occasionally, there are some teeny tiny blisters on the plantar of the foot that quickly dry up and leave a collarette of scales, which has been described as very typical for Trichophyton rubrum.

It may spread to the nail and then particularly is responsible for cases of distal subungual onychomycosis. It can also spread to

other body parts, which we will see in a minute.

The second most common species of dermatophyte is Trichophyton mentagrophytes, usually responsible for about 15 percent of cases. It tends to be causative for the vesicular type, and it may also spread to the nails, but it tends to mostly cause superficial white nail involvement.

Finally, we have Epidermophyton floccosum, which tends to affect about 7 percent of the cases, and then there are other species, which are rare, also recovered in cultures of larger studies.

[Slide.]

This is a typical representation of an interdigital tinea pedis.

[Slide.]

Here we have the tinea plantaris with the tiny collarettes. These were vesicles that broke readily, and as you can see, clearly resembles dryness of the foot. Many patients will look at these and think it is just dryness, and even some physicians may consider this dryness and not treat it. Rarely, it will be symptomatic.

[Slide.]

Here we have the vesicular type, more abrupt, more acute, more likely to have symptoms.

[Slide.]

This is the typical moccasin type, which again many patients will look at this and think, oh, my God, my feet are very dry, and they won't even suspect they have a fungus. Oftentimes, it will itch, and even some physicians may call this just dry skin.

[Slide.]

Now, let's talk about the dermatomycosis syndrome described for Trichophyton rubrum. The hallmark is the moccasin type infection, and from here it can spread. There can be spreading between household members back and forth. It can spread directly to the nails or to the interdigital area of the feet.

Then, by spreading distally, it can go into the hands and from there to the fingernails. It can go to areas of the body, sometimes it may infect the hair follicles, producing a distinct

clinical picture referred to as Majocchi's granuloma.

It can go to the groin also, and then it is called tinea cruris. These types of spreading usually occur when we dress and bring our clothes up, passing by the foot, or with towels we may use for different areas of the body.

[Slide.]

Now, there are some predisposing factors that could be important. It has been said repeatedly that tinea pedis is far more common in closed communities like army barracks and boarding schools, or among people who frequent public baths and swimming pools.

It is probably important to have some local trauma for the infection to set in, trauma like you can develop if you go on a long march and your feet are going to be sweaty and hot and occluded by occlusive foot gear, and you may suffer from immersion into water or end up with wet feet just from your own perspiration.

If the shoes are very tight fitting, there

may be repeated friction and trauma, which also may contribute to set up a portal of infection for the dermatophyte.

It has been said that usually, it is important to have a species of organism to be able to cause infection. This was demonstrated in Vietnam, for instance, until they found that it was the hair of rats that was the vehicle for the infection of many of the soldiers with Trichophyton.

Again, if you look at a household, it is said, at least in one study, that about 17 percent of the members of the household are likely to have concomitant tinea pedis, and there may be a familial predisposition based on perhaps inadequate immunological response that may facilitate these patients to develop a chronic infection.

[Slide.]

Now, tinea pedis may become complicated if the patient is either immunosuppressed or has any atopic constitution, or is diabetic, or has compromised circulation, or there is repeated

trauma, again ill-fitting shoes or tight-fitting shoes, and many of these things are more likely to appear among the geriatric population.

[Slide.]

One interesting complication from tinea pedis could be cellulitis. It is probably not exceedingly common, but among people who do have cellulitis of the lower extremities, a great number of them seem to have a pre-existing tinea pedis. This might have been unrecognized for a long time by patient and physician.

Treatment may not have been given, or, if given, maybe was used too short a period of time, or perhaps the nail was not treated and reinfection kept taking place, or maybe it was a diabetic patient who had decreased sensory perception and would not recognize the pruritus that otherwise may alert one of having the infection.

[Slide.]

Let's talk a little bit about epidemiology. A number of studies have rated the degree of infection among the population at large,

and do find rates as low as 15 percent and as high as 70 percent.

It has been said that among people who attend the general clinic, if one were to look at their feet, about 40 percent of them tend to have tinea pedis, oftentimes unsuspected by the patient.

However, among the patients who do go to a doctor to seek treatment for the tinea pedis, interestingly, many of them do have already nail involvement with a fungus. There are a number of cases that remain undiagnosed for a long time.

Interestingly, dermatophytes have been isolated from the feet of normal individuals in varying rates. They have been isolated from public showers, from swimming pools, and from shoes and socks of affected individuals.

[Slide.]

Now, what happens to a person who has been treated afterwards? It has been very hard to find some data that I can share with you about this.

Luckily, I found one set of two papers which look at the same population, one by

Bergstresser, where they treated a number of people with 200 fungals, twice a day, either for one week or for four weeks, and then, a second paper by Elewski and others, where they look at the same patients 15 to 18 months later.

[Slide.]

So, let me show you what they found. There were 193 evaluable patients with interdigital tinea pedis. Again, the treatment was twice a day, and it was either terbinafine cream in this case or clotrimazole cream, and there were 2 ounces for each drug treatment, one week or four weeks.

They looked at it 15 to 18 months later, and for this particular part of the study, they only reported the mycology cure rates.

[Slide.]

There were 193 patients evaluable in the study. Of these, 130 were declared mycology cure at the end of 12 weeks of the study. Of these, they were able to follow up 93 during the 15 to 18 months of the second part of the study, and, of these 93, 44 felt that they needed more treatments,

so we consider this either insufficiently treated, or a relapse, or a reinfection, and there is really no way at this point to distinguish which one of the three possibilities we are dealing with here.

Then, they looked at the patients who didn't feel they had need for more treatment. There was it appeared to be cure, and they took cultures. Of these 49, 24 developed a positive culture anyway.

As a sideline, of these 24, 8 of them had an organism that this time was identified with a different name than the one given at baseline. It is hard to tell whether one of the two might have been misdiagnosed or whether this actually represents infection with a different organism.

So, all together, we see that there were 78 percent of the people who had originally been called "mycology cure," who relapsed or reinfected at some time after the treatment.

[Slide.]

Now, let's go a little bit into how we make a diagnosis of tinea pedis. The main part

here is clinical. We look at the signs and symptoms and try to recognize what may be part of the typical picture.

It can be aided by mycology, which consists of a direct microscopic examination, usually referred to as KOH, and of which there are many variants, and then the culture.

The nice thing about the KOH is that it can provide a quick diagnosis, confirming the clinical impression, and therefore it would help to avoid delaying giving the indicated treatment or avoid prescribing a treatment that may not be appropriate.

[Slide.]

Now, if a physician wants to treat tinea pedis and goes to the literature to see how to treat it, you will find information similar to this. This is just one example.

I look at this current textbook, "Treatment of Skin Disease," by Lebohl, published by Mosby in 2003, and they report results for terbinafine from different studies, clotrimazole,

miconazole, and a couple of others.

Oftentimes, they give the results for mycology cure and other times they just say cure rates and do not specify what kind of cure it was, but looking at the numbers here in the right column, I suspect that they are mostly referring to mycology cures.

Sometimes they tell us how long were those patients treated that reached these rate numbers, and oftentimes they will tell us the dosage that was used, but sometimes they don't tell us. They just say, well, terbinafine 97 percent cures, and we don't know what this means. It is unfortunate that this information is so scant that it is hard for the clinician to really figure out what these numbers represent.

I would like you to sort of keep an idea in mind about the magnitude of these rates when the statistician brings data from the studies that she had reviewed, just keep this in mind.

[Slide.]

Now, let's talk a little bit about

clinical trials for tinea pedis. I would like to focus a little bit on dose ranging studies and on clinical trials for safety and efficacy.

[Slide.]

Dose ranging studies for tinea pedis are particularly always recommended by the Agency when drug developers come here for meetings and orientation. Unfortunately, most of the time this recommendation is ignored. This is too bad because with dose ranging studies, it could be helpful to try to determine what is the most interesting dose that may have the best safety and efficacy profile.

Now, in dose ranging studies, usually, there are three elements that can be studied: drug strength, drug concentration, the frequency of application, and the duration of treatment.

We have some limitations here. Drug strength, sometimes there are certain higher doses that we cannot study either because they may have an unsafe profile or for chemistry reasons, perhaps the drug reaches maximum solubility and we cannot study any concentrations above that.

Now, frequency of application also has some limitations. We can expect compliance of patients to reach up to a certain limit. If we tell a patient to apply something once a day or twice a day, they are likely to do it. If we tell them to use it 74 times a day, they are not likely to do it, so studying things more than twice a day probably is not very practical.

So, we are left with duration of treatment which is where we have the greatest latitude, however, marketing pressures seem to make drug developers aim for ever decreasing durations of treatment, perhaps so they can advertise that a product can kill the organism in fewer days than the other competing product. Sometimes these may be at the expense of efficacy.

[Slide.]

Now, in clinical safety and efficacy trials, I would like to focus about how do we assess results of these trials and what the outcomes from these assessments will be.

[Slide.]

What we assess or what has been assessed routinely is mycology, again direct microscopic examination and mycology culture, and clinical, a variety of signs and symptoms, and there are studies which have just looked at a couple of these, others that look at many.

Others make a composite of this, others may use what is called the investigator's global assessment, which is kind of like a comprehensive picture of what the disease looks like at that particular point.

[Slide.]

The outcomes from these assessments are usually mycology cure, which involves having a negative KOH in a negative culture. We don't like this term very much at the FDA. We would like to refer to it as negative culture because perhaps it is not really a cure in many cases unless it is accompanied by a clinical cure, as well.

Then, we have clinical outcomes. One is effective treatment, which requires not only negative mycology or mycology cure, but also

absence of symptoms and at most, some residual signs remaining.

Here, I should introduce or remind you of a concept of skin turnover. The epidermis has a maximum speed at which it can turn over its cells, which is about four weeks, so you could have a patient who is actually a cure, and may still have some residual erythema or some residual scaling.

However, after these four weeks, we should be expecting that these residual signs should not be present in a patient who is a cure.

Then, we go into complete cure, which is the gold standard, where mycology is negative or mycology cure, and there are no signs or symptoms left of the disease.

[Slide.]

Now, in clinical safety and efficacy studies, oftentimes the inclusion/exclusion criteria that come with the protocols do not seem to mimic the population which could be expected to actually use these products in the real world once the product is approved.

For instance, they tend to include only people who are very healthy and who perhaps have disease limited to just a small area, such as toe webs, and exclude more difficult cases to treat that might reduce their overall efficacy rate, so they exclude people with onychomycosis or who have the moccasin type, which they apparently think is harder to treat, and they will exclude people who are diabetic or immunosuppressed, or who may have compromised circulation, but all of these patients would be expected, they will be users of the product later on.

At this point, I would like to introduce Dr. Kathleen Fritsch, who will give you a summary of her review of some studies.

Thank you for your attention.

DR. GANLEY: If anyone had questions for Dr. Porres now, they could probably ask them.

DR. CANTILENA: We actually have time slotted, actually, plenty of time before lunch, but I guess if there are specific questions, perhaps we have time for one or two specific questions for Dr.

Porres before we go to the next speaker.

Yes, Dr. Ten Have.

DR. TEN HAVE: I have a question regarding the definition of the efficacy rates on page 9 that were reported. I missed the definition. Could you just repeat it?

DR. PORRES: In the handout, page 9?

DR. TEN HAVE: Handout, page 9.

DR. PORRES: The question, if I understood, is how is cure defined here? Okay.

DR. TEN HAVE: How are the efficacy rates defined based on a cure definition?

DR. PORRES: I am glad you asked that question, because the clinician, looking at this information in textbooks, should be asking the same question. The point is that when you look at the sources in the literature, they don't tell you anything. They just give you some rates and hope that you will think that these products are all wonderful, and they don't tell you how these numbers are derived, and you are lost.

So, that is precisely the point I was

trying to make.

DR. CANTILENA: So, the answer is they are really not well defined.

DR. PORRES: They don't tell us, they just give us a summary.

DR. CANTILENA: Dr. Wood.

DR. WOOD: My question may be an extension of the last one. On the last slide, you talk about the exclusion criteria that include harder cases to treat. I presume you mean by that, that the outcome is poorer, is that right, that the cure rate is lower?

DR. PORRES: The people who may be harder to treat--

DR. WOOD: I understand that is what it says, but do you mean by that, that they are harder to treat because the efficacy is lower in that group? I mean diabetics aren't harder to treat per se, and they must either have poorer outcome, or do you mean that diabetics can't rub the stuff on their foot, you know, what do you mean by that?

Just to finish the question, I assume what

is meant there is that the outcome is poorer in these patients, what are the data to support that?

DR. PORRES: I think you will have to ask the drug developers why do they want to exclude those patients in the first place. They don't give us a rationale, they just want to exclude them maybe to keep the study neater, and I am not aware of any data that actually shows whether they are easier to treat or more difficult to treat, but that is the way they design their protocols.

Now, the moccasin type--

DR. WOOD: So, the slide says you excluded harder cases.

DR. PORRES: Yes.

DR. WOOD: Are there data to support them being harder, or is that just--

DR. PORRES: They assumed they are going to be harder.

DR. WOOD: I see.

DR. PORRES: For instance, if there is nail involvement, they may be more prone to have reinfection from the nail if they are not treating

the nail at the same time, so they suspect that those are going to complicate the outcomes.

DR. WOOD: But you have no data to say that the outcome is poorer in these patients?

DR. PORRES: No.

DR. WOOD: That is what I am trying to get at.

DR. PORRES: We don't have the data.

DR. WOOD: It relates directly to the question. That is why I am pushing this part.

DR. PORRES: No.

DR. CANTILENA: Dr. Fincham.

DR. FINCHAM: Dr. Porres, I am assuming that these criteria, either inclusion or exclusion, are set by the manufacturer, there is no constraints on those designs.

DR. PORRES: Well, they send us the protocols. We look at them, and sometimes, you know, we make suggestions. We encourage the study of all comers. Sometimes they insist they want to study just a very narrow group, and sometimes we are more influential than others.

DR. CANTILENA: A comment from Dr. Wilkin.

DR. WILKIN: Actually, you caught it right at the very end, and sometimes they do. We have had some tinea pedis trials where patients with onychomycosis, often the same fungus that is affecting the plantar surface of the foot is also in the nail.

We have had some trials like that, so I think it is not all or none, and it is true that we don't know for sure that they are harder, but we sense that there may be some lower efficacy, but we don't have good numbers on that, that is correct.

DR. CANTILENA: Dr. Alfano.

DR. ALFANO: My question relates to the fact that you spoke about predisposing factors, and you mentioned trauma is regularly associated to get this infection started.

What happens with those predisposing factors in the course of the disease, i.e., if the subject doesn't change their tight shoes, do they start with hyperkeratosis from the irritation from the shoes, and is it appropriate to expect that to

go away if they don't change their predisposing factors?

DR. PORRES: There is really no hard data looking at what happens on a series of cases from the beginning to the end, but this is the general gestalt, the general feel for what is felt, how this disease evolves, and it is felt that these factors are important in either facilitating development of the disease or in making it worse, but there is no hard data that anyone would show if you wear your shoes 10 minutes longer, you are more prone to have disease than it you wear them 10 minutes less, but it is felt that usually, that is the case, but there is no hard data for any of this. This is kind of like a field that has developed through the years, that most people seem to agree as a general concept.

DR. CANTILENA: Our final question over here. Dr. Benowitz.

DR. BENOWITZ: Two questions. The first one, you had said that as many as 70 percent of the general population can have positive cultures.

Given that in the recurrent studies, does a persistent positive culture with a clinical response mean that there will be a clinical recurrence?

DR. PORRES: Could you rephrase the question again? I am sorry.

DR. BENOWITZ: You said that as many as 70 percent of the population, assumingly not clinically infected, can have positive cultures.

DR. PORRES: No, no, that is not what I said, I am sorry. What I said is that some people, published reports looking at the incidence of tinea pedis in a particular population like maybe in India or Canada, or somewhere, and they report that they found 70 percent of the people at large had the disease.

DR. BENOWITZ: Oh, had the clinical infection. I guess the other part is still valid.

If you have a positive culture, but you have a clinical response, does that always translate into a later clinical recurrence?

DR. PORRES: If you have--

DR. BENOWITZ: You have been treated, you have a clinical response, but you do not have a mycologic response, does that always predict a clinical recurrence?

DR. PORRES: Well, if there is clinical cure, you say, but the culture is still positive?

DR. BENOWITZ: Yes.

DR. PORRES: That would never be called a success by definition, so I don't think anybody has ever looked to see what happened to the patient afterwards. It is just declared a failure, and there is no follow-up.

DR. BENOWITZ: Is there any issue of a carrier state, like we see with other infections? Is that an issue here?

DR. PORRES: Possibly, there is no hard data, there is contamination with other household members or other school members or other army fellows, you know, but there is really no hard data for any of these things.

DR. BENOWITZ: Okay. The second question is if an expert dermatologist is seeing a patient

who has these infections, and they are diabetic or they are immunocompromised, would they be treated any differently from any other patient? What is the standard of care for treatment of these more high risk patients?

DR. PORRES: The dermatologist would want to make sure that whoever is taking care of the diabetes for that patient would have provided adequate treatment or if they are immunocompromised, that they have the adequate treatment, you know, just as a general feel for my practice, I have seen people who have maybe HIV or something else, and they have tinea, and I can figure they are much harder to treat and the treatment is much, much longer, and oftentimes they stop because they get tired of treating these for months or they stop when they feel better, thinking that maybe they have cured the problem, but it was just a little bit too early, and within a few months they come back with full-blown disease.

So, the dermatologist can treat the skin, but usually, we need the concurrence of the other

types of physicians who treat the other components like vascular disease or whatever.

DR. BENOWITZ: I guess my point is would a dermatologist initiate systemic antifungal therapy rather than try topical therapy first if someone is at high risk?

DR. PORRES: Well, that is an interesting question and I didn't want to address it here because we are talking about topical antifungals, but if you look at the textbooks and references on how to treat the disease, there are many who would say that you need to use also systemic treatment for tinea pedis together with topical antifungals. Some still say that.

DR. BENOWITZ: I think it is important for us because that really affects labeling for high risk patients. We need to know what patients need to understand about their disease.

DR. PORRES: You are absolutely correct, and that is why we are here today.

DR. CANTILENA: Thank you, Dr. Benowitz.

We have one final comment from Dr.

Schmidt, and then, since you work here, Dr. Wilkin, you can have the final, final comment.

DR. SCHMIDT: I think at least in Texas, I don't think we really cure these people of any of these things, and I think that moccasin type tinea, if someone has an immunologic defect where they just can't process and kill the T. rubrum, then, in your first slide of the person pulling the toes apart, the little piggies, you know, are too close.

I think the mechanical trauma comes first, and then the tinea is secondary, so I think it behooves us to have some like education, you know, for the patients, because unless you can keep the air flowing with Thinsulate socks, spacers, drying agents, powders, changing shoes, wearing wooden shoe trees, you know, there are a million things that you can do, you will never cure these people with this interdigital tinea, never ever in your lifetime.

Then, I think, the same way with this moccasin type tinea, I mean I think this stuff is in the environment, and these people are going to

get it recurrently, because it seems like people come in during the summer and their fungus flares up, and during the winter, even if you don't treat them, these things tend to clear up.

Now, I wanted to comment on this thing of whether we treat people more aggressively when they have problems. It's hard to treat patients who have diabetes or they have recurrent cellulitis. Usually, these people, it comes from the fourth and fifth toe web, you know, from this macerated interdigital tinea is the point of entry, and, yes, I do, I will sometimes treat these people systemically, but I think drying agents and good foot care is probably the most important thing.

The same thing with the onychomycosis, you know, just simple things will help this, but I never tell anybody I am going to cure them. I just say, listen, when this stuff comes back, you are just going to treat it again.

DR. CANTILENA: Dr. Wilkin.

DR. WILKIN: I would like to respond to Dr. Benowitz's question about after treatment, can

you still get the dermatophytes, and there is a paper in the Journal of the American Academy of Dermatology, February 1995, Dr. Elewski is the first author, it's a multi-authored publication.

Long-term outcome of patients with interdigital tinea pedis, treated with terbinafine or clotrimazole, and one of the points made is that even after successful treatment in the sense that the inflammatory signs and symptoms have gone away, one can still culture the organism.

So, I think this is the experience that most dermatologists have, as well, and then I was going to add the part that Dr. Schmidt has already taken care of, you know, the dermatologist, I think, attacks the tropical environment inside the shoe, which is what keeps the fungus going.

Also, sometimes the dermatophyte can actually survive on the inside surface of the shoe, so we know that some patients actually, eventually need to get a new pair of shoes, and there is a lot of weekly applications of topical products.

Certainly, that is off label, but I know

that that is done, a lot of drying powders, and, yes, there is a lot of attention, but I think in general the first approach is topical, but it is with a fairly comprehensive strategy for making it the wrong environment for the dermatophyte.

DR. CANTILENA: Thank you. Thank you, Dr. Porres.

Dr. Fritsch.

Study Design and Efficacy Results for Tinea Pedis Clinical Trials (Rx and OTC)

DR. FRITSCH: Good morning. I am Kathleen Fritsch. I am a biostatistician with the Division of Biometrics III. I will be presenting some more background information on the study design for tinea pedis clinical trials, and then I will be presenting some efficacy data from NDA submissions.

[Slide.]

First, I will be looking at the basic clinical trial design.

[Slide.]

Generally, these trials are randomized, double-blind, multicenter, vehicle-controlled

trials.

In the past, there generally have been two indications, the tinea pedis indication, the OTC equivalent of athlete's foot, and these trials will usually evaluate either all comers, with both the plantar and the interdigital variant, or study the subtypes individually, or if they focus their clinical trials primarily on the interdigital type, then, they get a more limited indication of athlete's foot between the toes or interdigital tinea pedis.

Most of the development over the last decade has focused on the interdigital variant. Most of the products approved for the full indication were approved more than a decade ago.

[Slide.]

In terms of patients that are evaluated in these studies, for randomization into the trial and receiving treatment, you need a positive KOH and clinical signs and symptoms.

In order to verify that tinea pedis is actually the diagnosis, in order to be analyzed for

efficacy, usually, the patients are also required to have a positive baseline culture, however, since it can take up to four weeks to get the results of a culture, the treatment is often completed by the time those baseline culture results are known.

However, the solution then is to just analyze for efficacy, what we call the modified intent to treat, or MITT population, those that have positive KOH, positive culture, and the appropriate clinical signs and symptoms.

In most clinical trials, we will find that about two-thirds of the patients will end up having a positive baseline culture, and that can have an impact on choosing the sample size for a study.

[Slide.]

As Dr. Porres mentioned, there are three efficacy endpoints that are analyzed in these clinical trials that involve mycological and clinical outcomes. They are nested within each other in that negative mycology is required for both effective treatment and complete cure.

The effective treatment is getting to a

mild state and also includes the patients that get to the complete cure state, and the complete cure state is the absence of the signs and symptoms.

So, they are nested within each other.

[Slide.]

Again, to put up the specific definitions for these three endpoints, negative mycology, also referred to as mycological cure, is a negative KOH and culture.

An effective treatment also requires the negative mycology and is some sort of a mild state of the disease, the clinical presentation. Generally, we say mild or no signs and no symptoms. From trial to trial, the specific definition for effective treatment does vary.

Our recommendation these days is to define it as, at most, mild erythema and scaling, but in the past trials, there may be other ways to define a mild state that have been used. Sometimes effective treatment is designated in the clinical trials as the primary endpoint.

Of course, the strongest endpoint is the

complete cure, which is the absence of signs and symptoms, negative mycology. This is often the primary endpoint in the clinical trials, and the Agency generally recommends to use complete cure as the primary endpoint.

Again, the signs and symptoms that are evaluated usually include erythema, pruritus, and scaling, and may include any of the other signs and symptoms, as well.

[Slide.]

For the study phases, there is usually a treatment period and a post-treatment follow-up period.

Most products have a treatment duration between one and four weeks. Then, the patients are followed for, at a minimum of at least two weeks after treatment. The amount of follow-up will generally depend on the length of treatment.

For a one-week product, the treatment period usually is at least five to eight weeks. If the treatment is for four weeks, the follow-up period may be shorter, it may be only two to four

weeks. In both cases, this puts the patients at about six to nine weeks after they have started their treatment for when they will be primarily evaluated.

[Slide.]

Again, the reason for following patients into the post-treatment follow-up period is to allow for the epidermal turnover, as Dr. Porres mentioned, may take at least four weeks, so we may not expect the clearance of signs until some point after treatment has ended, say, at least six weeks after the start of treatment even if the fungus is eradicated earlier.

Because of this, there may be a significant time lag in either weeks or possibly months between when treatment ends and when a cure could be assessed.

[Slide.]

The second part of my presentation will focus in on specific data that have been submitted to the Agency. I will be presenting the efficacy results from selected clinical trials.

[Slide.]

The clinical trials that I have selected for my presentation come from NDA reviews. The oldest one dates back to 1988, and all of the studies come from vehicle-controlled trials and were in general considered the pivotal trials for a particular drug product.

Using these criteria, I have identified nine drug products. They may involve different formulations or treatment regimens, and they represent six different active ingredients, so there are some multiple formulations and treatment regimens.

The nine products are roughly split between those that are available OTC and by prescription, and also split between those that are recommended for one week's use and for four weeks' use.

Of the nine, seven were designed for the indication of interdigital tinea pedis, and the two oldest ones have the indication for tinea pedis.

[Slide.]

To take a look at the size of the database that is available for each of these products, I will be presenting the products only by code letter A through I.

We see that the products have a database of roughly about 50 patients on an active ingredient up to about 250, and in some cases, we have two trials that were two vehicle-controlled trials, and in some cases, we have one. So, we do have a variety of sample sizes represented for our products here, so A through I.

[Slide.]

As I move into the displays of the actual data from these trials, I want to make a caveat that these data do not represent head-to-head comparisons of the products, therefore, we cannot make any direct comparisons of relative efficacy from one product to another.

Success rates in these trials are greatly influenced by the particular patients that are enrolled in a trial, types of concomitant diseases they may have, whether they have onychomycosis, how

severe the baseline clinical signs and symptoms must be could affect the success rates.

The specific clinical study procedures, how the samples are collected, who analyzes the skin samples, whether a target lesion is analyzed, whether the whole foot is analyzed, all that can influence the success rate.

As I mentioned before, the endpoints are identified differently in a trial, is it a global, is it specific symptoms, what symptoms are evaluated, all of that, how is missing data handled, all that can influence the success rates.

So, we will look at this in terms of trying to pick up general trends and patterns that we can.

[Slide.]

I have got data on the negative mycology, effective treatment, and complete cure rates for the nine products, so we will present those next.

[Slide.]

This first graph represents the negative mycology. These are the negative mycology rates at

end of treatment, so Week 1 for the one-week products, and Week 4 for the four-week products.

The orange bars represent the active. We can see what kind of eradication we can expect to find for a one-week treatment. For a one-week treatment, we can see that, for the most part, about 40 to 50 percent of patients will have negative KOH and negative culture by the end of treatment.

For the products that are used for four weeks, the negative mycology rate is somewhat higher at Week 4, about 60 to 70 percent of patients will have the negative mycology at the end of treatment.

[Slide.]

If we go to the primary timepoint that was specified in each particular protocol for the time of assessment, usually, Week 6, 8, or 9, we see that, in general, at this timepoint, patients can get to about 60, 70, or 80 percent negative mycology rates by the primary timepoint for evaluation, so that is about what we can expect for

getting rid of the dermatophyte, and it is fairly consistent across the products here.

Again, the endpoints that involve the clinical signs and symptoms are based on these patients that achieve negative mycology only.

[Slide.]

In terms of effective treatment, this will be getting negative KOH in culture and getting down to some sort of a mild state of disease.

We see that for Week 1, only a relatively small proportion of patients are actually able to get to the mild state by the time they are finished with their treatment regimen, about 2 percent to 18 percent of patients. So, the remaining subjects would have some sort of symptoms beyond just mild erythema and mild scaling remaining by the end of treatment.

At four weeks, where they have had a longer time to wait before they stop their treatment, roughly around half of the patients are able to get to a mild state of disease, and the remaining half would still have more severe signs

and symptoms remaining.

So, that is what a patient may be able to expect to see by the time they are finished with their treatment.

[Slide.]

By the time we get out to the Week 6 to 9, where the skin may have had a chance to turn over a little bit, we see again about 40, 50, 60 percent of patients will be able to get to the mild state with the negative mycology, and the remaining subjects would have more symptoms remaining.

[Slide.]

Finally, the gold standard of complete cure where we can completely eradicate these signs and symptoms, as well as the dermatophyte, for one week treatment, as may be expected because of the time for skin turnover, very few patients will be actually completely clear of their signs and symptoms.

Almost everybody has some signs or symptoms remaining or dermatophyte remaining by the end of one week of treatment. Even for those that

continue to four weeks, roughly, 15 percent of patients are able to get completely rid of their signs and symptoms, and the remainder will have at least something remaining even at the end of four weeks of treatment.

[Slide.]

To go out to the primary timepoint, again we see about the same value across the board. About 20 percent, maybe 30 percent in some cases, of patients are able to completely get rid of their signs and symptoms six to nine weeks after starting treatment, which is about two to four weeks after treatment for the four-week treatments and five to eight weeks after treatment for the one-week treatments.

[Slide.]

Next, I will go into some specific tables for the specific signs and symptoms, and I will present this information by visit. The visits that are evaluated in a particular clinical trial depend on the design.

I will be presenting data for erythema,

scaling, and pruritus, and for this presentation, since signs and symptoms have not been collected in the same way in all trials, I have the data available in the format I want for only two products, a one-week product and a four-week product.

[Slide.]

We start with erythema. This will be the percentage of subjects that will be clear of their erythema at a particular visit. On the left, Drug Product D is a one-week treatment, and Drug Product F is a four-week treatment.

If we take a look at the percentage of subjects, in this case, we started off with about 15 percent of subjects were clear of their erythema at baseline in this trial. After one week of treatment, that number improved to about 25 percent, and then as we go out in time to the time we may expect to see the skin turnover, by Week 4 to 6, we are getting up to about 50 percent.

This trial went out to 12 weeks, and by that point, we have about 50 to 60 percent of

patients clear of their erythema by the end of the trial, compared to about 30 percent on vehicle.

A similar pattern for this four-week treatment. It takes a while for the number of patients to get clear of their erythema. By about Week 4, again we are about 45 percent, 50 percent of patients. So, we can see kind of the time trajectory of how many weeks it takes to start to see clearance of the erythema.

[Slide.]

Scaling. In this case, all of the subjects that have scaling at baseline, and we see that for the one-week treatment, if we look at the number of patients that are clear of their scaling, about 2 percent of patients were clear of scaling by the end of treatment. Again, not too surprising based on the length of epidermal turnover.

By four weeks, we are up to a little over 10 percent, and we max out at about 25 percent. So, this may be the rate-limiting factor for why we see little complete clearance is scaling is persistent in the vast majority of patients.

Similarly, over here, by about Week 4, we are up to 20 percent, maxing out at about 30 percent of patients able to completely clear of their scaling.

[Slide.]

Finally, for pruritus, we will see that on this drug, for the one-week treatment, we do actually see a substantial bump from baseline to the end of treatment at Week 1, go from about 15 percent with no pruritus at baseline to about 45 percent by the end of treatment.

Again, we do see continued improvement for this product after treatment has ended, getting up to about 75 percent of patients by Week 9 who are clear of their pruritus, and the vehicle rate drops off, although interestingly, during the one week of treatment, the active and the vehicle have the same benefit in terms of pruritus, however, the active patients do continue to improve.

Similarly, for Drug Product F, we see continued improvement on the pruritus, in this case during the course of treatment, maxing out at about

70 percent again for the number of patients clear of their pruritus.

Again, also substantial vehicle benefit, however, the vehicle rate does drop off after treatment.

[Slide.]

The summary of the efficacy results. From this data, we can see that there is a time lag of several weeks between the end of treatment and when the signs and symptoms may be cleared, particularly for the one-week products where the treatment is stopped before the epidermal turnover can take place.

In most cases, patients will have signs and symptoms remaining into the post-treatment period, and rough ballpark figures of the typical cure rates for the various endpoints, complete cure rates are roughly 20, maybe 30 percent for most products.

Effective treatment may be about half of the patients. Negative mycology rates, around two-thirds to three-fourths of the patients will be

able to get to the negative mycology in the post-treatment period.

Thank you.

DR. CANTILENA: Thank you, Dr. Fritsch.

We have time for a couple of questions for Dr. Fritsch.

Dr. Benowitz.

DR. BENOWITZ: I am just curious. What is the basis for someone doing a one-week trial versus a four-week trial, are the products different, why is that done?

DR. FRITSCH: Basically, it is the sponsor's preference. If they want to market a one-week product and they think they can get the efficacy that they want in one week. We have not seen very much data that compares a product across multiple durations.

That is one of the reasons we have been asking for dose ranging. It is usually we either get results for one week, or we get results for four weeks. We have not seen much comparative data, but generally, it is the sponsor's decision

on what type of product they would like to market.

DR. BENOWITZ: So, if we looked at the products, they would basically be the same in both groups in terms of active ingredients?

DR. FRITSCH: In terms of for the data presentation I made, there is six different active ingredients that were represented.

DR. BENOWITZ: I understand. I am just saying that if you look at drugs that were selected for a one-week trial versus a four-week trial, they are basically the same medications in both, same active ingredients?

DR. FRITSCH: There is only one case where we have data both on a one-week use and a four-week use. Otherwise, the products that are one week are different than the products that are four weeks.

DR. BENOWITZ: I understand that the specific product name is different, but in terms of the active ingredients.

DR. FRITSCH: The active ingredients, yes.

DR. BENOWITZ: Are they also generally different or are they basically the same?

DR. FRITSCH: Generally, they are different. There is one product that is recommended for use for either one week or four weeks, and then there are products that are only recommended for one week, and there are products that are only recommended for four weeks.

So, generally, the one-week products are different from the four-week products in terms of active ingredients.

DR. BENOWITZ: Thanks.

DR. CANTILENA: Ms. Knudson.

MS. KNUDSON: I want to know, on these studies that you have just presented, do you have any idea how many patients dropped out of the studies and at what timepoints did they drop out?

DR. FRITSCH: Yes, that is generally included. For the most part, roughly, in maybe a six-week trial, there might be about 10 to 15 percent of patients that drop out. One of the difficulties with the data I have presented, our current standards would be to generally either count the patients that drop out as either failures

or last observation carried forward.

For the older trials, often the results that I have presented exclude the dropouts. I did not go back and try and correct for intent to treat the way that the older trials did, so that is one variability, that the older trials often ignored dropouts. Recently, we definitely count them in our results.

DR. CANTILENA: Thank you.

Dr. Ringel.

DR. RINGEL: I have a question about negative mycology. I was wondering if that is considered negative KOH and culture or only negative culture.

The reason I am asking is that most physicians consider culture in other areas of mycobiology to be a gold standard, whereas, as with dermatophytes, there are various reasons why a culture might be negative, where the KOH would be positive, either bacterial contamination, sampling error, the patient has been using topical antifungals.

So, I guess the question is if a KOH is positive, a culture is negative, is that considered positive mycology or negative mycology?

DR. FRITSCH: You must have both negative KOH and negative culture to be counted as negative mycology.

DR. RINGEL: Thank you.

DR. CANTILENA: Thank you. Now we have Mr. Kresel.

MR. KRESEL: My question was answered earlier.

DR. CANTILENA: Dr. Epps.

DR. EPPS: Partially, my question was addressed with the positive KOH, negative mycology, but how much within your group was just positive KOH and negative culture? Do you have any data regarding that?

DR. FRITSCH: Yes, the positive KOH and negative culture, I have seen a few. There is definitely some that come through with positive KOH and negative culture.

DR. EPPS: Because it may be that this is

not viable, but present--

DR. FRITSCH: There is lots of problems with the four-week, you know, a negative culture, did you have the fungus in the plate or not, that is definitely a problem, so there are definitely some that do come through.

DR. CANTILENA: Thank you.

Dr. Lam.

DR. LAM: I just want to clarify just to make sure. The data that you present only represent one strength of each of the products.

DR. FRITSCH: One strength of each product, yes.

DR. CANTILENA: Thank you. Any other questions from the committee? Dr. Wood.

DR. WOOD: The elephant in the room here is what the efficacy is with systemic therapy, as well. Is somebody going to talk about that?

I realize we are here to consider topical therapy, but as we get to some of these questions, my feelings about them would be substantially influenced by knowing what we are going to accept

as the expected efficacy rate from systemic therapy.

Clearly, given the efficacy rate shown here, and consumers' views of that will be different if there is effective therapy out there that is of an order of magnitude different.

So, is someone going to, for the record, show us that, an efficacy rate from terbinafine systemically?

DR. CANTILENA: Dr. Ganley, do you have anyone? If you have to look that up, we can certainly have that after lunch. So, why don't we have someone be checking on that. That is a good point.

Our next speaker from FDA, Dr. Mahayni.

History and Overview of OTC Topical Antifungal Drug Products Monograph

DR. MAHAYNI: Good morning, ladies and gentlemen. My name is Houda Mahayni. I am interdisciplinary scientist in the Division of Over-the-Counter Drug Products.

[Slide.]

I will give you a brief introduction about the mechanism by which OTC drugs are regulated. Then, I will describe an overview of the OTC Drug Monograph System. Finally, I will discuss the OTC drug monograph for topical antifungals with special emphasis on those ingredients used to treat athlete's foot tinea pedis.

[Slide.]

Most of you are familiar with the NDA process, so in order to introduce the monograph system, I am going to briefly contrast the two mechanisms by which OTC drug products are regulated, highlighting the key differences between the two mechanisms.

NDA is drug product-specific. It requires pre-market approval, and information submitted under the NDA is confidential, whereas, in the OTC drug monograph, is an active ingredient-specific, and ingredients are designate as GRASE, which is generally recognized as safe and effective. There is no need for pre-market approval. Finally, the information is public.

[Slide.]

I hope this introduction gives you a flavor of how the two mechanisms differ. I will not be talking about the NDA mechanism in this talk, but I will focus for the rest of this talk on the OTC Drug Monograph System.

[Slide.]

The OTC drug review began in 1972 as a review of the safety and effectiveness of OTC drugs on the market at that time. FDA initiated the OTC drug review by identifying a number of therapeutic categories for which FDA is to establish OTC drug monographs.

OTC drug monographs list the conditions of use that are generally recognized as safe and effective or GRASE, and on the next slide I will be talking to you about what is meant by the condition of use.

[Slide.]

What is really included in the monograph system is the conditions of use, and those include the active ingredients, whether it's single

ingredient or combination, dosage strength, dosage form, labeling requirements, such as uses, directions, and warnings, and finally, in some cases, final formulation testing.

[Slide.]

The OTC drug review is a four-step public rulemaking process, and each step builds upon the other. Here, I will be listing all the four steps and I will go over these steps in more detail in subsequent slides.

First, the advisory review panel meets. Then, after the panel meets, the FDA publishes the Advance Notice of Proposed Rulemaking, which is generally referred to as the ANPR.

Next, FDA publishes the tentative final monograph, or TFM, and finally, the FDA publishes the final rule, or FM.

[Slide.]

The panel is a group of experts in a particular OTC drug category. The panel was charged with reviewing the data of OTC ingredients marketed prior to 1975 and assessing whether these

ingredients are safe and effective for GRASE conditions for the OTC drug monograph.

The panel give the nomenclature Category I for ingredients, all conditions under which products are generally recognized as safe and effective, and are not misbranded.

Category II are for ingredients or conditions under which products are generally recognized not as safe and effective or are misbranded.

Category III are for ingredients or conditions when the available data are insufficient to permit final classification at the time.

Keep in mind that these classifications are not only given for ingredients, but for condition of use as defined earlier, which includes labeling requirements and final formulation testing.

[Slide.]

Next, the FDA publishes the Advance Notice of Proposed Rule, or ANPR, in the Federal Register to announce its intention of creating the OTC drug

monograph. The ANPR also contains the panel report, which lists recommended GRASE conditions.

Then, following the publication of the ANPR, interested persons may submit comments or additional data to the panel, and they are given 90 days to make those comments in.

[Slide.]

FDA next publishes the tentative final monograph, or TFM, in the Federal Register as its preliminary position regarding the safety and effectiveness of each active ingredient in particular category.

The TFM is based on FDA interpretation of data provided by the panel, the panel recommendations, and any new data submitted in response to the Advance Notice of Proposed Rule.

Following its publication, there is also an additional 90 days comment period for interested persons who may want to submit comments and additional data on what was contained in the TFM.

[Slide.]

FDA reviews all comments and data

submitted during the tentative final monograph comment period and amends the TFM to create the final monograph or final rule. The monograph is a set of rules published in the Federal Register.

The regulation gets published in the Code of Federal Regulations. That includes an effective date after which any product marketed under the monograph must comply with the conditions used that were described in the monograph.

As I said, each step in the monograph builds upon and is a continuation of the previous step. Although the FM is the final step in the OTC Drug Monograph System, FDA can amend the final monograph to include additional GRASE conditions, such as adding new active ingredients.

[Slide.]

Now that I gave you a general overview of the OTC Drug Monograph System, I am going to shift and talk specifically about the history of OTC topical antifungal monograph with special emphasis on those ingredients used to treat athlete's foot tinea pedis.

[Slide.]

The panel met in the late seventies and early eighties, and then FDA published the Advance Notice of Proposed Rulemaking in 1982.

The panel expressed its concern about the ingredients only mitigating symptoms rather than curing condition as is apparent by the statement that in order to best serve the consumers, an OTC product must provide more than temporary symptomatic relief of athlete's foot, jock itch, and ringworm.

The panel required at least one well-designed clinical study demonstrating an active ingredient treat athlete's foot as evidence of effectiveness, and it recommended an ingredient as GRASE if it was significantly more effective than vehicle.

[Slide.]

In reviewing the clinical trial, the panel defined a well-controlled study as one that met the following criteria: To be double-blinded and randomized, vehicle-controlled, test groups of

adequate size, entry criteria based on clinical signs and symptoms with diagnosis verified by positive KOH and culture, and standardized dosing regimen usually four weeks treatment for athlete's foot, and finally, the follow-up examinations performed at the end of treatment and final evaluation of clinical results corroborated by negative KOH and negative culture two weeks after treatment ends.

A relatively small percentage of the studies submitted to NDA met these criteria.

[Slide.]

The panel reviewed approximately 50 clinical studies along with in vitro and animal studies to assess the safety and effectiveness of about 35 active ingredients.

Of these clinical studies, roughly 10 were designed to demonstrate the effectiveness of active ingredients in treating athlete's foot, but most were poorly designed. This was because there was considerable variability in the study protocol.

Enrollment for most studies was based on

the diagnosis of tinea pedis by a physician instead of these studies, this diagnosis was confirmed by positive KOH and positive culture.

Treatment duration varied between two to six weeks with treatment duration being four weeks in most studies.

These studies assessed the efficacy at different timepoints and used different criteria for cure.

All these factors make it difficult to compare the cure rates of the monograph products to those of the NDA products. Based on this review of the study, the panel recommended that six active ingredients be classified as GRASE, and I will share with you these ingredients in the slide talking about the final monograph.

[Slide.]

In addition, the panel proposed the idea of simple and concise labeling that should enable the consumers to clearly understand the results that can be anticipated from the use of the product.

Example of indication recommended by the panel includes treat athlete's foot for the treatment of athlete's foot or for the relief of itching.

Labeling or products used for the treatment of athlete's foot should include the following warning: If irritation occurs or of there is no improvement within four weeks, discontinue use and consult a doctor or pharmacist.

Furthermore, the panel stated that directions should be clear and direct. They should provide the user with sufficient information to enable safe and effective use of the product.

Based on the clinical study, which generally involved four weeks' treatment, the panel determined that OTC topical antifungals should be applied twice a day for four weeks to be most effective.

[Slide.]

Seven years later, after the NPR was published, the Agency published the TFM. In the TFM, FDA reviewed 25 clinical studies. Those

studies were submitted following the publication of the ANPR or Advance Notice of Proposed Rule.

Six of these 25 studies addressed athlete's foot. Based on these studies, FDA agreed with the panel recommendation in terms of ingredients to be included in the monograph with the exception of two active ingredients, nystatin was classified as not GRASE, and they decided to include povidone and iodine as GRASE.

[Slide.]

After the TFM was published, FDA published the FM, the final monograph four years later. In the final monograph, FDA reviewed about 10 studies submitted after the tentative final monograph and found the following active ingredients as GRASE for the treatment of athlete's foot.

FDA found all other ingredients considered in this rulemaking not to be GRASE for us in OTC topical antifungals. In addition, the final monograph includes labeling similar to that recommended by the panel in the Advance Notice of Proposed Rule.

All of the active ingredients listed here, they were indicated for the treatment of athlete's foot, as well as for the relief of symptoms. Only one product tolnaftate was also indicated for the prevention of athlete's foot. In addition, all these active ingredients were also indicated for the treatment of ringworm, tinea corporis, and jock itch, tinea cruris.

[Slide.]

As I told you, final monograph can be amended following its publication. FDA published a proposed amendment and subsequently, a final rule in August 2000 to modify the labeling of OTC topical antifungal.

This amendment added the word "most" to the indication statement between the introductory phrase and the name of the condition for which the product was to be used, for instance, cures "most" athlete's foot.

FDA recognized that OTC topical antifungals do not cure or treat all conditions commonly thought by consumers to be athlete's foot

or jock itch.

FDA also noted that varying percentages of subjects were clinically and mycologically cured of athlete's foot infection, therefore, inserting the word "most" in this case would give and help the consumers know what to expect from these products.

This is important since consumers self-select OTC topical antifungals, and do not diagnose. The Agency believed that this labeling should more accurately inform the consumers what to expect from using these products.

Also, FDA pointed out that this amended label is consistent with the current labeling approved for OTC vaginal antifungal drug products marketed under NDA. Since these are also topical antifungals with different sites of administration and for consistency, OTC labeling for this particular class should be the same.

In addition to this amendment, in February 2002, after reviewing approximately eight clinical studies submitted after the FM, FDA proposed to add clotrimazole as GRASE active ingredients for the

treatment of athlete's foot, jock itch, and ringworm.

[Slide.]

In summary, OTC drug monographs allow determination of safety and effectiveness of an entire therapeutic drug class.

OTC topical antifungal monograph lists GRASE active ingredients and labeling for OTC drug products that treat athlete's foot, jock itch, and ringworm, as well as prevent athlete's foot, because ingredients found GRASE for one condition is given the same GRASE classification for other conditions because of the similarity of these conditions.

From the data submitted the monographs, it is difficult to directly compare the cure rates for monograph and NDA drug products that treat athlete's foot because they were not directly comparable due to considerable variability in the study protocol.

Finally, by including the word "most" in the indication, we can say to consumers what to

expect from using these products and what to expect from them.

Thank you.

DR. CANTILENA: Thank you, Dr. Mahayni.

I guess we should ask that all depends what you mean by "most," but we will actually talk about that this afternoon.

Questions from the committee? Dr. Wood.

DR. WOOD: Well, that was going to be my question. "Most" certainly means, as you said, it is the last thing, it helps the consumer.

If I look at the slides in the last talk, on page 10, which of these studies support "most" in your view? On the Slide 19 on page 10, you added the word "most" because you felt that reflected the data.

Which of the studies specifically on Slide 19 do you think tell you that, or would tell me that?

DR. MAHAYNI: Actually, the word "most" was added because at the time, there was not a specific study, but because of the lower percentage

of cure rate for these ingredients, the word "most" was added to the monograph to indicate to consumers that it is not going to treat every clinical condition that will be presented.

DR. WOOD: Right, but "most" implies at least more than 50 percent, and most people I think would assume that it was closer to 100 than 50 percent. I don't think any interpretation of "most" implies less than 50 percent, does it? I mean is there a definition that you are aware of that implies that most people do something, implies less than 50 percent?

DR. CANTILENA: How about if we have actually Dr. Ganley answer the question, since he probably had more to do with that than Dr. Mahayni.

DR. GANLEY: This whole process started before I got to D.C., but I am generally accountable for it.

DR. CANTILENA: All right, there is the copout, so now you can answer.

DR. GANLEY: No, I accept responsibility for it.

I guess at the time, it is a rather complicated thing, is that it will treat most dermatophytes. Also, the thinking was that if you put just cures there without some qualifier, that people think that it is closer to 100 percent cure.

Now, "most" may not have been the appropriate adjective and maybe some other qualifying term, but I think that is one of the issues that we need to discuss, whether that really was a good idea and whether we need to revise the language a little bit. It gets back to how you convey information to the consumer as what their expectation can be, but I think I would acknowledge that it actually didn't accomplish what I think the original intent of the Agency was in that, to give some perception that it's not 100 percent cure, that it is something less than that.

I think if you look at the data for effective treatment and cures most, people will argue that effective treatment is a reasonable level of success also, and that generally is above 50 percent, so I mean you can discuss that today

and the logic, but I would acknowledge that it didn't solve the situation at all.

DR. WOOD: I guess there are two issues, does it cure and is it most, and I am thinking of this in terms of the treatment of heart failure. You know, it is perfectly legitimate to have a treatment for heart failure that is effective in most patients, but we probably wouldn't allow labeling that said it cured most patients, or HIV, or whatever it was we were treating.

I mean I think it is the juxtaposition of both that we need to be discussing.

DR. GANLEY: I think the difference I would argue there is that in heart failure, you are not going to cure the underlying condition, you are going to treat the symptoms and improve their survival potentially, you don't cure them of the disease, but infectious disease, you can cure people's disease, and that is where the difference is.

So, it does get a little tricky in how you are going to convey that information to the

consumer and what their expectation may be.

DR. WOOD: That is why I think it is important to have in the discussion, what the efficacy is for systemic therapy, because I think that was exactly my point earlier, where there is alternative therapy available that may have a very different efficacy rate, it is important then to revisit this to make sure that this provides some information that is at least contemporaneous for what the other therapies can do.

DR. CANTILENA: That is a very good point. We will have an opportunity this afternoon to discuss that further.

Dr. Lam.

DR. LAM: For the product to be classified as Category I, what type of cure are we talking about, are we talking about mycology cure or complete cure?

DR. MAHAYNI: No, Category I does not relate to actually cure, because most of these studies did not define the complete cure. The category is really reflected on what the

ingredients, Category I is ingredients that are seen as safe and effective, or generally recognized as safe and effective, and not misbranded.

But as far as cure rate, there were a variety of studies that had a different way of qualifying what is cure rate, and no way to compare them or say what is the cutoff rate for that.

DR. HOLEMAN: Matthew Holeman. If I could just sort of clarify real quick.

DR. CANTILENA: Okay.

DR. HOLEMAN: Basically, remember that most of the studies that these were based on were submitted to the Agency in the seventies, the late seventies, so the standards there were very different than our standards today.

So, as Houda pointed out in her talk today, there was a great variability in how these studies were designed, and some of these studies, I think the majority looked at just mycological cures. Some of them did include some clinical cure.

I don't know that any actually looked at

complete clinical cure, most of them were probably mycological, but it is really hard. There is a lot of variability in all these studies.

DR. CANTILENA: Dr. Fincham.

DR. FINCHAM: I just have more of a comment than a question. I think this is all very interesting, how we are deciding what cure means and what most means, but I guess at some point, we are all consumers, but I am concerned about the consumers that aren't in this room that see the advertisements for these products and see cure, they may not even look at most, but just see the word "cure" and make assumptions based upon that.

I don't expect anybody to have an answer to that, but it is a comment that I think we need to perhaps consider later.

DR. CANTILENA: Yes, I think we will have an answer this afternoon.

Go ahead, Mr. Kresel.

MR. KRESEL: I am sure that when the monograph was developed, there was probably debate over the terminology and what it should say, but

since the labeling doesn't define cure, and therefore I think it is very difficult for the consumer to really know what they are getting when it says "cures most," we might want to go back and talk about that debate between treats and cures.

DR. CANTILENA: Dr. Benowitz, the final question.

DR. BENOWITZ: Just a question about the GRASE criteria. For example, nystatin was not accepted as GRASE, so is that because of efficacy, or are there some safety issues with some of these products, as well?

DR. MAHAYNI: I don't recall for what purpose that was taken out of the GRASE category or classification.

DR. BENOWITZ: But just do you know, are there any safety issues for any of these products?

DR. MAHAYNI: For nystatin itself?

DR. BENOWITZ: No, just for the variety of antifungals. I know some probably don't work, but should we be thinking about any safety issues for any of these antifungals?

DR. MAHAYNI: For most what I have done for preparation of the advisory committee meeting, we focused on the efficacy. I didn't particularly look at the safety, I didn't go over what study was submitted to the monograph for safety purpose, because we were focusing here on efficacy rate, so I reviewed all the effectiveness studies that were listed in the monograph, so I can't answer your question.

DR. BENOWITZ: I am wondering if anyone at FDA has information about hypersensitivity or other safety issues involving these agents.

DR. CANTILENA: Dr. Ganley, does your staff have that?

DR. GANLEY: We can look for that, but I suspect that, you know, today, when we look at today, what we asked for in studies and what they may have looked at back in the seventies, there may have been safety information that looked at exposure, you know, to a group of individuals. It wasn't a specific study that would address that.

Today, there are irritation studies,

photocarcinogenicity studies, and a whole variety of different studies that may be asked of a topical agent, and John could probably address it better than I can.

But I would suspect that if you go back and look at that, it was basically data that was submitted about use in various populations, and there was no significant adverse effects.

DR. CANTILENA: We have a comment over here from Kresel.

MR. KRESEL: I was just going to say, because I am the oldest one here, and remember back then, there were very skimpy studies that were done, and there probably wasn't enough to really come to a conclusion, not that there was any particularly negative data and probably the sponsor didn't do an awful lot.

DR. CANTILENA: Thank you.

Did you have a comment, Dr. Bisno, that is related to this?

DR. BISNO: Just a comment which I will deal with slightly in my talk, which is if you look

at the 13 episodes that have been reported to the FDA, according to the information we got, about cellulitis related to these topical products, most of them, if you look at them, look like their hypersensitivity reactions someone got. They got it and then a day later they developed inflammation of some sort, it wasn't really compatible with what one would think would be a cellulitis.

So, at least in those very scanty reports, one would suspect that at least a number of them were actually hypersensitivity related in one way or another.

DR. CANTILENA: Dr. Katz.

DR. KATZ: In response to a previous question as far as nystatin, why that was excluded from the GRASE, I would assume that it was because it is in not effective, it is not effective for these conditions.

DR. CANTILENA: Dr. Schmidt.

DR. SCHMIDT: Ladies and gentlemen, you all are very lucky today, because you have somebody who is older than Dr. Kresel, and also we were

interested in these medications in the seventies, and actually, when I was a resident, I helped in some of these studies.

These studies, at least the ones we did, were very well done and I think, you know, as I recall, there were very few side effects with these different medications although some of these things, it seemed like the vehicles were almost as good as the medications.

So, I just want to say that you all are lucky.

DR. CANTILENA: We are very lucky. We have an investigator here, as well as an advisory committee member.

Dr. Whitmore.

DR. WHITMORE: With regard to contact hypersensitivity and such, I think the chemicals themselves are not big-time contact allergens by any means, and it would be more likely the excipient agents.

DR. CANTILENA: Thank you very much.

Our next FDA presenter is Dr. Shetty.

Topical Antifungal Drug Product Labeling

DR. SHETTY: My name is Daiva Shetty. I am a medical officer in the Division of Over-the-Counter Drug Products.

[Slide.]

My talk will consist of several different topics. First, I will briefly present some marketing and postmarketing safety data for topical and antifungal drug products. I will focus more in detail on labeling issues for this class of drugs and also provide some examples how we convey efficacy information to consumers.

[Slide.]

First, I will start with the marketing data.

[Slide.]

There are 11 active ingredients approved for tinea pedis indication through New Drug Applications for prescription and over-the-counter use. There are also, as mentioned earlier, 7 monograph active ingredients that the Agency found to be generally recognized as safe and effective.

Both prescription and over-the-counter products are widely used for the treatment of dermal fungal infections.

[Slide.]

The Division of Surveillance analyze the prescription and over-the-counter sales trends and drug use patterns for topical antifungals.

Two IMS health databases were used to gather this information, National Sales Perspectives and National Disease and Therapeutic Index.

[Slide.]

The first database, National Sales Perspectives, measures the volume of drug products, prescription and nonprescription, going from manufacturers into a market in terms of eaches. An each is IMS's unit of measure for single items, such as tubes, jars, or individual retail packages.

This database does not provide the demographics of consumers purchasing the drugs. It does not give the indication for use or the amount of drug actually used.

[Slide.]

This slide shows the National Sales Perspectives data for topical antifungals in 2003. Over-the-counter topical antifungal drug products accounted for over 20 million eaches, while prescription products accounted for around 16 million eaches in 2003.

This is somewhat surprising to us given that over-the-counter products are freely available to consumers for their purchase and use. Keep in mind that the sales data are for topical antifungal ingredients in general, and do not reflect the tinea pedis indication.

[Slide.]

Here is the table from the same database listing active ingredients, prescription and nonprescription, approved for the treatment of tinea pedis in terms of sales. We can see that monograph ingredients highlighted on this slide in yellow account for the highest volume sold.

[Slide.]

The second IMS health database, National

Disease and Therapeutic Index, estimates the use of drugs by collecting data on drug products mentioned, but not necessarily prescribed, during visits to a panel of approximately 2,000 to 3,000 office-based physicians.

These data are collected and projected nationally to reflect national prescribing patterns. It may include profiles and trends of diagnoses, patients, and treatment patterns. It does not, however, capture patients who self-diagnose and purchase over-the-counter drugs.

[Slide.]

My final slide on marketing displays data from National Disease and Therapeutic Index. The vertical axis shows the numbers of users, and the percentages of bar graphs reflect a fraction of all drugs.

In 2003, the most common agents recommended by a physician to treat tinea pedis were those listed on this slide, and all of them except for terbinafine are prescription products.

[Slide.]

In the second part of my talk, I will briefly summarize findings from the FDA's Adverse Event Reporting System. There is a full review included in your background packages.

[Slide.]

We requested the Office of Drug Safety to review all the adverse event reports received through the Adverse Event Reporting System for all topical antifungal agents focusing on two issues: lack of efficacy and cellulitis cases.

[Slide.]

There are certain limitations to these data. There are no adverse event reporting requirements for monograph ingredients. Therefore, reporting for those drug products may be significantly underrepresented.

The report gives only crude numbers for the active ingredients. That means that you don't have a denominator and cannot estimate the incidence of each report. Some ingredients are marketed in multiple formulations for several different indications which will not be reflected

in the report.

Finally, causality of what is the primary suspect drug in the report was not assessed.

[Slide.]

Given all the limitations, the search found a total of 4,741 reports for 15 active ingredients, of which the most common, 35 percent reported a lack of efficacy.

This is a very high percentage. In our experience, we don't usually see that a third of all reports would be associated with a lack of efficacy of the drug.

The majority of the lack of efficacy reports in AERS database were associated with these listed four ingredients, and the numbers in the package reflect year of approval of that particular drug in the U.S.

Given this high number of low efficacy reports, we worried if there are some consequences, such as missed or mistreated diagnosis.

[Slide.]

What we could do is search our database

for cellulitis reports. The Office of Drug Safety found 13 cases of cellulitis associated with those 15 topical antifungal agents.

Cellulitis in these 13 cases was reported as an adverse event, and was not a condition being treated. Although more cases of cellulitis were reported for terbinafine and miconazole, based on this small number of spontaneously submitted adverse event reports, we are unable to say that particular antifungal agents are associated with more or less cellulitis cases than other agents.

[Slide.]

More on the issue of cellulitis, you will hear later today presented by Dr. Bisno. I will summarize 13 AERS cases.

All 13 cases were diagnosed as cellulitis and were primarily of U.S. origin. The patients were using the antifungal agents for a variety of reasons, but tinea pedis is the predominant reason.

Cellulitis symptoms typically started one day after application of the topical agent, and the sites most often affected were the lower

extremities. One patient reported having diabetes and seven patients reported hospitalization.

Of the seven hospitalization cases, one patient was hospitalized for worsening Parkinson's disease, and cellulitis in this patient was diagnosed, but was not the reason for hospitalization.

The six remaining cases were for cellulitis, however, it was unclear in two cases that the cellulitis occurred before or after the administration of the antifungal agent.

[Slide.]

The last part of my presentation is over-the-counter labeling issues.

[Slide.]

There are three types of labeling for topical antifungal drug products: prescription labeling for prescription drug products and two types of over-the-counter drug labeling for monograph and NDA drug products.

Given the efficacy rates for this class of drugs and numerous consumer complaints on the lack

of efficacy, it is apparent that consumers may not understand that they may not achieve symptom relief or cure by the end of the treatment. Current labeling does not specifically communicate this message.

[Slide.]

I will start with prescription labeling. Information conveyed on prescription labeling is targeted at health care providers. It has detailed information on drug pharmacology, microbiology, preclinical and clinical data, indications, contraindications, warnings, and dosage and administration.

[Slide.]

This is an example of the indications and usage section on prescription labeling for topical antifungals drug products. The point of this slide is to show that at it lists specific conditions, that are in yellow and underlined, and specific fungi that particular ingredient is effective against.

[Slide.]

The Directions for Use Section in Prescription Labeling gives the duration of use for the particular product, for example, two weeks for tinea corporis or tinea cruris, and four weeks for tinea pedis.

[Slide.]

Expectations of treatment are also specified in Prescription Labeling. Sample of such a labeling is shown on this slide. If a patient shows no clinical improvement after four weeks of treatment, the diagnosis should be reviewed.

This information does not appear on patients' container labeling, and it is very dependent on a physician who is prescribing and giving instructions to the patient.

[Slide.]

The second type is labeling for over-the-counter monograph products.

[Slide.]

This is an example of over-the-counter drug facts labeling format, which appears on the carton of each over-the-counter drug. Labeling of

OTC monograph ingredients conveys indication in the Uses Section, which follows Active Ingredient Section.

There are two statements in the Uses Section on all monograph antifungal products.

The first is a required statement, and it states, "Treats or cures most athlete's foot."

The second is an optional statement, and states relieves or for relief of a list of symptoms, such as itching, burning, cracking, and scaling.

[Slide.]

Labeling for monograph ingredients specifies four week duration of treatment and directs the consumer to seek medical advice if symptoms persist at the end of the treatment.

Under the Directions Section, it states, "Use daily for four weeks, and if condition persists longer, ask a doctor."

[Slide.]

Also, the Warning Section states, "Stop use and ask a doctor if irritation occurs or if

there is no improvement within four weeks," which is the label duration of treatment.

[Slide.]

The third type of labeling is for over-the-counter NDA drug products. There are a few differences between the labeling of monograph ingredients and products marketed under NDAs.

[Slide.]

The Uses Section of NDA nonprescription product labeling is usually consistent with the Uses Section of the products marketed under the monograph except when conditions studied in clinical trials are somehow different.

For instance, if patients enrolled into clinical trials get only interdigital tinea pedis, this will be reflected in the Uses Section, as is shown on this slide, "Cures most athlete's foot between the toes, and effectiveness on bottom or side of foot is unknown."

The second bullet is also similar to optional indication statements as monograph ingredients.

[Slide.]

The Directions Section on the over-the-counter NDA drug labeling also reflects the treatment regimen studied in clinical trials. We have two types of over-the-counter antifungal drug products for tinea pedis approved under NDAs.

This is an example of product that is approved for four-week duration of treatment.

[Slide.]

This is an example of the labeling for product that is approved for one-week duration of treatment.

[Slide.]

The main difference between NDA and monograph product labeling is that NDA labeling does not specifically inform consumer about the time of expected outcome. The warning simply states, "Stop use and ask a doctor if too much irritation occurs or gets worse." There is no specific information on expected efficacy.

[Slide.]

Talking about efficacy, I would like to

show a few examples of over-the-counter labeling, how we convey this information to consumers.

[Slide.]

Most of over-the-counter products are indicated for acute symptom relief. Few have a lag time between the treatment initiation and completion, and the expected results. Efficacy rates usually are not presented on over-the-counter labeling, which few products have. If this information is present, it is presented in Drug Facts on the carton or in the package insert.

[Slide.]

One example is one of the newly-approved over-the-counter products that has a lag time between the initiation of treatment and complete response is omeprazole. The Uses Section and the Direction Section both state that it may take one to four days for full effect.

This information is included on the carton label, so consumers can read this statement when considering to purchase the product. The same information is included in the package insert.

[Slide.]

The next example is an over-the-counter product with the efficacy information is labeling for minoxidil. The following warning statement on the carton label is also available to consumers at the time of purchase.

Under the section When Using this Product, it states, "It takes time to regrow hair. Results may occur at two months with twice-a-day usage, and for some it may take four months to see results." The same information is included in the package insert.

[Slide.]

The last example is labeling for famotidine, which includes information about the efficacy rate of the product in the package insert. Two bar graphs demonstrate heartburn relief, prevention, or reduction for the drug product relative to placebo.

Because this information is in the package insert, it is not available to consumers at the time of purchase, and we don't know if consumers

reach this information at all.

[Slide.]

Today, we are seeking your advice. Should the following be in the over-the-counter topical antifungal drug label? Efficacy rates, time to symptom relief, expected time to cure, when to see a doctor, and whether ancillary measures to prevent tinea pedis, such as changing socks, wearing well-fitting, ventilated shoes, or cleaning showers should be emphasized on the label.

This concludes my talk.

DR. CANTILENA: Thank you, Dr. Shetty.

We have time for questions from the committee. Dr. Lam.

DR. LAM: I want to go back to the Adverse Event Reporting System data that you presented, specifically regarding the 35 percent lack of efficacy data.

Do you have information whether that was mostly associated with the one-week regimen, or the four-week regimen, or a combination of both?

DR. SHETTY: This is all, combination of

all.

DR. LAM: Okay. So, we don't even have a sense whether it is primary one week, because the data clearly showed that one week--

DR. SHETTY: We have more reports for one-week products. Maybe the reviewer for the database will answer your question.

DR. CANTILENA: Yes, there is a comment over here?

DR. PITTS: My name is Marilyn Pitts. Actually, for the lack of efficacy reports, because of the extreme volume, we were unable to look at those reports individually, so we don't know the duration of treatment. We don't know if's a one-week or four-week or three-week, or even if the patient used it once a day or twice a day. So, we don't have that information.

DR. LAM: I will say that if there is a way that we can get a sense, it will be important for us to consider some of the issues either this afternoon or tomorrow. There is no way to do that?

DR. CANTILENA: There probably are

thousands, right?

DR. PITTS: There are thousands, there is almost 1,700 reports. It takes a long time to even pull the images and then to go through and categorize and get that information. It is extremely time-consuming and difficult to get that.

DR. CANTILENA: You know, we have really about three hours before we come back after lunch.

[Laughter.]

DR. CANTILENA: There is a lot of FDA employees. It is not going to happen, Dr. Lam.

DR. LAM: Are we going to consider the question whether--in your executive summary, you indicated that some of the manufacturers are considering developing products of less than one-week treatment duration--so, are we going to consider that at all today or not?

DR. GANLEY: I think it is done in the context of understanding what the cure rates are or effective treatments that we see, and the lack of dose-response information.

In that context, if someone did a study

that showed three days of treatment was as good as one month of treatment, and they figured out what the correct concentration is, well, that is pretty good, I think.

The issue I think is we don't get that information. It is really what beats vehicle and what kind of study is done, and I think that is where the committee has to start addressing, you know, from a dose-response, and one of the questions actually addresses that.

I think that is the context, but I have no objection to have a one-day or a three, and we have had inquiries about a one-day treatment product. So, it is what is the bar that we want to set here, is it just that you beat vehicle or is it that we try to maximize the efficacy for consumers.

DR. CANTILENA: We have Clapp, Raimer, Schmidt, and Katz.

DR. CLAPP: This is just a question really based on curiosity. Because of the sheer volume of complaints you have had, or consumer complaints, what is the method by which a consumer's concern of

lack of efficacy gets to the FDA?

DR. MAHAYNI: Well, they just report like any other adverse event. It is actually a complaint, but they call to Adverse Event Reporting System.

DR. CLAPP: But how does the consumer get to the Adverse Event Reporting System? I don't think many physicians do it on this level.

DR. MAHAYNI: Maybe they call the number on the package and then it comes. I don't know they come to us.

MR. KRESEL: Can I comment because pharmacovigilance is part of my department, as well? They call the number that is on the bottle, and then we are required to report it to FDA.

DR. CANTILENA: And then FDA holds an advisory committee.

Yes. Did you have a comment about it?

DR. PITTS: Right, the Med Watch form is also available via the internet. There is also a 1-800 number. But I recognize that patients have to recognize that there is a system in place, and I

don't think the carton actually has that information specifically, because even for health care providers, to recognize there is a system in place where if you have a complaint about a product, then, you should call.

DR. CANTILENA: Thank you.

Dr. Raimer.

DR. RAIMER: I was just going to mention that most of the complaints were against agents that you could over the counter, so a lot of the patients probably had psoriasis or probably had eczema or probably did not have tinea in the first place, so there is no way to really judge whether the patient even had tinea to start with.

So, a lot of the complaints, they have similar symptoms, so it would be difficult to know what the patient really had in the first place.

DR. CANTILENA: So, you are saying there is a problem in the setting of an OTC, you know, self-diagnosis?

DR. RAIMER: Yes.

DR. CANTILENA: Well, that is another

issue that is not on our list of issues.

DR. PITTS: I am sorry, could I make a clarification? Actually, we believe that the reports for the over-the-counter products are underrepresented. If you look at the number of reports, the topical terbinafine and topical miconazole, those were previously prescription products, and if we were to probably look at that, we probably would see that most of those or some of those occurred more during the prescription process as opposed to the OTC process, so I don't have any idea.

DR. RAIMER: Even then, a lot of physicians do not do the mycology, they don't the KOH, they judge just clinically, so even then, I think a lot of those probably don't really represent tinea.

DR. CANTILENA: Dr. Schmidt.

DR. SCHMIDT: Before too long, I would like to address this about the cellulitis issue and get this on the table.

These case reports are real dogs, you

know, as far as cellulitis. I don't think any of these people had really an adverse reaction to any of these medications, and I don't think they were cellulitis. I think they were contact dermatitis.

There was one patient that had TEN probably from Enbrel, and I think to put this down as these 13 cases of cellulitis, this really needs to be brought up and discussed.

DR. CANTILENA: I am not sure what that is, but there is an opportunity right after our next speaker, we will be actually talking about the complications.

DR. PITTS: Can I respond to that? Actually, the prescriber or the reporter identified the cases as cellulitis, we did not make any judgment call in terms of whether they were cellulitis or not, but this was what was actually reported by the health care practitioner that submitted the report for those cases.

We are not making any judgment call as to whether or not they are good cases or bad cases. These are just the cases that were reported.

DR. SCHMIDT: Woof, woof, woof.

DR. CANTILENA: I think Dr. Schmidt has just made a judgment call.

[Laughter.]

DR. CANTILENA: Dr. Katz.

DR. KATZ: I wanted to reemphasize that we should keep in mind the likelihood that the reports of lack of efficacy must represent a minuscule, tiny minuscule portion of people who have lack of efficacy, because the average folks out there are going to use this for what they perceive to be, as Dr. Raimer said, tinea pedis, and it doesn't work. They think it says it should relieve symptoms, it doesn't work in two or three applications, so they stop using it, and they take it as a loss.

So, I wouldn't be surprised, if a survey was done at the 0.1 percent of reports you are getting.

DR. CANTILENA: Dr. Benowitz and then Dr. Alfano.

DR. BENOWITZ: It was striking to me that there was almost as many prescriptions by

physicians for topical antifungals as OTC uses, and my question is, is this for insurance purposes, or is there some evidence that the antifungals that are available by prescription only work better or why is this the case? It is very striking to me that there is such a huge volume of prescriptions.

I guess that question might be to my dermatology colleagues about why that is occurring.

DR. CANTILENA: Anyone? Comments from the Dermatology Committee?

MR. KATZ: Might it be that some of them were prescribed prior to its becoming OTC, for instance, clotrimazole has been OTC probably for, what, five or eight years, so maybe a lot of those reports were when it was prescription?

DR. BENOWITZ: This was 2003.

MR. KATZ: 2003. I would be very surprised because in recent years, we don't write prescriptions for that. We just write it for the patients to get it at the drugstore. We may write it down on a prescription, but without its being a signed prescription.

DR. SHETTY: Maybe the physicians are still used to prescribe or advice to use products that were prescription recently.

DR. SCHMIDT: May I comment just a minute? I think a lot of this, I don't really write for prescription topical antifungals anymore. You know, the majority of them, they may have a funny name, but they will have the medication that is a prescription, but I think a lot of this is marketing by some of the drug companies.

I think, to me, there are a lot of people who will still write prescriptions for things, and I think a lot of it is a marketing effort by the drug companies.

DR. CANTILENA: Other comments?

DR. WOOD: As I understand this, we don't know that this is OTC, do we? I mean the Rx's may well be for systemic antifungals for this indication.

DR. SHETTY: Only topical antifungals.

DR. WOOD: Are you sure? Are you sure of that?

DR. SHETTY: Yes. We took out the systemic and we took out some ketoconazole.

DR. WOOD: So, the 15.7 million prescription were eaches for itches, that were all topical, is that right?

DR. SHETTY: Yes.

DR. GANLEY: I think that it was pointed out that we can't separate out, particularly for the prescription, which ones were for other conditions other than tinea pedis, and even for the OTCs, there is other claims. I think tinea pedis, of the three that are over the counter, is probably the most common, but that is the difficulty.

But is it a little surprising I think when you see the percentages here or the number of eaches for each. I think what is interesting, too, is if you look at the National Sales Perspective, which was Slide 8, the Clotrimazole and betamethasone was the highest there in the number of eaches.

But if you look at Slide 10, only 12 percent of those prescriptions accounted for tinea

pedis, so the 90 percent of those, you would have to assume then were related to other conditions where if someone saw a rash, didn't know if it required an antifungal or a steroid, so they gave them the combination product.

So, it is difficult data to look at, but it is the best that we can do with it.

DR. CANTILENA: Thank you.

Did you have a comment, Dr. Whitmore, on this topic?

DR. WHITMORE: I was going to agree with Dr. Schmidt as far as why prescriptions are written for prescription antifungals. Marketing definitely is a big one, and the pharmaceuticals will come out with studies where they have certain efficacy rates in their control study or whatever, which is better than X drug.

Also, oftentimes patients will have used their clotrimazole for two or three days or whatever, a short period of time, come in to the physician and say I am not better, so a prescription is written for something else.

DR. CANTILENA: Dr. Alfano.

DR. ALFANO: Dr. Shetty, your Slide 12, you said you searched the AERS data as of March 16th. What is the start date on that data?

DR. SHETTY: All the reports that were received.

DR. ALFANO: So, this is all reports like in the history of man? I guess my point is so we saw 20 million eaches, whatever that translates to in terms of treatments, just for the year of 2003, so we are talking about tens of millions, if not hundreds of millions, of doses, treatments in this database for a condition for which the previous data presented said 40 percent of people who present to hospitals have the condition and 15 to 70 percent of free-living Americans have the condition.

So, I guess the trouble I am having is, you know, the perception that this is such a large database, it actually seems to be a very tiny database relative to the number of individuals who have the condition and who have treated the

condition.

DR. PITTS: If I can respond, the AERS database, this is all reports in the database for those agents, for the topical agents, and we know that there is a significant amount of underreporting that occurs between recognizing that there is an adverse event and then having that person report it.

With the topical agents, I would suspect that there is even less of a reason for people to draw a correlation, but there is a different time period where they came on the market, so it is really for all the ones that we have for the life that we have, but these are two different databases between the drug use data and the adverse event databases. Those are different databases.

DR. CANTILENA: Dr. Katz.

DR. KATZ: I just want to clarify something. What was mentioned, the over-the-counter products are being prescribed, were you referring to page 5 of this last presentation, where in 2003, most physicians

recommended antifungals for tinea pedis, is that what you were referring to?

DR. BENOWITZ: No, what I was referring to was actually Slide 7, just showing the volume.

DR. KATZ: What page is that?

DR. BENOWITZ: Page 4, I was just referring to the volume of prescribed topicals.

DR. KATZ: That doesn't mean prescribed, number one.

DR. SHETTY: No, this is all in terms of eaches, whatever goes from manufacturer into the marketplace.

DR. KATZ: That is not prescribed.

DR. SHETTY: That is not prescribed.

DR. KATZ: And on page 5, where it says "National Disease and Therapeutic Index 2003"--

DR. SHETTY: This is a different database.

DR. KATZ: That is physician recommended.

DR. SHETTY: That physician mentioned during the visit.

DR. KATZ: That doesn't physician prescribed.

DR. SHETTY: No, that doesn't.

DR. KATZ: So, we should have that straight, because frequently, we will write--not frequently--always we will write if we want patient for tinea pedis to use clotrimazole, miconazole, we will write on the prescription, for patient to remember, so we will write on the prescription without signing it, without the patient's name on the top, just so they remember.

That is physician recommended. That includes not OTC, because Clotrimazole/betamethasone is not OTC, I don't know what Naftifine is, so I think that may have been the source of confusion.

DR. GANLEY: I just want to clarify, on that Slide 10, for the National Disease and Therapeutic Index, that could have been OTC or prescription.

DR. SHETTY: Right, Butenafine is nonprescription.

DR. GANLEY: Right, so it does suggest that the Ciclopirox, which I think is the Rx drug,

is the most prescribed for tinea pedis. You would have to think that if that is a prescription drug, and that is the most recommended, that they actually prescribed it. That's the only thing I can take away from it.

DR. CANTILENA: We have a final comment over here from Mr. Kresel.

MR. KRESEL: I was just going to comment on the AERS database again and that is what then you look at a class of drugs that doesn't have a significant serious adverse event profile, it is not uncommon then to see that the most common consumer complaint would be lack of efficacy.

My experience in getting consumer complaints is that consumers learn early on that if they call the sponsor and complain that their product didn't work, they will get a refund.

DR. CANTILENA: That certainly is an incentive, and I think we all have an incentive to take a break. We will return at 10:30.

[Break.]

DR. CANTILENA: Our first speaker for

after the break here will be Dr. Alan Bisno from the University of Miami, School of Medicine, infectious disease complications of tinea pedis.

Infectious Disease Complications of Tinea Pedis

DR. BISNO: Good morning. My assignment this morning has been to discuss the relationship of tinea pedis and cellulitis of the lower extremities. I am embarrassed to do this because, as I am going to tell you in a little while, there is much more that we don't know than what we do know about this particular subject.

What I am going to do is start off with some introductory remarks about the epidemiology and nature and clinical nature of cellulitis in general, the problem of recurrent cellulitis and its control, and then go on to discuss in more detail what data there are available on tinea pedis and cellulitis of the lower extremities.

Looking around this august group at the table, I know that I am bringing coals to Newcastle for most of you, but I have to apologize for that.

[Slide.]

First of all, what is known about the factors that predispose to lower extremity cellulitis, because certainly, tinea pedis is not the only one, and there is sort of two groups of factors that are known to predispose.

First, is anything causing cutaneous disruption, trauma or surgery, burns or ulcers. Varicella is an interesting one, it is not limited to the lower extremities obviously, but pediatricians have known and infectious disease people have known for many years that children who get varicella may often get secondary cellulitis and even life-threatening bacteremias due to streptococcal infection of the varicella, so it's a good reason to have children immunized against varicella.

Then, there is dermatophyte infections of all kinds, so cutaneous disruption is one issue, and then there are systemic factors that also predispose to cellulitis including lymphedema and venous insufficiency, obesity is a major risk factor, as I will discuss, ischemia, IV drug abuse.

Obviously, we see lots of cellulitis in individuals who are parenteral drug abusers, both IV and skin poppers, and then immunosuppression.

So, all of these are factors predisposing to lower extremity cellulitis.

[Slide.]

This is a typical case of cellulitis. I don't know how well it shows here, but it is a diffuse inflammatory process involving the skin and subcutaneous tissues, and if this projects well enough, which in this lighting it might not, those of you who may be able to see that it is occurring along the site of a saphenous venectomy which was performed for coronary artery bypass grafting.

[Slide.]

Erysipelas is a little bit different. This is one of my patients with erysipelas, and it involves the more superficial areas of the skin, such that the lymphatics are greatly involved, and this leads to some of the special features of erysipelas, namely, that it is raised above the surrounding area, unlike the cellulitis that I

showed you in the last slide, and that unlike cellulitis, there is a sharp demarcation between the involved and the uninvolved area.

[Slide.]

I just show this picture of classic facial erysipelas, which isn't really pertinent to what we are discussing today, simply to mention that nowadays, more and more, we don't see erysipelas in that area, but we do see it in lower extremities, as shown by this patient.

You will have to accept my word, because of the lighting in here, that this is raised and well demarcated, and it is a case of erysipelas of the lower extremities, also happens to be one of those in the post-saphenous venectomy group.

[Slide.]

Sometimes this goes on to more extensive problems. These bullae and vesicles with dark-colored material in them don't necessarily mean that there is going to be an adverse outcome, but they are very worrisome in terms of the possibility, to me, they signify a lot of local

toxin production, and some patients with cellulitis do go on to have deeper tissue infection which can even be life-threatening.

I have taken care of one patient recently who has had three episodes of cellulitis, an obese, homeless patient with severe tinea pedis who had been in the intensive care unit three times, twice in shock, because of this kind of a problem.

[Slide.]

Well, the microbial etiology of erysipelas and cellulitis differs a little bit in that classic erysipelas, when you see the man that I showed you in the first slide, this is virtually always due to beta-hemolytic strep, mostly Group A, but now always.

But the terms cellulitis and erysipelas are often used interchangeably, particularly in the European literature, so many of the studies that I quote or that you will see talk about erysipelas, and they say erysipelas and cellulitis interchangeably, and you can't really tell whether they are talking about erysipelas or cellulitis.

In truth, that is not such a big deal because many cases are not so clear-cut as the examples that I have shown you, and it really is not always possible to classify it as one or another.

The only reason I bring it up is because although classic erysipelas is virtually always beta-hemolytic strep, cellulitis can be due to a wide variety of organisms. The list of organisms that can cause it is extremely long, but that is for another session.

But in most cases, nevertheless, the vast majority of cases are due to beta-hemolytic strep or Staphylococcus aureus. When you see typical lower extremity cellulitis with diffuse spreading erythema, and not localized pus, that is usually not staphylococcal, it is usually to beta-hemolytic strep, but not necessarily Group A. It can be A, B, C, or G.

[Slide.]

It is important for us to discuss recurrent cellulitis because this is an important

issue in relationship to what we are going to be talking about in terms of tinea pedis.

Many patients with episodes of cellulitis experience recurrent attacks. The percentage of patients in whom this occurs is variable depending upon the risk factors.

DeGodoy and associates did a study of a large number of patients, and did lymphatic scintigraphy on these patients and found that 77 percent of such patients had abnormalities of lymphatic drainage on scintigraphy, and it is believed that lymphatic drainage is progressive with recurrent episodes, thus exacerbating the problem, so we would really like to prevent recurrent cellulitis.

[Slide.]

I am going to show a couple of slides on antimicrobial prophylaxis of recurrent cellulitis for a couple of reasons. The first is that we will get some idea of the baseline rates of recurrence, and the second is that since control of tinea pedis is one of the things we are going to be discussing

today, that is only one method of preventing recurrent cellulitis, and now you have taught me this morning that most of these things don't work anyway, so I have to look at alternative ways to try to prevent recurrent cellulitis.

It is generally written in the literature that patients who have frequent episodes of recurrent cellulitis should be put on continuous antimicrobial therapy to prevent this. Many of you who practice dermatology in this group may have run into this issue, but it is surprising how little real data there are and how marginally effective such antimicrobial prophylaxis is.

For instance, in this study by Wang, et al., 31 patients with definite or presumptive streptococcal cellulitis of the lower extremities were treated with monthly benzathine penicillin G injections, and 70 patients who declined and 14 who received incomplete prophylaxis served as controls.

The recurrence rate was 12.9 percent in the treated patients and 19 percent in the controls, which wasn't statistically significant.

Interestingly enough, benzathine penicillin G was spectacularly effective in reducing recurrences in patients who didn't have any predisposing factors, but not in those with predisposing factors.

I have a hard time interpreting this study since the patients I see with recurrence all have predisposing factors. One predisposing factor they didn't mention in the study, however, was tinea pedis, and that may have been a major unrecognized predisposing factor in this particular study.

[Slide.]

Here is another one of 40 patients with venous insufficiency or "lymphatic congestion," who had suffered two or more episodes of erysipelas during the previous three years.

Twenty patients received oral penicillin or erythro for a median of 15 months with two recurrences versus 8 in 20 untreated controls. That is 40 percent, that is pretty impressive to me, but the p-value is only 0.06, and the authors themselves concluded that continuous prophylaxis is

indicated only in patient with a high recurrence rate.

There are other things you can do in these patients, such as giving them a prescription of antibiotic to have in their pocket in case they have the earliest signs at onset, they can frequently truncate the attacks.

[Slide.]

With that introduction, let's talk about tinea pedis and lower extremity cellulitis. Here, I am really on very shaky grounds, because I am an infectious disease person, I am not a dermatologist, and I am going to quote some dermatologic literature, and it may or may not be current, so you guys can please straighten me out in the discussion period.

I am quoting at least authority in the person of Dr. Albert Kligman, who published back in the 1970s the following: that the recovery of fungi decreases as athlete's foot becomes progressively more severe; that aerobic microflora expands as the disease becomes more and more

serious.

Athlete's foot represents a continuum from a relatively asymptomatic, scaling fungal eruption to a symptomatic, macerated, hyperkeratotic process that results from the overgrowth of resident organisms if the stratum corneum is damaged by preexistent fungi.

Overgrowth of the same organisms in normal, fungus-free interspaces does not produce lesions.

[Slide.]

In a more recent review in the Clinics in Podiatric Medical Surgery in 1996, the author made many of the same points.

With progression of the process of dermatophytosis, the normal protective skin barrier becomes macerated and friable.

As the process continues, the skin becomes debilitated and weakens as an effective barrier against infection.

Fissures may occur, providing a portal of entry for any opportunistic organism in the area,

resulting in cellulitis.

[Slide.]

Let's get on more specifically to tinea pedis and lower extremity cellulitis.

This really dates back to the earliest studies that were published about saphenous venectomy and coronary artery bypass grafts and cellulitis.

The first of the two studies that were published was that by Greenberg, et al., from Dr. Roman Kasankosis' group, and my own study with Dr. Larry Baddour, who was a fellow of mine, is now a professor at the Mayo Clinic, in the Annals of Internal Medicine in 1982. I am not sure, sir, of you were the editor in 1982, but if you were, thank you for accepting the paper.

Anyway, the initial studies focused upon patients who had undergone saphenous venectomy, and many of these infections were due to non-Group A beta-hemolytic streptococci, often B, C, or G, to the extent that you could get them. In most cases of cellulitis, as you know, you don't get a

microbiologic diagnosis.

[Slide.]

Of these two studies, Greenberg, et al., really have precedence in terms of the tinea pedis issue because they described 9 men, age 48 to 72 years, who developed cellulitis in the saphenous venectomy extremity. Five of the 9 patients had recurrent episodes.

The first infection was within 8 months post-op in 8 patients, but one was 8 1/2 years later. I should interject here that actually, as we have had more experience with this, these things happen frequently months and many years afterwards. It is something that the cardiovascular surgeons never recognize because they don't see those patients at that point.

Positive blood cultures in that study, in one patient, yielded beta-strep which weren't further characterized.

All 9 had mild to severe tinea pedis of the involved leg, and they state there were no recurrences after aggressive topical or oral

antifungal therapy. That is all the information that is given, so we don't know how long it was given, how long it was followed, and that sort of thing.

[Slide.]

Dr. Baddour and I went back to our original studies and looked at our patients again, and we detailed 9 patients with post-CABG cellulitis, 5 of whom experienced from 2 to more than 20 recurrences.

At the time were reported this in the 1980s, it is amazing that clinicians were not recognizing this as cellulitis. They were frequently thinking it was some sort of a deep venous thrombosis, and people were anticoagulated and all kinds of other things were done to them, so they ended up having many, many recurrences.

But anyway, 7 of these patients had tinea pedis, and in 2 instances, control of dermatophytosis was associated with cessation of attacks. I have to admit to you I can't remember now, 20 years later, how long we followed these

patients, and they are only 2, so I am guilty of the same thing that I critiqued the last study for.

[Slide.]

Now, more recently, Dr. Semel and Goldin picked up on our work and did something very interesting, and their paper I think is included in the packet that you have. They studied 20 patient with lower extremity cellulitis, but they excluded patients with trauma or peripheral vascular disease or chronic leg ulcers. I am not sure why, but I suspect that those particular conditions are more likely to be associated with staphylococcal than with streptococcal infections.

Anyway, they found athlete's foot present in 20 or 84 percent of the 24 episodes studied. Beta strep were isolated from ipsilateral two web spaces in 17 or 85 percent of the 20 cases.

Then, they took 30 controls seen in a dermatologist's office for treatment of athlete's foot, but without cellulitis, and not a single one of them were they able to recover beta strep. So, they concluded that only beta strep are recovered

more frequently from patients than controls

[Slide.]

Now, I am going to quote a few other studies are less informative, but the literature is spotty in this regard.

Thirty Venezuelan patients with erysipelas were reported, who were in otherwise good health. Forty-three percent of them had tinea pedis and in 7 of 30 or 23 percent tinea pedis was found to be the unique predisposing factor, but there were no controls.

Again, I don't know what the base prevalence of tinea pedis is in Venezuelan patients, is it 43 percent or is it 10 percent. I don't have that information.

[Slide.]

Koutkia, et al., did a prospective but uncontrolled study of 62 hospitalized patients with cellulitis, and they identified a large number of possible predisposing factors here. You can see that tinea pedis was present in 32 percent. Again, with the data that we have presented this morning

where the range of tinea pedis in normal populations can be 15 to 40 percent, is that a true association or not? Again, it's an uncontrolled study.

Interestingly enough, fully a quarter of the patients in their study were studied as post-CABG patients.

[Slide.]

The best study to date so far is the Dupuy, et al., study, and this is a case-controlled study of 167 patients hospitalized in 7 French hospitals for lower extremity cellulitis, and they compared it with 249 hospitalized controls.

In a multivariate analysis, significant risk factors were disruption of the cutaneous barrier, such as ulcer, wounds, or dermatosis, lymphedema, venous insufficiency, leg edema and overweight.

I should mention again obesity is a very powerful risk factor. We just completed now a prospective case-controlled study of patient with recurrent cellulitis in which we found BMI was a

highly strong predictor of cellulitis. It was statistically significant with recurrent cellulitis.

But at any rate, in Dupuy's study, toe-web intertrigo was present in 66 percent of patients and 23 percent of controls, for an odds ratio of 6.6, and toe-web intertrigo was a strong risk factor, an odds ratio of 13.9 with a population attributable risk of 61 percent.

[Slide.]

I had a slide on the FDA adverse event reports, but I am not going to beat this dead horse since Dr. Schmidt has already woofed it to death, so I am not going to say any more about that.

[Slide.]

What are the unresolved issues that we have to deal with? What is the risk of normal individuals with tinea pedis developing cellulitis at some time in their life? We don't have any information on this whatsoever that I am aware of.

Does the magnitude of risk justify a warning? Certainly, if we don't know the magnitude

of risk, we really can't say whether it justifies a warning, but I think the risk in normal individuals with tinea pedis has got to be extremely low. Again, we might have to stratify that as to what kind of tinea pedis are we talking about, are we talking about the kind of things we saw in the first slides with minor scaling, are we talking about really macerated toes, which I think may be an entirely different level of risk.

Are the beta-hemolytic strep strains recovered from between the toes of patients with tinea pedis and cellulitis, such as those by the Semel and Goldin study, are those truly organisms responsible for cellulitis? We don't know that. I am unaware of reports of the same strain being recovered from toe cultures in cellulitis during a single attack of cellulitis, none in the literature that I know of.

I personally have a case where I have recovered strep over about 10 years, three times, from a patient with tinea pedis and cellulitis, and looked at the M proteins under PCR, and, indeed,

this is the same strain over and over, but was never recovered during the time of his acute illness. Usually, these patients get whopped on antibiotics as soon as they get in, and you don't get positive cultures often from between the toes, so that is an unresolved issue.

Another issue, unresolved issue, which I didn't put on this slide, is do we really have any idea whether treating tinea pedis will actually prevent recurrences. I have given you all the data I know, and there are a couple of articles with observational data on a very small number of patients.

Here is what we really need to do. We really need to have a controlled trial of patients with athlete's foot to look at, in this controlled fashion, those who are well treated and those who aren't treated in terms of the incidence of cellulitis.

But let's think about how you accomplish that. Obviously, in the general population, the incidence is so low that you would have to study

thousands and thousands of patients for months to years, so you are not going to be able to do it.

So, the best one would be patients with recurrent cellulitis. There, you might have a chance, particularly with people with frequently recurrent cellulitis. Then, you could have a controlled trial of treating the tinea pedis of patient with recurrent cellulitis and tinea pedis, and not treating it in another group of recurrent cellulitis and tinea pedis.

You may have little problems with the Human Utilization Committee, but even if you could get it through there, you would only be studying probably one therapy or one therapeutic regimen. Again, you people have told me that half the time it is not going to work anyway, so I don't know how you can study this problem in a really effective manner, but certainly that is the kind of information we need and we don't have.

[Slide.]

So, what are the issues for the committee at this point? Tinea pedis is only one of a number

of risk factors for the development of lower extremity cellulitis, but one thing about it, it is one of the most modifiable of those factors, at least I thought it was before I walked in this room today.

Now, the committee might wish to add a caution about the importance of eradication of tinea pedis in patients with such risk factors as lymphedema, venous insufficiency, edema of the legs, marked obesity, saphenous venectomy, or for CABG, or previous episodes of cellulitis.

So, I would say that if you are going to do anything at all, the best you could do, at least in my humble opinion, is to put In at least a warning about the importance of assiduous treatment of tinea pedis in patients with these established risk factors.

Thank you very much.

DR. CANTILENA: Thank you, Dr. Bisno.

Questions from the committee for Dr. Bisno? Yes, Dr. Epps.

DR. EPPS: I don't know whether it is more

of a question or a comment. Within the differential of a web space tinea pedis would be erythrasma, which is actually a bacterial infection.

DR. BISNO: Corynebacterium minutissimum.

DR. EPPS: Right.

DR. BISNO: I recently had a bacteremic patient with that, interestingly enough.

DR. EPPS: I wondered whether some of these cases of cellulitis, whether, in fact, they had tinea, whether they had erythrasma, and perhaps that could be an confounding issue.

DR. BISNO: I guess so, but look at the prevalence in the population of tinea pedis versus erythrasma. I think there has got to be a magnitude of order difference. I may be wrong about that, again, I am not a dermatologist.

DR. CANTILENA: Dr. Schmidt.

DR. WHITMORE: Dr. Bisno, I had a question for you regarding strep colonizing the skin. It is not going to do that unless the integrity is disrupted, is that correct?

DR. BISNO: I am sorry?

DR. WHITMORE: Strep is not going to be growing in the skin unless the integrity of the skin is disrupted.

DR. BISNO: We used to think that, but it is not entirely true, and the way that we know that is in studies of children, underprivileged children with poor personal hygiene in areas where there is a lot of streptococcal pyoderma, and the studies by Wannamaker and Digianni and their associates in Minnesota many years ago showed that in those circumstances, you do get colonization of the skin with the pyoderma types of streptococci and then presumably due to trauma, abrasions, or insect bites, it gets converted into pyoderma.

So, at least in certain instances, it could colonize normal skin, but generally, I think in general the answer is you wouldn't expect that to be part of the normal flora in a population of people who weren't underprivileged or who were able to maintain normal hygiene.

DR. WHITMORE: The only reason I ask that

is because if that were true, which apparently it is not, then, we could select out patients who have disrupted skin, who are then actually put at risk for cellulitis because of their tinea, such as cracking in the web space or vesicular bullous on the foot where there is disruption.

DR. BISNO: That is a possibility. I mean it seems to me that even with those strictures, you are going to be treating an awful lot of people. Of course, you would be treating those patients anyway, so I guess that would be fine, you would be wanting to do that anyway.

DR. SCHMIDT: My clinical impression is that treating these things does help the tinea, but the biggest problem that we see clinically, at least in Houston, is many of these people are these massively obese female who are completely immobile, and I don't really think that these people who have these recurrent cellulitises, at least in my experience, really live that long, you know, that there is something else that kills them, usually the obesity.

I have one other question. When you said obesity, you used the term--in Texas, we use TDF, too damn fat--but you said DMI.

DR. BISNO: Body mass index.

DR. SCHMIDT: Oh, that sounds a lot better. Thank you.

DR. CANTILENA: We should probably strike that from the transcript, just so we don't get in trouble with Texas.

DR. BISNO: I think you have identified one group, that is for sure, but there are lots of other people who don't have those, particularly saphenous venectomy group, people who have had, let's say, nodal dissections for cancer and have chronic lymphedema.

There are a number of other factors, and another area that we are seeing a lot of problems with, as I alluded to in one of the case discussions is the homeless, because they are out there, they can't really maintain good personal hygiene, they have horrible feet, and they are at risk for this, so I think that obese, and I

wouldn't necessarily--I don't know about the sexual predilection for obesity, you know, we see obese men, too--and I work at the VA a lot.

At any rate, I think obesity is certainly a major issue, but I don't think it's the only issue.

DR. CANTILENA: Yes, Dr. Davidoff.

DR. DAVIDOFF: One of the predisposing factors that is not on your second slide is diabetes, and yet, as a former diabetologist, I was a little surprised because certainly one of the great concerns of diabetologists and podiatrists is foot infection. Perhaps you could comment on that.

DR. BISNO: Where something like controlled studies have been done on this, as in the DuPuy study, and actually even in our prospective case-controlled study, a lot of things you can't see in hospital records, but diabetes you certainly can, and it hasn't emerged as an independent risk factor.

So, yes, I agree, I am always worried about diabetes, and I am always worried more

staphylococcal and streptococcal infections, but nevertheless, I was careful not to say that because I don't have the data to back it up.

DR. CANTILENA: Go ahead, Dr. Fincham.

DR. FINCHAM: I was also curious about that because you did reference the Koutkia article that listed 50 percent diabetes.

DR. BISNO: That is the percentage in the general population. I mean yes, I think we all have a feeling, a gut feeling that diabetes is a bad thing for infection and for the feet, but in terms of these kinds of infections, I don't have a chapter and verse to be able to state that.

DR. CANTILENA: Thank you, Dr. Bisno, a very excellent presentation.

Our next speaker this morning would be Dr. Ghannoum who is from Case Western Reserve University talking about the microbiology aspect.

Microbiology and Dermatophyte Resistance Related to the Treatment of Tinea Pedis

DR. GHANNOUM: Good morning, everybody, and thank you for inviting me to participate in

this session.

What I am going to try to talk to you today is about really the knowledge we have as far as antifungal susceptibility is concerned. Again, this is really a new field, and I am going to present to you a lot of the data which was generated in the last, I would say five or so years.

[Slide.]

I thought I would put my conflict of interest at the beginning. I direct the Center for Medical Mycology and I would say the vast majority of companies that do work with antifungals, we work with them as part of grants and contracts.

Also, I act sometimes as consultant and speaker's bureau member for different companies, so it is not like one particular company, and I thought I would point to some of the relevant companies which we had grants, contracts, or speaker's bureau listed here.

[Slide.]

Let's talk now about antifungal agents and

resistance. As you know, in recent years, there are a number of compounds which have been introduced to treat fungal infections, and these are quite efficacious compounds, they work very well including the classes of allylamines and azoles, and really this is very, very good news as far as treating superficial infections.

However, like with the introduction of any antimicrobial, the likelihood or the potential of resistance development is there.

This has been very clearly illustrated when we look at systemic infections particularly with Diflucan or fluconazole when it was introduced.

[Slide.]

I did a literature search, just to give you an idea when resistance usually occurs. I did a Medline search when the drug is introduced, and then a number of papers on resistance that came out after an introduction of the drug. You notice like, for example, 5FC was introduced around here, then, you see this is the total papers on

antifungal resistance increases.

The same, you put miconazole, ketoconazole, again, you see the blips, and fluconazole or terconazole, again, you can see I would say resistance is reported about two years after the introduction of new antifungal agents.

However, most of these studies I focused on are systemic antifungals, because really we don't have many papers, actually, we have nearly none that address this issue.

[Slide.]

I want now to focus a little bit on the dermatophytes. In spite of the wide clinical use of topical antifungal agents, also agents to treat dermatophytosis, very little data is available on the antifungal susceptibility, as I just alluded to.

This is possibly due to the fact that we really do not have a method, which is reference method documented that can measure antifungal susceptibility, and this is not a surprise. We had the same situation with systemic antifungal agents

for 30 or 35 years.

We only had amphotericin B, so you really don't need to do this, however, when we start seeing the new agents, then, there was a need for developing a method, and the same thing is true when we talk about the topical antifungals.

Griseofulvin was the one and now we have the classes of compounds that are also there. Because of this, there is really a need to develop a method.

[Slide.]

With that in mind, what we did in my group at the Center for Medical Mycology in Cleveland, in 1998, we started to put a program to develop a method for measuring antifungal susceptibility.

The compounds which we focused on are to dermatophytes. These are the compounds which we focused on - terbinafine, griseofulvin, intraconazole, and fluconazole.

[Slide.]

As a result of this program, we published two papers on them, Norris, et al., and Jessup, et

al. In these articles, we were able to determine that optimal conditions for doing antifungal susceptibility. The method is microdilution method, what type of media used, the inoculum, really all what you need if you want to do the proper antifungal susceptibility as dermatophytes are concerned.

Once those papers are published, I am a member of the NCCLS, the National Committee for Clinical Laboratory Standards, I was asked to really head the group to develop antifungal susceptibility to the dermatophytes.

[Slide.]

Under the auspices of the NCCLS, we did a number of studies. The first one was a intra- and inter-laboratory multicenter study to determine whether the developed method is really reproducible by other people in a way to try to form a document for that.

Also, currently, we are conducting a quality control study to define some organisms, so that labs, when they want to do this, they have

their QC isolates and they will be able to really know that the method they are performing is the right one.

This is in preparation for our next meeting in January 2005. That is when the NCCLS for antifungal agents meet. We hope to have all this method approve and become part of the document M38.

[Slide.]

Once the method was developed, we started asking the question is there a resistance issue as far as dermatophytes are concerned. With that, we, at the Center, we started really monitoring the antifungal susceptibility of dermatophytes.

We had a number of dermatophytes. We collected isolates where they come from different sources. We had a set of isolates, sequential isolates obtained from patient with onychomycosis. They were enrolled in part of the clinical trial.

We had routine clinical specimens. Our lab received specimens from about 400, 500 physicians, where we identified isolates through

KOH, and this sort of thing, so we collected those also.

We were the central lab for clinical trials for some topical agents, also those organisms, and finally, we did a couple of epidemiological studies, one on onychomycosis and one recently in tinea capitis, and we collected also those isolates. These have been published in the American Journal of Dermatology, and this one also.

In total, we have over 2,000 isolates which we tested.

[Slide.]

I am going to share with you some of the data we collected over the last few years.

This is the dermatophytes which we collected from epidemiological studies, the two epidemiological studies that we mentioned. This is the organism, rubrum, mentagrophytes, tonsurans, and canis, and this is the number of each species, in total 117 isolates were collected.

This is the terbinafine susceptibility,

and you can see this is the MIC in microgram per ml. It went from less than 0.001 to 0.004, and you can see really 95 percent of the isolates were inhibited by 0.002 micrograms per ml, so it is quite good activity.

[Slide.]

This is the same isolates. We looked at fluconazole, who did it do. Again, you can see this is a broader range really of MICs, but I would say the vast majority could be inhibited from here to here, 0.5 to 4 micrograms per ml.

A few isolates had I would say susceptible dose dependent sort of MICs, two and four of them had 16 or 32 micrograms per ml.

[Slide.]

We looked at itraconazole. Itraconazole did I think the same, a good job. The vast majority of organisms are inhibited within this range. We had got 7 and like 8 isolates, 0.5 and 1, which usually at least in the yeast area, because we had developed breakpoints, you would say maybe you suspect a little bit resistance, but this

is a very, very big maybe, because we don't have breakpoints developed for dermatophytes.

[Slide.]

Now, this is for griseofulvin. Again, these are from the epidemiological studies, and you see the vast majorities are quite susceptible and they responded well.

[Slide.]

Now, I move into some isolates which we got from the clinical trials, so really some of them saw patients, others did not see patients or the epidemiological part.

The same picture could be painted. You can see here for terbinafine, again look at this. Really, the vast majority are within what we expect.

[Slide.]

This is fluconazole. Again, we see the same sort of susceptibility. There is nothing that is up there.

[Slide.]

With itraconazole, the same story.

Remember I told you about 0.5 and 1, some isolates tend to be a little bit high, but not too high.

[Slide.]

With griseofulvin, we saw something a little bit more interesting, because unlike the isolates which came from the epidemiological study, we see a number here 22 and 5 isolates with MIC, which I would say higher than what we saw from epidemiologic.

So, there is some feeling here that at least griseofulvin, the MIC is going up a little bit, and this had been observed by a colleague of mine in his study from New York Labs, where he showed that there is a little bit of increase in MIC against griseofulvin.

[Slide.]

Now, putting everything together for terbinafine, 1,300 isolates, and you can see the range of MIC, less than 0.001 to 0.25, and MIC50, which is the minimum inhibitor concentration that inhibited 50 percent of isolates, 0.002 and 0.015, the concentration that inhibited 90 percent of

isolates. So, in general, I would say it is quite active.

[Slide.]

This is the same story, but in a histogram format, and I am showing you about fluconazole. This is cumulative data, putting everything together, and you can see T. rubrum, T. mentagrophytes, and I would say here is where the crux of the isolates, most of them are inhibited.

[Slide.]

Itraconazole, we saw those here at 0.5 and 1, a little bit higher.

[Slide.]

Griseofulvin, the same thing. These are isolates which tend to be a little bit higher.

[Slide.]

To summarize this part of the talk, I would say that all the antifungal agents we looked at, fluconazole, griseofulvin, itraconazole, and terbinafine are active against the tested organisms.

Really, no resistance to these drugs was

detected, a question mark about griseofulvin.

Now, terbinafine, when you compare everything as far as the level of MIC, I would say showed the most potent antifungal activity relative to the other agents.

Now, some clinical isolates I mentioned had a little bit of elevated MIC to griseofulvin.

[Slide.]

We then focused a little bit more on a subset of isolates. Remember those were about 1,300. We looked at the total number, we continued with terbinafine. What we found is 99.4 percent of the isolates tested, they had an MIC listed as 0.06 micrograms per ml.

However, we detected a set of sequential isolates. You remember I told you we had some isolates from the same patient over a period that had elevated MICs. Because of this, we focused on them and we wanted to try to understand.

[Slide.]

Now, these isolates came from a clinical trial that has 1,500 patients. They were treated

to determine the efficacy and safety of oral terbinafine. The selection criteria for this was culture positive at the initial visit. In between, it could be at least in one or more visits, the positive culture also, and then at the end of the study, the culture was positive, as well, so obviously, we did not get rid of the culture.

Now, in total, we had 38 patients positive for T. rubrum throughout the study. We again focused on these and we looked at the number of organisms. It was 140 sequential isolates from these 38 patients.

[Slide.]

Then, we wanted to know why are these patients failing. The answer could be one of these three possibilities. It could be due to decrease in antifungal susceptibility of the infecting organism, MIC going higher.

It could be due to reinfection with a new genetically unrelated strain, or it could host factors.

[Slide.]

So, we started to answer each of these questions.

First, is there a decrease in antifungal susceptibility of the sequential isolates? We had 140 isolates. We did MIC for them, and what we found in all cases, the MIC of terbinafine from each patient set were either identical or within one tube dilution. When there is one tube dilution, really, there is no difference, so I would say they are identical at least if you look at any of the MIC, that one to two tube dilutions are not considered significantly different.

The same results were obtained within each set against the other drugs, fluconazole, itraconazole, and griseofulvin, showing you that there is no cross-resistance. All of them were actually susceptible.

One exception we noted was where one organism, griseofulvin had a MIC 3-fold increase.

[Slide.]

Now, this is just to show you--I am not going to give all the data--just a representative

example, and here we have MIC against flu, itra, terb, and griseo. You can see low and the same. We did not see an increase as these patients were treated for the 12-week period.

[Slide.]

However, one patient had the sequential isolate that had elevated MIC out of the 38. Look at this. This was published by my group in Antimicrobial Agents and Chemotherapy last year.

These are the different isolates at different visits, and here we put two isolates which are really standard, just to make sure we, as you said, quality control and they are susceptible to terbinafine.

You can see here we used two different methods, macrodilution method and microdilution method, to measure the MIC. At the very front, 4 microgram per ml, and remember most of the isolates, really 99.4 percent of the isolates had an MIC of 0.002. So, this is a significant increase in MIC.

When you look at using the microdilution

method, all the isolates had elevated MIC. Using another method, the macrodilution, it made it even more interesting where at the beginning it was 4, but by the end of the study, the MIC microgram per ml was greater than 128, so it increased.

So, that really puzzled us, and we wanted to know more.

[Slide.]

But before I go into these, I just want to conclude about the 38 patients. Patient failure is not due to a decrease in antifungal susceptibility, because MICs were very similar, only one exception where all six isolates of T. rubrum were found to have greatly reduced susceptibility. These, we analyzed them a little bit further.

[Slide.]

We wanted to know is there cross-resistance to other classes of antifungals. Suppose something happens and we have high MIC for something, does it go across to other drugs. The answer is really put simply no. Here, we see at least the azoles type of compound and griseofulvin.

Look at the MIC, the same sequential isolate. It is about the same irrespective of where it came from.

[Slide.]

When you look at other compounds in the same class, which is allylamine, we wanted to ask the question is there cross-resistance to other squalene epoxidase inhibitors., and for this we used again our control. This we know is susceptible to all these agents, 0.002, so it is obviously susceptible, however, look at this.

The naftifine, butenafine, tolnaftate, and tolciclate, they all had high numbers indicating that there is a cross-resistance to squalene epoxidase.

[Slide.]

Now, the question then, is it possible that the patient got infected with another strain, which was more resistant, so we looked at that. We wanted to do genetically related studies to see whether they are the same or not.

So, we performed RAPD analysis, which is

random amplified polymorphic DNA analysis.

[Slide.]

I am not going to bore you with the method. This is standard method. This is how you extract the DNA. This is how you do the analysis, you know, just to give you the cycle PCR, and this sort of thing, so I am not going to go over that.

[Slide.]

I am going to just show you the results of that.

This shows you, this is the letter, and this is the standard ATCC just to make sure we have T. rubrum, and if you look at the other lanes, they are all very similar, indicating that the isolates obtained at sequential visits represented a single T. rubrum isolate, so it is not something which came new.

[Slide.]

The last possibility is, is it possible that the patient failure is due to host-related factors?

To do that, we know, as I told you, this

is part of the clinical trial, so the clinical data was all available, it was reviewed, and for the 38 patients who failed, found the following points which we thought could be really host related.

The first one, they had all these patients, the 38, 53 percent of them have a history of prior use of antifungals, so they have been using antifungals for a long time.

Family history of onychomycosis, 60 percent of patients had one or more member of their family with history of onychomycosis. Does it mean that they are genetically predisposed? I think a lot of people ask this question. I think maybe there is some truth to it, but unfortunately, we don't have the study that proved it.

The last one, 70 percent were over 45 years old. I am not saying this is old, I passed that a long time ago, but in a study which we published with Boni Elewski, what we did, we looked at patients who are 53 years old and compared them, and we found that people are more predisposed to have onychomycosis if they are 53 years and older

compared to those 53 years and younger.

With that in mind, age is really a contributing factor.

[Slide.]

Summary. Our data indicate that the failure of patients to clear onychomycosis is not related to resistance development with one exception, that patient which we analyzed. Not due to reinfection with a new T. rubrum strain, and may be attributed to host-related factors including family history of onychomycosis, prior antifungal treatment, an age.

So, now I am going to try to put everything together is these last two slides.

[Slide.]

Where are we with dermatophyte susceptibility? I can tell you a method to measure antifungal susceptibility is now established, unlike before which we didn't have.

Only a few studies using this method have addressed whether resistance existed or not, which some of it you just saw.

Based on these studies, the resistance, I don't believe it is a problem, most compelling data at least for terbinafine, which I shared with you.

There is a lack of data concerning the susceptibility profile of agents. The method is new, nobody used it and look at it. We don't have that.

For dermatophytes, unlike for yeasts, the in vitro-in vivo correlation is also lacking, like we need a lot of data from MIC and clinical data, and try to see is there a correlation with the in vitro data and the in vivo. We did this for the yeast, and it was published as part of the NCCLS.

There is no breakpoints established for any of the drugs, the breakpoints which can tell you let's say 60 microgram is resistant, less than it's susceptible. We don't have that for dermatophytes. Obviously, the committee established it for the yeast.

Now, information about the mechanism of resistance is also not available. These strains which I talked to you obviously we did some

molecular studies, and we believe there is a mutation in the squalene epoxidase. This stuff is not published yet, but that's about the information as far as that is available for us on the mechanism of resistance.

[Slide.]

What needs to be done? This is just me sitting trying to think, okay, what do you think should be done. Of course, it is up to the committee to decide what they want to do.

We need to establish baseline data concerning antifungal agents, which will also allow us to observe trends. If we have a baseline at least for the compounds which are available, we know what is now, we can look after two, three years, and that could give us information whether there is an increase in MIC or not.

Surveillance studies to determine the true frequency of antifungal resistance also should be implemented.

Studies to establish in vitro-in vivo correlation should be undertaken. Sometime this

could be done in animal models at the beginning where you see there is strain with high MIC, another strain with low MIC. You infect animal, treat them, and then see whether it worked or not based on the susceptibility.

Data should be collected on both clinical and MIC from patients treated with various agents in an effort to establish breakpoints for different agents.

Finally, I believe MIC data using the developed method should be collected as part of the drug approval study. At least we know where the agent is.

[Slide.]

These are the people in my lab who did the work I just presented. Mary Bradley, who did the DNA typing and followed the sequential. Nancy Isham, a lot of the data which I showed you, she did it. Steve Leidich is the molecular biologist who really tried to understand the fact that we have mutation at the squalene epoxidase. Pranab Mukherjee also was helpful in the biochemical

characterization of these isolates.

Thank you very much.

DR. CANTILENA: Thank you, Dr. Ghannoum.

Any questions from the committee? Dr. Katz.

Committee Discussion

DR. KATZ: That's a very nice presentation. I just have one comment and one question. The comment, as far as patient failure and host susceptibility, and you question genetics, there is work showing people, not with onychomycosis, but with tinea pedis, with having defective delayed hypersensitivity to Trichophyton antigen in people who have familial tinea pedis, clinically, right through four generations getting tinea pedis.

So, that's in the literature some 20, 30 years ago.

DR. GHANNOUM: I just would comment I think Nadir Ziaz and Tozzi from Italy, yes, I agree.

DR. KATZ: My question on page 13,

characterization of the sequential T. rubrum isolates with elevated MICs, I wondered whether you note any clinical correlation with those with high MICs, treatment failures or anything different clinically.

Was that done or was it a laboratory--

DR. GHANNOUM: What we did was purely laboratory, but then we went and looked at the clinical data after this and tried to find a correlation, and really, the only factors which we found, as I said, age, and so on, but there was nothing.

DR. KATZ: No correlation of failure?

DR. GHANNOUM: Not as much, no.

DR. CANTILENA: Thank you.

Dr. Wood.

DR. WOOD: I guess my questions are directed sort of where we may end up going towards labeling. I have I suppose a genetic resistance to including stuff in labeling for which there is not good data to support it.

So, I have a number of questions that

occurred to me in listening to this.

The first one is are there any data that support a relationship between MIC or other laboratory-measured resistance and outcome in terms of efficacy in therapy. The reason I think that is critical is that the data you show, shows most of these isolates respond to less than 0.002 micrograms per ml, and this is a 1 percent topical application, so even if you move one order of magnitude, you are still vastly below the concentrations that the organisms are exposed to.

So, the first question is are there data that show a relationship between resistance and outcome, and how rigorous is that given the efficacy data that we saw earlier, which is not terrific.

DR. GHANNOUM: I think this is a good question. The data as far as dermatophytes are concerned, I don't think they exist, as I said, but we have data where there is an in vitro-in vivo correlation for Diflucan, for example, and oropharyngeal candidiasis, and that was published

by the NCCLS in Journal of Clinical Microbiology.

Based on that data, we had breakpoints. This has not been done for dermatophytes, so obviously, we need to have this collected, but that data is robust, it was 600 patients. It showed that--I can give you an example with fluconazole.

If the MIC is less or equal to 8 micrograms per ml, then, you consider it susceptible, and the success rate was 90 percent. If you go down in the MIC, let's say greater or equal to 64, then, the outcome is about 60 percent success rate.

Now, obviously, fungal infections, that is one which is very important for us to consider, the disease of immunocompromise. These patients, even sometimes if you have a good correlation, it is not necessarily that you are going to see success because we have so many underlying factors which need to be taken into consideration.

DR. WOOD: Well, 60 percent is still a lot better than the outcome in the clinical trials on Slide 19.

DR. GHANNOUM: Yes.

DR. WOOD: The second point relates to my fear that some of this might appear in labeling. Most of the host factors that you cite sort of relate to a potentially circular argument, so the fact that you have treated yourself before with an antifungal may reflect the fact you didn't respond to an antifungal before.

It may reflect even the fact that you don't have a fungal infection, and you didn't respond last time, and you don't respond this time, and so on. I mean I could go through it, lots of examples, but I think we have to be careful in taking relationships that are not well documented and including these as host factors that may affect response to therapy when these are not part of a randomized trial or appropriately controlled for.

DR. GHANNOUM: First of all, I go from the back. I agree with you that it is very important to do more of these and collect the data. The data which I showed you is really what is available, and that is the best thing we could do because we had a

set of isolates from patients who were enrolled in clinical trial, and we had the clinical data, so that is the best case scenario.

Now, one thing is really clear. In the dermatology literature, really sometimes people don't even do KOH or culture, and then they go and treat, or they go sometimes and they say, look at their feet, and we know, for example, although I know we are talking about tinea pedis, but let's say onychomycosis, 50 percent of the time the cause of infection is nonfungal.

Again, here, I am sure there are some other differential diagnosis which is included, but if the treating physicians don't do the identification and the KOH, and then you are right, maybe they don't have that, but at least with the limited amount of data, that is what I can say.

DR. CANTILENA: Thank you.

Dr. Benowitz.

DR. BENOWITZ: To follow up on the comments of Dr. Wood, it would seem to me, since the concentrations are so high topically, it should

never be a resistance issue, and one thing, I am not sure it was your presentation or someone else's, the question of just access, are these topical preparations, is the drug getting to the fungus, or is there some sort of barrier in the skin or the keratin or something, why are we not seeing 100 percent mycological cure in a week if you are giving such high concentrations to susceptible fungi.

DR. GHANNOUM: I think, as far as the access is concerned, there are some studies where they showed that there is skin level. Let's say, for example, I know for at least two compounds, itraconazole and terbinafine, there are some studies by Fagerman where he showed they take, you know, the skin shaving, and they were able to isolate the drug, and the drug is there, so I think it is reaching there.

Now, why they are not doing it, is it the patient compliance, is it the fact that there are other underlying diseases? I think this needs to be addressed, so I have no idea.

DR. CANTILENA: Thank you.

Dr. Wilkerson.

DR. WILKERSON: I think that was an excellent point. I mean we have obviously learned today that we treat many and cure few. So, in this situation, I don't think we really know the pharmacokinetics.

We know that if we put 1 percent of compound in a cream, that it works for a few people, and one of the paradoxes has always been, extending over to onychomycosis, here, we have got something sticking out on the outside of the body, yet to be treated effectively, you have to treat someone orally instead of treating them topically.

My guess is that the nature of these compounds is that we really don't reach very high concentration effective levels. Otherwise, this data doesn't make any sense.

At 0.002 micrograms per milliliter, we ought to be overwhelming these things, and obviously, there is a drug availability issue here which has not been addressed in the studies to

date, so there is a problem there in terms of yes, the drug is there, but it is not in a bioavailable form, otherwise, it doesn't make any sense.

My second comment is that since we have learned that we are not curing a whole lot of people, I want to know what your feeling is if you pulse treat someone with an antifungal versus continually treating someone, knowing what we know from the bacteriological literature that if you exposed organisms to sublethal amounts, are we, in fact, going to grow numerous strains of resistant organisms, and if we are looking at prophylaxis, which may come into our labeling later on here, is it better to pulse someone with higher concentrations and have holiday periods, or is it better to treat them continuous.

Do we know that fungi and bacterial resistance behave in the same way? Along those lines, do fungi lose their resistance over time if they are no longer exposed to the drug, or do they maintain it like bacteria do?

DR. GHANNOUM: I agree with you with the

first one, but as far as pulse versus continuous--

DR. WILKERSON: I am speaking strictly topical, not oral therapy.

DR. GHANNOUM: Yes. I really believe when you have a fungal infection, it is better to treat it continuously, at least from our experience. You see, in dermatophytes, we don't have much information, but our experience with the other agents, again, like Diflucan, we noticed why did we have resistance there develop? Because they underdose, they use to give 50 milligram.

So, definitely, it's a recipe for resistance development, and we know in the lab if you take something, put it in some concentration, after some time you see MIC climbing. So, as a microbiologist, I believe it is very important to give continuous therapy to at least eliminate the chance of the resistance development.

The last question was?

DR. WILKERSON: Over time, if you have a resistant organism, does it lose its resistance, or does it maintain it like most bacteria do over a

period of time once a drug is no longer present?

DR. GHANNOUM: I think, again from our knowledge with the other agents, it keeps it. I have a strain, for example, took from a patient. The baseline was susceptible. After 15 episodes, its resistant MIC is quite high, and we have been using it for a long time now as controls, and it is still there, so I don't think it loses it.

DR. WILKERSON: The obvious implication for this is that we need to have regimens that lead to the highest rate of eradication as possible as opposed to just maintaining the infectious state.

DR. GHANNOUM: Right.

DR. CANTILENA: Thank you.

We have a question from Dr. Whitmore.

DR. WHITMORE: What Mike was just saying about failure rates and why we have such high failure rates, one of the things that is different with topicals versus systemic is if somebody tells you they take a pill, you know they have swallowed it. They might not absorb it properly, but you know at least they have swallowed it.

If somebody tells you they have put their antifungal on their tinea pedis, they might have put it just right in that one crack, who know how they are applying it.

DR. GHANNOUM: Also, a lot of time we have the same shoes, I mean they use the same shoes, we have the environment which is humid, and really, there are many, many factors which you need to address, and unfortunately, we really don't have relative good data.

I mean I am new to the area of dermatophytes, my work, you know, time passes so quickly, the last eight, nine years I have been focusing a lot on dermatophytes, but before that, when I came into it, I tried to look at, there isn't relevant information. So, I think it is very important for us to have a better understanding of the pathophysiology of the disease.

DR. CANTILENA: Any further questions?

Okay. If not, we will pause for lunch now and return to start the open public hearing at 1 o'clock.

[Whereupon, at 11:40 a.m., the proceedings were recessed, to be resumed at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:00 p.m.]

DR. CANTILENA: Before we begin the open public hearing, the following statement is read from the Food and Drug Administration.

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

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

For example, the financial information can include a company or a group's payment of your travel, lodging, or other expenses in connection

with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

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

Now that that is in the record, I think if you look at the open public hearing, who is scheduled, I think that we probably won't have a hard time with the conflict of interest, but it is something we have to do anyway.

I will ask the committee actually to hold your questions until the end of the entire session and then we will have time for questions and answers at the end of the time period.

The first group in the open public hearing is the Consumer Healthcare Products Association who will lead off and then I will ask you to then introduce the other speakers for the open public hearing.

Thank you.

Open Public Hearing

Consumer Healthcare Products Association

Doug Bierer, Ph.D.

DR. BIERER: Good Afternoon. My name is Doug Bierer. I am the Vice President of Regulatory and Scientific Affairs for the Consumer Healthcare Products Association.

CHPA represents the vast majority of the distributors and manufacturers of topical antifungal products which are used for the treatment of tinea pedis.

Our presentation today from industry will consist of three parts. In the first part of our presentation, Dr. Boni Elewski, who is a well-known clinical dermatologist and expert in the field of topical fungal diseases, will talk about clinical endpoints, resistance, and safety.

I will provide a few comments about the reported lack of efficacy, as well as some suggestions for enhanced labeling for OTC antifungal drug products.

The second portion will be turned over to

Schering-Plough Consumer HealthCare products, and the third portion will be Novartis Consumer Health, and they will make their separate presentations.

Dr. Boni Elewski, as I mentioned before, has considerable experience both as a practicing dermatologist, as well as clinical researcher, for fungal infections. She is very widely published about cutaneous fungal infection and shared guidelines of Care Committee for the treatment of tinea pedis for the American Academy of Dermatology.

Boni E. Elewski, M.D.

DR. ELEWSKI: Good afternoon, everyone, Mr. Chairman, ladies and gentlemen. It is my pleasure to talk to you today about one of my favorite topics, tinea pedis.

Before I begin my discussion, I want to add that I am a consultant under this capacity, working with CHPA, and I have also have been, and am, a consultant for many of the companies whose products will be discussed today, including both Novartis, who will be discussing today, and

Schering-Plough.

[Slide.]

So, I am going to spend some time reviewing the scope of the problem, and then we will look at strategic issues regarding this problem.

Tinea pedis is a common fungal infection caused by the dermatophyte fungi. The most common is Trichophyton rubrum. I happen to really like Trichophyton rubrum. Its first case in the United States, interestingly enough, was in Birmingham, Alabama, in 1922. I happen to live in Birmingham, Alabama, and so I tell my patients that we live in the fungus capital of the world, and I believe that actually.

It is an infectious disease that affects the interdigital spaces and contiguous skin and has been mentioned this morning, it affects up to 70 percent of the population.

Dr. Rappon, in his textbook, wrote that our lifetime risk factor of getting tinea pedis living here in the United States is 70 percent, and

it's more likely to get it if you do certain habits, such as you go to swimming pools or gyms or health spas, and there have been a lot of data coming from large studies and surveys looking at how common it is among swimmers, among people who go to gyms, and so forth, but must of the data from swimmers is very compelling, and people who go to swimming pools at any age have a very high risk of getting tinea pedis, which again confirms that it is an infectious disease.

[Slide.]

Well, what does it look like? What we see is generally a dry, scaling process in the toe webs, most common between the third and fourth, and fourth and fifth web space.

As you see here, this is a typical patient with interdigital tinea pedis. Keep in mind that interdigital tinea pedis is what we are talking about today, not moccasin tinea pedis, but particularly interdigital tinea pedis.

I would like to say as a sidebar that if this patient came into my office with a simple

scaling process like you see, and this scale in between the toe webs, the treatment of choice would be a topical antifungal.

A topical antifungal would be my preference, much better over an oral antifungal because it will be applied directly to the infection, as I will be addressing later. I would not recommend an oral antifungal for treating this simple scaling process

[Slide.]

So, interdigital tinea pedis is very easily recognized by the consumer. It is common. People who have it often have friends and relatives who have it. They go to the gym, and their colleagues at the gym, friends at the gym, friends at the swimming pool had it, so they know what it looks like.

It also has consistent symptoms, itching and burning in the toe webs. There is also consistent signs - erythema or redness, scaling, hyperkeratosis, and fissures or cracking, and these are also the same signs that we capture when we do

a study.

[Slide.]

So, what do we do for treating tinea pedis over the counter? Well, first of all, I am happy to say that there is a large selection of effective over-the-counter antifungal drugs available for treating tinea pedis, some of which are monographed, and some are NDA switches at the full prescription strength.

I would like to add that because they are both prescription and over the counter for some of these drugs, over the counter is as effective as the prescription topical antifungal and as safe as the prescription topical antifungal.

[Slide.]

So, how do we treat tinea pedis over the counter? Well, number one, you apply the antifungal to the affected area and to the adjacent skin once or twice a day as recommended by the manufacturer. You also treat for one or four weeks as recommended on the OTC label.

Keep in mind that the signs and symptoms

generally improve during or shortly after the treatment course. That is a point I will come back to, because I think it was a very important point to address this morning.

[Slide.]

What is the real purpose to treat this infectious process? Well, the real objective is to eliminate the dermatophyte, to eliminate the fungus. The fungus resides, in this particular process, it's a superficial fungal infection and it resides in the outer layers of the stratum corneum, as you see here.

I don't have a pointer, but it's these blue little dots that you see in the outer layer of the skin. The red part here is the stratum corneum, and then you are getting into the epidermis and dermis, the lower part of the epidermis and the dermis here, below there.

So, the very outer layer of the stratum corneum is where the infection resides, and because it is in the outer layer of the stratum corneum, when you apply topical antifungal, it is going to

exceed the MIC of the dermatophyte. It will reach the area.

You won't have to worry about it getting there, because it will get there because you are applying it right on top of where the fungus is residing, so it is getting to the area and easily will exceed the MIC of the organism. This is not an issue.

It may be an issue, however, if you use an oral agent, because if you take an oral agent to treat this, you have to get it absorbed, it may have to be metabolized, and then has to get into the skin.

It is either going to get into the skin through passive diffusion, through excretion through the sweat, or through excretion through the sebum, which is why a drug like amphotericin B, which is, of course, a very potent drug for treating systemic infection, does not work at all for interdigital tinea pedis, because it will not get into the superficial layer of the stratum corneum at high enough levels to kill the

dermatophyte.

So, many patients at our institution who come in with a systemic infection and are given a drug, such as amphotericin B, may still have dermatophytosis.

[Slide.]

So, topical antifungals, the message is, are very effective applied to these superficial infections. So, what happens after you apply the topical antifungal during and after the course of treatment?

From my experience seeing patients, and I see patients almost every day, I am in the medical dermatology trenches, and I have been doing this for close to 25 years, itching and burning and generally alleviated very early in the therapy. Fortunately, for patients who suffer with itching, shortly after you start applying it, the itching and burning seem to go away.

As mentioned however this morning, some clinical signs may take longer to resolve, and in some instances, from my experience, may not fully

resolve at all. There may be erythema or inflammation, scaling and hyperkeratosis, and the fissures and cracking.

[Slide.]

So, let's explore these healing dynamics and why one process may resolve faster and one takes longer to resolve, and what might be underlying risk factors that cause one person to heal at a different rate than another person.

First, the erythema. Erythema again is redness. Erythema is inflammation in the skin, and, of course, it's a response to the infection of the dermatophyte in the stratum corneum. As the dermatophyte is eliminated erythema is improved.

One of the speakers this morning showed the erythema going away, and it generally goes away fairly quickly, but now always. Occasionally, you have erythema at the end of treatment, and I will address those points later.

[Slide.]

Scaling and hyperkeratosis is also caused by the dermatophyte living happily in the stratum

corneum, but occasionally, scaling and hyperkeratosis may not completely resolve after the dermatophyte is eliminated.

One, patients may have an anatomic occlusion, they may have a hammertoe, they may have toe overlap. They may have arthritis where two toes are rubbing against each other, causing some friction or causing some scale or a callus from the anatomy of the patient or the deformity of the foot.

We also may have pre-existing skin diseases, and one may have psoriasis. Someone else may have atopic eczema, and as a sidebar, people who are atopic or have an atopic diaphysis have the highest rate of getting tinea pedis to begin with, and these people may also have underlying atopic dermatitis, which could be some reason why they may have some scale and hyperkeratosis.

Some people I like to refer to also as fast healers. Remember we have to wait until the skin turns over, which can take four weeks and some patients even longer.

Other people are faster healers, and since we are arbitrarily assessing this data at one given point in time, it may vary from person to person, because we are all people, we are all different, and no two people do anything exactly the same.

So, from my experience, residual scaling and hyperkeratosis is not uncommon after the elimination of the dermatophyte. Most always it eventually goes away, but occasionally, you still have some that may be totally unrelated to the dermatophyte.

It may be that they had a soft corn, it may be that they had a hammertoe, it may be that they have something else. So, these studies may not take all this data into account, they are just taking in the dry data, scale, is there a flake, is there some redness, and we will come back to that point in a few moments.

[Slide.]

Next, fissures or cracking. Again, this may occur due to the presence of a dermatophyte in the stratum corneum, although you can have fissures

and cracking due to other reasons, too, if someone has a hammertoe or someone has a toe overlap or some other anatomical occlusion, they may have fissures for other reasons.

But resolution of fissures generally is fairly reliable except some fissures are very deep, and then it may take longer for them to resolve, or someone may have other confounding factors that may delay healing, such as they have peripheral vascular disease, and so forth, and that is not all excluded in patient studies or in your real practice, of course.

So, from my experience, occasionally, you see fissures and cracking after the elimination of the dermatophyte, but from my experience, it is much less common to see than simple scaling after the elimination of the dermatophyte.

[Slide.]

So, we have to have a system of evaluating all this in our practice, but more importantly, since the issues is studies, in our studies.

Study methodology are twofold. One, the

microbiology parameters, microbiological parameters, and, two, clinical efficacy parameters.

[Slide.]

Well, what are microbiological parameters? We addressed this, let me recap. First, we have the KOH. A KOH shows the presence or absence of fungal elements. It does not capture, however, whether the fungal elements are dead or whether they are alive. You don't know. You just know that the fungus is there or that it's not there. That is an important point, we will come back to that.

We also a fungal culture which identifies the organism by the genus and by the species. It also tells you whether there is viable fungi there. So, sometimes you can use the positive or negative fungal culture and correlate it with the KOH to see whether they are viable or nonviable, but again, we don't have a lot of data to look at that, but the main objective is mycological cure.

Mycological cure, by the definition that we live by is negative KOH and negative culture.

In most studies, from looking at the data presented this morning, it appeared that more than half the people in the studies had a mycological cure of about 80 percent or higher.

That doesn't surprise me, and I would predict that those who are not mycologically cured probably had some persistent scale, and the persistent scale had some nonviable fungal elements, and the nonviable fungal elements made the mycological cure falsely low.

So, what I am getting at it is in my experience, I think we can cure a lot of patients with interdigital tinea pedis, it depends on how we define cure, and we are going to hit that again in just a moment.

[Slide.]

So, we have the microbiological parameters. Now, let's look at the clinical efficacy parameters. Here, we have two. Complete cure, that means mycological cure plus absolutely no sign and absolutely no symptom. Effective treatment. Effective treatment is mycological

cure, so negative KOH, negative culture, plus no more than mild signs or mild symptoms.

Again, in a study, most studies are generally looking at this in a 4-point scale, zero being absent, 1 mild, 2 moderate, 3 severe. So, when the patient or the subject was enrolled in the study, they were moderate to severe in one of the parameters, and at the end of the study they may end up as mild.

That can be very frustrating to me as an investigator, especially when I have a patient who is totally clear clinically, not a flake to be found, not a fissure to be seen, no erythema lurking in the toe webs, yet, they murmur "but it itches" or "I think it itches." Then, I have to say perhaps mild itching, so they would be a failure, it can be very frustrating.

It also might be frustrating if I see something, such as erythema, but my gut feeling is that the erythema or the flakes of scale I see, or a little callus I see is not due to the tinea pedis, but it is due to a toe overlap or due to an

anatomic occlusion.

Nonetheless, it is there, it may be better because we got rid of the dermatophyte, but the fact that it is there, I will have to tick "mild," which will bring the whole results of the data down. So, keep all that in mind.

[Slide.]

Which brings me to the point, when we say cure, what do we mean by cure, what is meaningful? How I do this in my practice and how I do this when I look at the data from a study, if I am evaluating a drug, what are my personal objectives?

Well, objective number one is you want to eliminate the dermatophyte. After all, it is an infection, and that is how we define these to begin with. They are dermatophytosis, so you want to eliminate the dermatophyte. So, by the definition we are using, we would have to say mycological cure.

Also, for practical purposes, no more than mild signs and symptoms, and I am going to stick with that, because there are frequently a patient

at the point of time that the study ends, their symptoms are on the way down, and they went from severe to moderate, and now there is a flake of scale or a speck of erythema, and they are still improved, but not 100 percent, or they may have some underlying process that causes this.

[Slide.]

So, when I say "mild," the mild could be due to the fact that they have an underlying dermatosis, they have psoriasis which we are not capturing, they have eczema, they have xerosis.

We talked about this morning that people who have dry feet, also often have fungal infections, but you can't say that everyone with a dry foot has fungal infections, and if you think that, we will look at everyone's feet here, we can do cultures and see how many of you have fungal infections if you have dry feet. I doubt that we would correlate that with a very high figure.

Also, keep in mind that treating tinea pedis with an antifungal cream will certainly not make the skin better than it was prior to the

infection, it can't be done, so all we can do is restore the skin to the baseline status it was before the patient acquired the infection.

[Slide.]

So, what I think is the most meaningful datapoint that I like to hold my hat on is effective treatment. Effective treatment means the dermatophyte is eliminated and we have improved the patient significantly, down to just a trivial point, which may be and probably is unrelated to the process, or if it is related, it is going down a slower slope than other patients.

[Slide.]

So, clinical insights that I have built up now. Current over-the-counter antifungal drugs, in my opinion, deliver very safe and effective treatment especially since we are treating an infection that is in the very superficial layers of the skin. When you apply an antifungal to this area, you are getting it onto the infective organism and killing organism.

In my opinion, the clinical meaningful

endpoint is effective treatment. Because of this, I don't think dose response studies are needed, because topical antifungals easily reach the dermatophytes in excess of the MICs.

[Slide.]

Likewise, as Dr. Ghannoum so eloquently pointed out today, there is really no concern about dermatophyte antifungal resistance, and even if there were organisms that had a borderline resistant issue, because you are applying it in such a high amount, it will readily exceed the MIC of the dermatophyte living in the very superficial layers of the skin.

This is not the same situation as we have with oral drugs where you have to worry about them getting there in high enough numbers, and there are so many factors that can confound that from happening, whether the patient absorbed it correctly, whether there is any other process that might have impaired the drug from getting to the target point of infection.

So, in my experience, when used as

directed, topical antifungals are very effective at eliminating the fungus.

[Slide.]

There are a couple of other issues I want to address. One came up this morning as secondary bacterial infections. As we have discussed, there are rare reports of secondary bacterial infections, i.e., cellulitis associated with tinea pedis.

In my 25 years of being out in the trenches, seeing patients, I have never seen a patient with interdigital tinea pedis or moccasin tinea pedis developing a bacterial cellulitis. I have never seen it. I know it has been reported, I am aware of the literature.

The explanation for this the authors have postulated is that the presence of the dermatophyte damages the stratum corneum, causing loss of barrier function, resulting in microfissures or obvious fissures that serve as portals of entry for secondary bacterial infection.

Having said that, it would make even more sense to state that prompt and effective treatment

is clearly essential, and therefore, over-the-counter topical antifungals are important because they eliminate the dermatophyte to allow the skin to naturally replace itself and restore its barrier function.

I will leave you back with Doug.

Doug Bierer, Ph.D.

DR. BIERER: I would like to provide some perspective on lack of efficacy reports that have been reported by FDA.

[Slide.]

FDA reported that 35 percent of all adverse events of topical antifungal agents were due to lack of efficacy. This is from their AERS database. The database actually goes back in the late sixties and encompasses about 30 years. It includes reports of both OTC, as well as Rx drugs.

In those reports, it is unclear whether the reports of lack of efficacy were specifically related to tinea pedis or perhaps one of the other labeled indications, or actually may have been used for another disorder all together.

In order to help put these lack of efficacy reports into perspective, CHPA looked at lack of efficacy reported for OTC topical antifungals related to the number of units sold.

[Slide.]

CHPA collected the number of lack of efficacy reports from seven OTC manufacturers, who actually distribute probably the vast majority of OTC antifungal products used to treat tinea pedis, and we looked at the years from 1999 to the year 2003, over a four-year period.

We saw or found that there was 1,468 reports of lack of efficacy, but during that same period of time, greater than 180 million units were sold and used by consumers. If you translate this out, this calculates into less than 9 lack of efficacy reports per million units sold.

Even if these are underreported, as people have commented this morning, it still is a very low rate of lack of efficacy reports for such a drug.

One of the other areas that we wanted to talk about was that we believe that some of the

concerns raised by the FDA perhaps can be handled through enhanced labeling of OTS antifungal products, and I would like to take you through a couple of our suggestions that we have.

We believe that these should be applied to not only OTC monograph products, but also OTC products which are regulated under new drug applications or NDA.

[Slide.]

As we talked a little bit earlier this morning, and I just mention lack of efficacy, actually could be due to some consumers stopping treatment prematurely, not completing the full course of therapy.

FDA had suggested that we may want to look at different devices for showing consumers what could be expected, and one of the suggestions was perhaps looking at GRASE or tables on package labels. We believe that these are quite confusing to consumers since most consumers cannot understand data or tables, and overwhelming consumers with complicated data should be avoided. However, we

believe that consumers do need simple and concise label statements of how to use the products in order to achieve the maximum benefit from the products.

[Slide.]

Therefore, we are proposing that we add the statement under directions for all OTC products, which is use daily as directed for the full treatment time even if symptoms improve.

[Slide.]

Also, along directions, the FDA asked whether labeling should convey lag time between the completion of treatment and the resolution of symptoms, and we believe it is also helpful to educate consumers on what can be expected under use conditions.

[Slide.]

Therefore, we are proposing to add another statement for directions for one-week use products, that symptoms may continue to improve after one week of treatment as the skin naturally replaces itself.

As you heard this morning, the use of one-week products, there is an increase in efficacy and clinical cure, as well as effective treatment, as time progresses beyond the one week, so we believe this statement would be important for one-week products.

[Slide.]

Lastly, we believe that to address the FDA's concern about secondary bacterial infection, that is, cellulitis, we propose adding labeling information about when to see a doctor.

[Slide.]

We would propose to add a new statement, which is new symptoms develop or condition worsens, and this statement would be added after the phrase, "Stop use and ask a doctor if--the warning part, which is currently on OTC product labeling--so, the statement would read, "Stop use and ask a doctor if"--bullet point--"new symptoms develop or conditions worsen."

[Slide.]

This slide just reviews the three proposed

label additions that we would recommend to enhance labeling for OTS drug products, and we believe that these will not only reinforce consumer compliance, but also further decrease the potential of serious adverse events.

DR. ELEWSKI: Let me conclude with some key points.

[Slide.]

First, clinical cure, as I mentioned, I feel should be defined as effective treatment. Dose response studies are not needed because topical antifungals easily reach dermatophytes in excess of MICs.

Dermatophyte resistance is not a concern. The risk of secondary bacterial infections is very low. OTC antifungals play an important role by restoring the barrier function of the skin and allowing the skin to naturally replace itself.

[Slide.]

The proposed enhanced labeling will reinforce consumer compliance and decrease potential serious adverse events. Current OTC

products are safe and provide effective treatment when used as directed.

Now, we are going to take a few questions if you have any now.

DR. CANTILENA: Actually, I think we are going to hold questions, and we will have all three groups go ahead and speak, and then we will do questions at the end.

DR. ELEWSKI: Okay.

Schering-Plough

John Clayton, M.D.

DR. CLAYTON: Good afternoon. I am John Clayton, Senior Vice President, Scientific and Regulatory Affairs for Schering-Plough HealthCare products.

I think the conflict of interest is obvious. My paycheck comes from there.

I certainly welcome the opportunity to share with you Schering-Plough's experience and views over a number of years of marketing over-the-counter OTC products for treating topical fungal infections, as well as Rx products.

[Slide.]

Our agenda for the afternoon, for my presentation, is to share with you based on our marketing history, our clinical experience, consumer experience, some consumer research, our recommendations and conclusions that hopefully will be helpful to you in your deliberations.

[Slide.]

By way of background, Schering-Plough has been a leader in research and marketing of Rx and OTC topical antifungals for the treatment of tinea pedis for more than 40 years.

[Slide.]

We began marketing tolnaftate in the sixties and actually developed tolnaftate in this country, as well as clotrimazole in this country, for tinea pedis.

Products currently that Schering-Plough markets OTC represent about 44 percent of the units sold in the U.S., and the brands include those listed on this slide, some of which you hopefully are familiar with, and the antifungal agents used

in these products are betenafine hydrochloride, clotrimazole, tolnaftate, or miconazole nitrate. All of these ingredients have marketing history Rx and were approved under NDAs originally.

[Slide.]

In terms of clinical experience, obviously, the ages of these products is different, as was suggested in presentations this morning. Therefore, the clinical endpoints, the designs of clinical trials, while state of the art in their day, vary, but overall, the clinical trials through a variety of designs have demonstrated the safety and efficacy of these products at the current dosing levels.

Even though the study endpoints have changed dramatically over these past four decades, significant clinical efficacy has consistently been demonstrated for all of these ingredients through various types of clinical trials.

[Slide.]

I certainly concur, the company certainly concurs with the presentation and recommendation of

CHPA presented through Dr. Elewski, that complete cure endpoint definition is an unrealistic parameter of efficacy based on the natural course of healing. That is, it truly understates the efficacy of these products.

We believe that it is a more appropriate indicator, the effective treatment, which is defined as negative mycology, both culture and KOH, and minimal erythema and scaling is a more appropriate descriptor of efficacy.

[Slide.]

In our consumer experience, just looking at the data that we have collected over the past 12, 13 years of more than 230 million units sold of our various antifungal ingredients, that extensive patient and consumer experience confirms that these products are very effective.

In our experience, the complaint rates regarding lack of efficacy have been extremely low, 2 per million calculating over the past 5 years, which I think is the most meaningful data that we have.

The consumer letters that we received unsolicited, surprisingly enough, almost achieve the same level, indicating to us the success that they have had with a variety of products, anecdotal for certain, but the fact is the consumers appear to be satisfied with the products.

[Slide.]

One of the more quantitative and structured ways that we have used to achieve information about consumers that use these products is through a consumer tracking study. We have conducting the study annually over the past 10 years to get the views and practices that consumers will share with us.

These are consumers that actually suffer athlete's foot, have suffered athlete's foot within the preceding 12 months. The most recent tracking study that we completed was in October of last year that included 350 consumers between the ages of 18 and 64 years of age.

As I said, they reported they had suffered from athlete's foot within the previous 12 months,

and distribution was 70 percent male and 30 percent female, which in the variety of studies we have done, this seems to be about the--I will say incidence, but in terms of usage of products to treat--it is about 70 percent male, 30 percent female.

This particular research study was done by way of the internet.

[Slide.]

A number of interesting observations out of the study. Consumers purchase the OTC topical antifungals driven by the need for symptom relief.

Universally, consumers that suffer the itching an burning of athlete's foot will self-treat, 95 percent of the time they will seek some type of therapeutic agent to treat their condition. Approximately, 80 percent purchase 4-week products, and approximately 20 percent purchase products, I have less than or equal to 4-week.

As was noted this morning, one product has labeling for 1 week, another product has labeling

for 1 or for 4 weeks, an optional dosing regimen, the difference being two times per day for the 1-week treatment versus one time per day for the 4-week treatment.

Again, intense itching and burning are the primary drivers, and 69 percent rate the symptoms as bothersome or very bothersome.

[Slide.]

Consumers tell us that relief begins within a matter of a few days following initiation of treatment. I am sure we are talking about the bothersome symptoms that drove them to buy the product in the first place, so 60 percent say that these products, in their opinion, provide fast relief of their symptoms.

Consumers also tend to discontinue use of these products despite the labeling upon achieving relief of their symptoms.

We found in our survey in September of last year that the average treatment period was 7.3 days.

[Slide.]

You may say that probably has been influenced by newer products that offer alternative dosing regimens, but looking back at our 1997 study, similar design, consumers reported an average treatment time of 8.8 days at that point in time, so none of the shorter course therapy products were labeled for shorter use back in 1997 OTC.

Interesting, too, is that only 6 percent report that they treat greater than 14 days, again driven by relief of symptoms, discontinuation of use of product.

More than 50 percent treat 5 days or less on average.

Despite that, the consumer satisfaction with OTC antifungals was extremely strong.

One point that is not on target with the treatment time, but interesting, that I wanted to share with you, is that 42 percent of the individuals in our most recent study indicated that they are experiencing athlete's foot less often now than they were 2 years ago.

We don't have a reason for that, we can speculate that it is a change in footwear, improvement of the hygiene, I am not sure what it might be, but it was interesting to note that they are complaining less frequently.

[Slide.]

Our conclusions from the consumer research data are that consumers are highly satisfied with the performance of currently marketed OTC products.

Consumers consistently experience fast relief of symptoms, as was noted that more than 60 percent have reported that. Therefore, most consumers do not use the product for the entire label treatment period, yet, are driven by the symptom relief that they get from the products.

[Slide.]

As a result of this, while the information that we have on lack of efficacy in our experience is that it is reported infrequently, we still believe that based on the consumer research learnings, that there is a likelihood that we could improve the efficacy rate for consumers by

reinforcing the need to apply these products throughout the entire directed labeled treatment period.

We do think that therapeutic success can be enhanced, and similar to what CHPA presented, we recommend that the Direction Section of the label include a statement to remind the consumer to use daily, as directed, for the full treatment period even as their symptoms improve.

[Slide.]

Dr. Bisno gave us a lecture this morning and education on the complications of tinea pedis and particularly as it relates to cellulitis or the potential for cellulitis to develop.

In our experience, it is extremely rare, and I won't rehash the discussion of the morning.

[Slide.]

Despite that, we believe that because of concerns of other infections that may occur either through improper usage of the product, that is, using the product for a short duration of period, or because they have mischaracterized their

condition, that an additional warning statement should be added to products, that if there is no improvement, stop use and ask a doctor if there is no improvement within a matter of days, and I am not sure that 14 is the right number of days, but within some reasonable period of time, or if the condition worsens.

[Slide.]

Our conclusions are that the current products are very effective in treating tinea pedis as demonstrated through a variety of clinical trials and through our consumer satisfaction testing.

Products are extremely safe based on extensive marketing history.

We believe that the effective treatment is the appropriate clinical endpoint for making decisions about efficacy of product, and that we support the enhancement of existing product labeling to improve consumer compliance, as well as treatment success.

Thanks very much.

DR. CANTILENA: Thank you.

Our final presentation in the open public hearing is from Novartis.

Novartis

Helmut H. Albrecht, M.D., M.S., FFPM

DR. ALBRECHT: Good afternoon, Dr. Cantilena, members of the Committee, Drs. Wilkin and Ganley, FDA staff.

[Slide.]

I am Dr. Helmut Albrecht, Vice President of Clinical and Medical Development at Novartis Consumer Health.

As a leader and innovator in the topical antifungal category, we are here to discuss how terbinafine fits into today's dialogue, specifically, addressing the issues outlined by the Agency including efficacy, safety, and labeling.

We have extensive experience in the category. Novartis markets terbinafine in a variety of forms including an Rx table and topical OTC products introduced through an NDA.

We also market monograph products in this

category. We understand the terbinafine compounds and how consumers use the product based on years of market availability and millions of usage occasions.

We have heard what the FDA has to say and agree with much of it, an we will discuss our position on how antifungals can be used more appropriately by consumers to maximize their full potential.

We look forward to the committee's input to help us enhance our label, to guide future development in the interests of improving public health.

[Slide.]

I will provide context and commentary for the committee's considerations. First, we concur with the Agency that labeling could be enhanced to improve compliance. This will optimize treatment benefits, reduce the incidence of lack of effectiveness reports, and minimize the possibility of adverse events.

[Slide.]

Next, we will show how our compound terbinafine offers unique properties that should be communicated to consumers through labeling, and we will comment on the need for appropriate clinical endpoints to guide product development, consumer expectations, and labeling.

[Slide.]

Here, we see a presentation of interdigital tinea pedis or athlete's foot as it is seen clinically with signs and symptoms. Doctors and consumers may perceive this condition differently. Doctors appreciate that it is an infectious disease, and they understand that some signs and symptoms may persist for weeks even after the causative fungus has been killed.

In contrast, consumers have a different understanding of athlete's foot. Our market research indicates that they start and stop treatment primarily based on the onset and resolution of the most troublesome symptoms, including itching and burning. These symptoms often last for a week or less.

[Slide.]

On this slide, we show the natural history of the athlete's foot condition and its treatment. The mycology is shown in the green, symptoms shown in yellow, and signs as shown in red.

As you can see, the signs of the condition, such as mild erythema and scaling, can often persist for sometime beyond resolution of the symptoms and after the fungus has been eliminated.

The actual repair and healing of the skin progresses at its own rate, and there is no need for further treatment.

This healing process reflects the time it takes for the skin to heal and it is influenced by several factors including individual skin types, foot condition, and healing rates.

As you would agree, the primary goal of therapy is to effectively eliminate the fungus. Once the fungus is eliminated, there is nothing more you can do with an antifungal product.

We conducted a market research study involving more than 300 consumers. Our findings

demonstrate that consumers initiate treatment based on symptoms, such as itching and burning, and discontinue treatment based on resolution of these symptoms, which commonly resolve within one week or less.

If a consumer treats for only 1 week, even if the product is recommended for 4 weeks, this has significant implications for those products that require 4 weeks of treatment.

These findings provide a rationale for our belief that effective treatment is the appropriate clinical endpoint for guiding consumer expectations and labeling.

Effective treatment reflects resolution of both mycology, here in the green, and symptoms, here in the yellow.

[Slide.]

Now, I would like to turn your attention to terbinafine, which we market under the brand name Lamisil AT. Terbinafine is a synthetic antifungal of the allylamine class. It has broad spectrum fungicidal activity including the

dermatophytes that cause the athlete's foot.

This property is based on the compound's unique mechanism of action which involves specific inhibition of squalene epoxidase, a key enzyme in ergosterol biosynthesis of fungi.

As such, the fungicidal activity of terbinafine is distinct from the fungistatic activity of the azole compounds in this category.

Terbinafine offers proven efficacy with only 1 week of treatment, with no need for additional therapy. Terbinafine was introduced in 1992 and switched to OTC status in 1999.

Since then, there have been more than 200 million exposures to the compound with no identification of safety issues, trends, or development of significant persistence.

It is worth noting that terbinafine is the only active ingredient in the Lamisil AT line, and therefore has consistent labeling and dosing instructions, reducing the likelihood for consumer confusion.

[Slide.]

Let us now focus on the efficacy of terbinafine. This morning, we heard a lot about the clinical effectiveness from pooled data. Please allow me to show you the actual efficacy results from the terbinafine pivotal studies for the cream product.

[Slide.]

First, I show in vitro and in vivo evidence of the activity of terbinafine where it is needed to kill the fungus. Minimum inhibitory concentrations or MIC values show a high degree of antifungal activity at very low concentrations, providing antidermatophyte potential that is 100 times more effective than Butenafine and 1,000-fold more potent that clotrimazole.

In contrast to what you may have heard this morning, terbinafine does indeed reach the site where it is needed. After 1 week of topical application, concentrations in the skin are 1,000 times the MIC. Seven days post-therapy, concentrations in the skin are still 100 times the MIC. In fact, therapeutic values remain in the

skin 5 weeks post-dosing.

[Slide.]

Terbinafine has been extensively studied and safety and efficacy have been clearly demonstrated in 15 well-controlled clinical studies. This shows from a representative pivotal study in tinea pedis from the NDA filing for the OTC switch of Lamisil AT 1 percent cream.

The y axis shows for each of the three clinical endpoints the percentage of subjects who successfully achieved them. The red bars represent terbinafine and the green bars represent placebo.

The two columns on the left show the result of mycological cure. This is, of course, the prerequisite for the other endpoints - effective treatment and complete cure. So, effective treatment results are shown in the middle, and the bars on the right show complete cure.

It is important to note that all three endpoints represent the same patient experience. The differences in the values simply represent the

different clinical parameters.

As mentioned previously, complete cure is heavily weighted by signs of the condition, and therefore is always found at a lower rate.

These next two slides represent data from one of our studies comparing terbinafine and clotrimazole at 6 weeks post-baseline.

[Slide.]

We are showing you 1-week data because this is how we understand consumers to use these products. As you can see, at this point in time, terbinafine is highly effective and far superior to clotrimazole on each of the three endpoints.

[Slide.]

These are results from the same study showing efficacy at 6 weeks post-baseline following 4 weeks of treatment with the two products. You can see that 4 weeks of treatment with terbinafine produces no additional benefit over the 1-week data shown in the last slide.

After 1 or 4 weeks of treatment, terbinafine has essentially equivalent efficacy for

all three endpoints. This is not the case with clotrimazole even if it is used for the full 4 weeks as it is currently labeled.

[Slide.]

This slide demonstrates the impact of these different treatment outcomes at 12 weeks. As you can see, only 9 percent of patients go on to have relapse on terbinafine with 1 week of treatment, and 11 percent with 4 weeks of treatment, compared to higher rates with clotrimazole of 47 and 30 percent, respectively.

This reflects the potency and sensitivity of terbinafine.

[Slide.]

This slide shows the same data just viewed now in a line format to allow us to look at the time course of the effect on mycology over the 12 weeks evaluation.

As you can see, the red lines which represent terbinafine treatment, there is no difference between the 1 week and 4 week treatment. There is, in contrast, clotrimazole, in the yellow,

where the 4-week treatment shows a remarkable difference from the 1-week treatment, highlighting the potential impact on treatment outcomes in those who do not complete the 4-week treatment course.

[Slide.]

This shows the same depiction for signs and symptoms for the 12-week assessment period. This slide also serves as a nice overview of the effectiveness of terbinafine. As you can see, it produced comparable efficacy at 1 and 4 weeks.

Within days of initiating treatment, signs and symptoms are reduced. However, after about 6 weeks, you can see a plateau in the effect, demonstrating that some signs persist over an extended period of time.

The clotrimazole data demonstrate that when used for a full 4 weeks course, favorable resolution of signs and symptoms comparable to terbinafine can be achieved. However, when used for only 1 week, as consumers often do, the results are significantly less favorable.

This confirms what Dr. Elewski presented

earlier from the clinical experience in her patients.

Now, in response to FDA's questions, I would like to present our perspective on new product development requirements.

[Slide.]

There are two different types of development approaches in this category involving either new chemical entity or an NDA line extension of a currently available compound.

All new developments, whether NCEs or line extensions, should require a statistically significant separation from placebo using the complete cure endpoint to demonstrate efficacy as required for Rx drugs, where NCE studies may also be required to define the appropriate dose.

With respect to line extensions, where the dose of the active has already been effectively established, the dermal pharmacokinetics and MIC values for the new formulation of the known drug should guide dose decisionmaking.

Based on this approach, line extensions

would require clinical evaluations to establish the appropriate frequency and duration, but would not necessitate dose ranging studies.

[Slide.]

Having established the effectiveness of terbinafine and provided our perspective on new product development, I would like to spend a few moments of my presentation responding to the questions regarding safety and labeling raised by the Agency.

[Slide.]

Starting with the lack of effectiveness or LOE reports, the Agency has noted that there has been an increasing number of these reports in their AERS database. In fact, overall, the number of adverse reports we receive for topical Lamisil is quite small.

LOE reports are captured as part of the adverse event reporting. As you see in the middle row at the bottom of this chart, it represents the absolute number of LOE reports received for topical Lamisil.

Below that, we see the number of units sold during the same time frame. Consequently, the graph gives you the ratio of these numbers and demonstrates a declining rate of LOE reports as a percentage of product purchases since the launch of the OTC product.

[Slide.]

In the interest of understanding whether effectiveness has changed over time, we compared studies conducted over the last decade and found no difference in efficacy.

Other analyses have confirmed that the species of dermatophytes in our studies that cause athlete's foot are the same over time. They continue to be fully susceptible to terbinafine.

[Slide.]

The Agency also raised the questions of whether the risk of cellulitis is increased in inadequately treated tinea pedis. It is well understood that cellulitis is rare, and is not related to the drug per se. In fact, it could even be misdiagnosed, as we heard this morning.

In the AERS database, a review of all 15 topical antifungals, there were only cases of collection since 1965. Since 1993, cases have been reported in connection with Lamisil. The relationship between cellulitis and drug treatment in these cases is unclear.

There also does not appear to be an increase in cellulitis reports over time. However, inadequately treated tinea pedis may make individuals more prone to this infection.

The data indicate that certain subpopulations, such as people with diabetes, may be at the higher risk of cellulitis, but that the risk may actually be reduced by effective antifungal treatment.

Our recommended label changes would include a warning for people with diabetes and other identified risks.

[Slide.]

Regarding other labeling changes, we have given great consideration to the issues raised by the FDA, and are pleased to share our labeling

recommendations, which are intended to optimize the consumer benefit with terbinafine, and what do we know about the patient experience.

We know they are equally satisfied whether they achieve the effective treatment or complete cure endpoints.

[Slide.]

As you can see in this chart, the comparison evaluates patient global assessment scores from the analysis of one of our clinical trials. Patients who achieve either effective treatment or complete cure were selected and had equivalent findings on the global assessment scale.

Based on clinical and consumer experience, we conclude that effective treatment should be the basis for setting consumer expectations for product performance, and therefore be reflected in labeling.

[Slide.]

If this committee recommends that new label be developed for NDA products to set consumer expectations about treatment outcomes, we recommend

that effective treatment be the guide. These improvements will set appropriate expectations, enhance compliance, optimize treatment outcomes, and provide stronger safety guidance.

Consequently, monograph products should add similar language indicating the required duration of treatment and indicate if no reliable clinical data are available. We would like to take you through our current thinking on propose labeling changes for the class using terbinafine as an example.

We agree that there is potential confusing language in the current PDP or primary display panel of the packages.

[Slide.]

We recommend removing "Cures most athlete's foot" and replacing that language with "Athlete's foot treatment."

To enhance compliance, we also recommend making treatment duration prominent in this primary display panel. For example, we would replace current language with information that helps

consumers understand they are treating an infection, and for the full course of treatment.

This is the most important language to communicate in the label. All products in this category should clearly delineate the required duration of treatment.

In the case of Lamisil, the statement would be, "Must be used twice daily for full 7 days to eliminate fungal infection."

We also recommend moving the language on "Relieves itching and burning" to the Drug Facts.

[Slide.]

Here, we remind the consumer about completing the full course of treatment even if symptoms resolve. What we want to do is help consumers manage the expectations toward treating symptoms and signs.

This copy may read, "Many get relief from their symptoms (itching and burning) after 1 week of treatment. Signs such as redness will last longer until the outer layer of skin naturally replaces itself."

Additionally, we recommend strengthening the warnings specific to diabetics. For example, that language would read, "Stop use and ask a doctor if condition worsens or new symptoms develop; this is especially important if you have diabetes."

In short, these changes will improve health outcomes for the millions of consumers with athlete's foot who count on these safe and effective treatments.

We intend to test, refine, and implement enhanced labeling that will more clearly guide those who use our antifungal products, so that their expectations are well met and their outcomes improved.

[Slide.]

In conclusion, we have provided data from a variety of sources that confirm the safety, effectiveness, and unique benefits of terbinafine when used for 1 week with no evidence of increased lack of effectiveness or resistance development.

While we recognize complete cure as the

appropriate endpoint for the approval of OTS topical antifungals, effective treatment is the most meaningful endpoint for communicating efficacy information in labeling.

We have provided commentary on how future products might be developed and have highlighted the rationale by which new chemical entities should be held to a higher standard than line extensions based on separation from placebo.

Finally, we share the goal of improving consumer health outcomes. We have presented our proposed labeling and delineated its clear purpose.

We thank the committee for your time and interest and look forward to your input and guidance, as well, to further collaboration with FDA to bring label improvements that maximize the safety and effectiveness of these important therapies.

I will be glad to address any questions you may have.

Thank you very much.

DR. CANTILENA: Thank you, Dr. Albrecht.

I will actually ask all the speakers from the open public hearing to come up to the podium and we will open this up to questions from the committee members. You can just identify who you are asking, if you know, and we will start with Dr. Fincham.

DR. FINCHAM: I have a question for Dr. Albrecht. You presented data from two studies, 2506-01 and 2508-01. In the 2506-01, you listed the sample size as 67. Was that in both treatment arms or was that total patients?

DR. ALBRECHT: No, that is total, that is total patients, one of our pivotal studies in the NDA.

DR. FINCHAM: So, approximately 35 in each.

DR. ALBRECHT: Yes.

DR. FINCHAM: In the second study, on one slide, you said the sample size was 97.

DR. ALBRECHT: Yes.

DR. FINCHAM: And in the other slide it was listed as 193.

DR. ALBRECHT: Yes. Actually, the total size is 193. In fact, these data were presented this morning by the FDA, as well. The 97 relates to two treatment groups I showed in that chart, which is the 1 week and the 4 week, so we have broken that up. It is 97 for the 1 week and 96 for the 4 weeks, so it adds up to the 193. That was the total study size, 4 treatment legs, 1 week terbinafine, 1 week clotrimazole, 4 weeks clotrimazole, and 4 weeks terbinafine.

DR. FINCHAM: Just a follow-up question, if I might, sir. How were the subjects chosen to be in each of those arms?

DR. ALBRECHT: They were randomly assigned to the treatments.

DR. CANTILENA: Other questions on the committee? Dr. Davidoff.

DR. DAVIDOFF: I have a comment and a question.

The comment relates to the apparent close tie between changes in symptoms, or appearance of symptoms, or disappearance of symptoms, to where

the people start or stop therapy, because I was noticing, looking back at the data that Dr. Fritsch presented this morning, that the vehicle actually in the first week appears to be responsible for eliminating the symptom of pruritus--that is page 12 of her slides--and for a sizable portion of the relief of pruritus even in the 4-week treatment with Drug Product F.

I suppose that argues for being especially cautious about having patients stop treatment prematurely, because the treatment decision may be based on something that has nothing to do with the active drug. That was just really a comment, and I would be curious whether you have any thoughts on that.

The question had to do with the proposed statement of encouraging patients to be sure to take the full number of prescribed days of treatment, which I think everybody in medicine would agree with it in general that undertreatment and partial treatment is a bad thing particularly in light of potential emergence of resistant

strains in bacteriological infections.

However, it seems to me that it is quite possible, given some other data, that even a shorter period of treatment than 7 days might actually be as for, say, terbinafine, may be as effective as 7 days.

My question is, are there data on that, because the drug apparently is there in such large quantities and persists even after you stop using it, that it is possible the organism is effectively eliminated on Day 2, so it would be a little hard to justify that statement, if that is the case.

DR. ALBRECHT: Thank you for the question. Perhaps to the first question you had, which was, of course, the drug product works as a composite. It is the drug in the composition and the vehicle. Of course, if you have a very good emollient vehicle, it will help to heal the condition.

In the case of our product, it is very clear that terbinafine is such powerful fungicidal agent that it certainly kills the fungus, and then is symptoms persist, that is just the dynamics of

the disease, as I showed.

Now, in response to your other question, we actually have clinical data from controlled studies that show that terbinafine is effective in eradicating the fungal disease and eliminating the symptoms after 5 days. We have the studies both with 7 days and 5 days in the same study leg.

There also is, it's not on the market, terbinafine Rx derm gel preparation, which is effective both in 7 days and 5 days with a single day application.

So, again, I think the potency of the antifungal compound is extremely important.

DR. DAVIDOFF: So, then, it isn't entirely justified to recommend treatment for the full 7 days on the basis of the data.

DR. ALBRECHT: Well, we have a labeling for 7 days, we have not pursued a shorter treatment period, but I think if your patient should tell you they only treated for 6 days, you should probably feel quite comfortable that at least the fungus is being killed.

DR. CANTILENA: We have a comment over here from Dr. Wilkin.

DR. WILKIN: I would be interested if you are aware of any literature that speaks to allylamines, and I am actually blocking which ones were tested, but I thought they had modest cyclooxygenase inhibitor reactivity, some anti-inflammatory activity.

Dr. Elewski seems to know that part.

DR. ELEWSKI: I know that. There was a study done by I believe Ted Rosen in Texas, and he looked at that in sunburns. I think he actually did a study where he burned red skin from a sunburn to see what gets rid of the erythema the fastest, and judging what gets rid of erythema from a sunburn, he was looking at an allylamine with a trade name Naftifine. It actually was a fairly good eliminator of inflammation.

Consequently, some other drugs have been look at it this same fashion, Ciclopirox, which was mentioned this morning, is one of the more common prescription products, and so forth.

So, I don't think it is a function of allylamines only, because Ciclopirox had it, and ketoconazole, I think had something similar, but it was done in a different way, but the paper was Ted Rosen, and it was looking at burns, if that helps.

DR. WILKIN: But the moiety we are talking about now is an allylamine.

DR. ELEWSKI: Right, Naftifine is an allylamine.

DR. WILKIN: And also terbinafine.

DR. ELEWSKI: Right.

DR. CANTILENA: Dr. Katz.

DR. KATZ: I have a question for Dr. Clayton concerning the consumer research data that you referred to, done on internet.

How did you locate those patients in the first place and what was the percent of people who responded to that survey?

DR. CLAYTON: The patients or the consumers are identified through screeners of symptoms that they complain of, so it is done through a variety of signs.

DR. KATZ: How do you get the names to contact them on the internet?

DR. CLAYTON: I can't tell you. A firm is employed that is skilled at surveying by internet.

DR. KATZ: Do you know the percentage of response?

DR. CLAYTON: I don't know the percentage of response.

DR. KATZ: We need to know. Provides fast relief, 60 percent of the respondents, so how do we know that is not 6 percent of the respondents, the others didn't bother responding?

DR. CLAYTON: These are 350 that actually completed the survey.

DR. KATZ: But maybe 3,000 were surveyed. I mean we have no idea of this data that is being presented.

DR. CLAYTON: I apologize for the fact that it wasn't complete. This survey that I reported today is very consistent with the others we have done for the past 10 years. Some of them have been one by mail panels, some of them have

been done by internet.

This particular most recent one was done that way, but it is done through a statistical model that is used to validate the representation. I apologize for not having that information for you today.

DR. GANLEY: Could I comment on that, too?

DR. CANTILENA: Go ahead.

DR. GANLEY: We have seen some of these before, and there are internet sites where you can sign up and fill out a questionnaire and give some history about yourself. They create a database.

For example, if you have a history of athlete's foot, they may ask you that question, and then when someone comes in for a survey, they will send out to all the respondents, you know, they may have several hundred thousand respondents and 10,000 or 50,000 say that they have a history of athlete's foot, and then they will go out and send e-mails to all of those people, asking them if they are interested in participating in a survey.

A certain percentage will come back and

say yes. Now, the one thing about these sites is that you collect points by the more surveys that you fill out, and if you collect enough points, you will get some type of gift.

DR. KATZ: That is the point of my question.

DR. GANLEY: John, you can correct me if I am wrong.

DR. CLAYTON: As Dr. Ganley said, some are that way. I, unfortunately don't have that information today. Again, it has been done by a variety of different methods over these 10 years, the data have been extremely consistent throughout except for the trends that we have noted.

DR. KATZ: But that type of survey would be highly questionable as far as the validity of who is responding to the internet and getting points and getting prizes for responding. I think you would have to agree that the scientific validity of such a survey would be subject to question.

DR. CLAYTON: There have been standards

set for these types of surveys as a general statement. I am not addressing all that are out on the internet, but particularly the firms that we employ to do these types of things, they are validated against a certain model. Unfortunately, as I said, that was done by a market research group, and I apologize for not having that information.

DR. CANTILENA: I think we can move on.

Dr. Ringel.

DR. RINGEL: I think this question is best addressed to Dr. Elewski because she has had so much experience, breadth of experience with many different products.

We have heard that most cases of tinea pedis, in fact, are moccasin style tinea pedis, whereas, I believe most of the studies have been done with interdigital tinea pedis.

I was wondering if you or the companies that you have consulted for have data about the cure rates, mycological and clinical, for patients both with moccasin style and/or interdigital,

first, and secondly, with patients who have onychomycosis along with their interdigital tinea pedis since probably those are the majority of patients who are going to be treated.

DR. ELEWSKI: The most common type of tinea pedis that we see is the interdigital. The interdigital is by far the most common, much more common than moccasin. The interdigital is when the toe webs, you know, that we went over, the web spaces are infected, and the prime organism is Trichophyton rubrum.

By the time someone has actually gone on to get the moccasin type tinea pedis, many of these people, if not all, have some form of onychomycosis by that point, so treatment with a topical antifungal poses some challenges because if you use a topical antifungal for moccasin, you probably could eventually eradicate the dermatophyte from the bottom of the foot, but the problem is you still have dermatophytosis in the nail, which will eventually--what I teach our residents are the fungi are greedy and they want to continue to grow,

and if you get rid of it from the bottom of the foot, the plantar surface, it may eventually come back from the nail.

So, unless you eradicate the fungus in the nail, then, you probably will have recurrence down the road, but interdigital tinea pedis can occur without onychomycosis, in fact, it generally does especially in the epidemics that you see from swimming pools, gyms, and health spas, and so forth.

The interdigital, simple and complicated, is a simple scaling process, and these people don't have onychomycosis.

DR. RINGEL: Perhaps someone at the FDA could help me. I believe in the package that we got before the meeting, moccasin style tinea pedis was about 50 percent, isn't that correct?

At any rate, do you have data for clearance of moccasin style tinea pedis?

DR. ELEWSKI: Well, for moccasin--the antifungals we are talking about now, that are OTC, are for interdigital tinea pedis--for moccasin

tinea pedis, there have been studies looking at it for topical antifungals, and it has to be done longer.

For example, and I could probably defer to Novartis, because there has been a study looking at it, and it is 1 week for interdigital, I understand it would it would be 4 weeks for moccasin tinea pedis.

DR. ALBRECHT: It's 2 weeks.

DR. ELEWSKI: Oh, it's 2 weeks.

DR. ALBRECHT: The Lamisil AT cream is labeled for 2 weeks of treatment for moccasin.

DR. RINGEL: So, do you think that should be on the labeling what kind of tinea pedis is being treated?

DR. ALBRECHT: It is on the labeling. If you look at our labeling, in fact, there is even images for interdigital foot as opposed to another image for the sides of the foot, which indicates to the consumer the plantar form. So, there are two indications on the label, and they are differently instructed in terms of duration of treatment and

the imagery, how to apply the product.

DR. WHITMORE: I don't think we saw efficacy data on that, and I think Dr. Ringel and I would also like to know the effectiveness, the efficacy of the study with the plantar for 2 weeks as indicated on the label.

DR. ALBRECHT: Right. Again, the meeting was focused on interdigital, so I didn't put the data into my presentation. Do we have them handy?

DR. CANTILENA: You could have life-line, if you would like, and call home, or we can poll the audience, that's right.

[Laughter.]

DR. CANTILENA: Dr. Whitmore.

DR. WHITMORE: Are there different studies done with each of the different vehicles, for instance, Lotramin Ultra Cream versus Lotramin Antifungal Cream and also with Lamisil Spray versus Cream? Is there a superior vehicle that produces better clearance, or why the different vehicles?

DR. ALBRECHT: Different vehicles because the consumers actually like variety. In fact,

consumers are very form loyal, if consumers like a cream or consumers like a spray or a powder, so we do separate studies on the cream, and we have separate studies in our solution, and the efficacy of both vehicles is quite comparable.

DR. WHITMORE: Is the same true for Lotramin Ultra Cream?

DR. CLAYTON: Actually, Lotramin Ultra Cream is only in cream form, so it is the only dosage form, but comparative studies against other active ingredients, I don't believe they have been done. There may be a few out there, but not pivotal type, large-scale studies.

DR. WHITMORE: Do you use anything to direct consumers to which they should purchase?

DR. CLAYTON: Other than through advertising, not directly. I mean the labeling certainly describes the treatment regimens specifically, but only through those means of communication.

DR. CANTILENA: Thank you.

Dr. Benowitz.

DR. BENOWITZ: I have two questions. Dr. Elewski would probably be the one to address them.

The first is you made the point that you think effective therapy is equivalent to cure by the criteria we heard this morning. I am just wondering, do you know of any data on relapse using those two criteria, or may recurrence or long-term outcomes?

DR. ELEWSKI: I don't have data on that, but let me expound a little bit on what you said for effective therapy, because one thing I didn't use as an analogy is acne. You know, it is hard to evaluate skin studies, and if you are treating, for example, something like acne, what do you say is the endpoint, is it getting rid of the comedones, is it getting rid of the pustules, is it getting rid of the papules or nodules or cysts, of is it getting rid of the scarring or the oil?

So, at the end of the study, if you still have scarring or you still have oil, does that mean you still have acne? No. Likewise, that is what I was getting at for effective treatment, if you have

a little bit of erythema, a little it of scale that may be unrelated, it could be effective treatment.

As for data, probably the best study was the study that was alluded to this morning looking at Lamisil/Terbinafine 1 week versus 4 weeks, and looked at it after--I wrote this many years ago, so it is hard to remember--I think it was 48 percent in those who used it for a month, and it was 42 percent in those who used it for a week, had no recurrence at 1 year or longer.

Of those that recurred, one-third actually had a new organism, implying that they didn't really recur, they got a new infection. So, that is probably the best study looking at that, that I know of, unless any of the industry colleagues want to add to that.

DR. BENOWITZ: I was just trying to be sure that the finding of mild symptoms really means the same thing as a cure in terms of recurrence rates, because the efficacy or efficient, whatever the term is, shows about 80 percent outcome for that endpoint, but yet there is about a 40 percent

recurrence rate.

I am just trying to figure out can we really be sure that what you are saying in terms of effective outcome is the same as cure.

DR. ELEWSKI: The issue, I think, is the word "recurrence," because how do you define recurrence? Is it recurrence meaning you never got rid of the infection in the first place, so the infection recurred? Or is recurrence that they got rid of the infection, but they put their feet back in their fungal-ridden shoes, as someone mentioned already? You have fungus in your shoes, as Dr. Wilkin mentioned, and they got a new infection.

So, it is very hard to sort this out. I know Dr. Ghannoum and I at one point were looking at doing molecular strain types on initial infections to see if someone got a new infection, which we could call a recurrence, if you wish, whether it was really a recurrence or whether it was a new infection.

You could do this if you found the molecular strain of infection A, and then six

months down the road, they get a new infection, what is the molecular strain type of that new infection, you know, looking at the DNA pattern of the organism.

We have never done that. I don't know if you have.

DR. GHANNOUM: Actually, you know, we were trying to do that. At that time, there was no method which allows differentiation of different strains, that allows you to differentiate rubrum from mentagrophytes, but not between rubrum.

Now, the good news is there is a method that allows people to differentiate between two different strains for T. rubrum, for example, or mentagrophytes, and I think maybe pretty soon we will be able to have some sequential isolates to follow that.

DR. BENOWITZ: I understand that. That is not really my point. I think there are probably no data.

My point is just however you look at recurrence, do we know it is the same for someone

who has a complete cure by the definition we heard this morning, versus effective treatment.

DR. ELEWSKI: I can tell you from my own practice, from my own patients, when I have a patient and they finish their treatment, and I see them a month later, and the majority of their symptoms and signs are resolved, and they may have just a wee it of something left, and I follow them again, for other reasons, they come in for problem A or B or C down the road, they generally are still free of fungus.

Some of them will go on to get something new. I am particularly interested in this, so I like to do cultures. I am out there doing cultures where many people don't. Often it is a different organism. I just like to do that for academic interest, but I have never published that.

No, there is no data that I am aware of.

DR. BENOWITZ: The second question that I had is you made a statement and supplied some evidence for why you thought there was no need to do dose responses.

My question is, why was the particular dose chosen, has been chosen for the various drug, and without doing a dose response, how can you be sure that you don't need to do a dose response?

DR. ELEWSKI: I think I should defer that to the companies who have the drugs.

Do you want to comment on that?

DR. ALBRECHT: I can offer comment. I think I showed the data that we, based on the MIC values, and then based on the availability of the drug in the skin, it was determined that we had an effective dose at a low level, and therefore, no safety issue involved, pursued that further for clinical development.

DR. CLAYTON: I would give a similar response except that there are also some studies that have been done with some of the drugs using guinea pig models, infected guinea pig models to determine various concentrations, and differences in outcomes on those.

I am not aware of many, if any, clinical trials that are comparing true dose response.

DR. ELEWSKI: The objective is to exceed the MIC of the fungus and eradicate the organism. I think we are doing that with the antifungals available for superficial cutaneous fungal infections, which is the issue on the table.

DR. BENOWITZ: So, can we be as sure for concentrations in the skin? I know for blood it's simpler because there is organism in the blood and we get a concentration of an antibiotic in the blood, and we can sort of make sense out of the MIC, but can we extrapolate that to skin concentrations versus MIC acting on fungus in the skin?

DR. ELEWSKI: I can't really comment on that. I don't know if anyone else wants to.

DR. CANTILENA: Okay. No one is going to move on that. Is there a comment? You had your hand up, Dr. Wilkin.

DR. WILKIN: I think Dr. Benowitz asked a really key question, and that is what is the gold standard for cure. I think that is what you were going after. Dr. Elewski has obviously thought a

lot about this, and many of the things that you have thought about, our dermatology group at FDA, you know, I have to say that we think in many of the details along the same line. I think that may be a general dermatology perspective.

One of the difficulties that we have had to wrestle with is since we are looking at just the three things, one is the KOH, that is, you scrape and you look and see if there is any evidence of the hyphae present.

There is an enormous sampling error difficulty. One of the exercises that a first year resident gets to do, or a fourth year medical student rotating on Dermatology, is you have them scrape the foot and do a KOH. They can't find it the first time, and you have them do it again, and they can't find it.

Finally, on the third time, they may locate it. So, it's not the easiest thing to do even in the hands of a skilled investigator, sometimes there is one small area. So, I think there are enormous sampling errors with the KOH.

The culture may be the same. We do actually have some information that helps us understand the culture. The entry criteria for the kinds of studies that we are discussing today are patients who have a positive KOH, and they look to the clinician as though they have the presentation of tinea pedis. That is what gets the patient into the study.

So, that patient would be in the intent-to-treat group. They also get a culture at baseline, and then three weeks later, either a dermatophyte grows out or it doesn't, and it doesn't grow out one-third of the time, so the MITT group is typically on the order of 65 percent of the ITT group.

That tells me that there is that same problem with the culture, is that when it is negative, it may have less informative value, that there can be enormous sampling errors.

Nonetheless, we are willing to take mycological negativity, if you will, negative KOH, negative culture, and then look at the skin signs,

and I think as Dr. Elewski has pointed out, the skin has a very limited repertoire in response to any kind of noxious agent, be it atopic dermatitis, contact dermatitis, or tinea pedis, or the dermatophyte.

I mean it can scale, it can get red. It doesn't really have many other things in its vocabulary. So, there is some confusion when you get down to the 1-plus erythema and 1-plus scale. It is probably true that some of those patients represent a cure and some of them don't. I think it may go both ways.

It may be too high a hurdle on the foot to actually demand zero clinical signs and symptoms, but we like looking at that because it is such a pristine group. I mean it's a nice comparator from one product to the next, especially when we are comparing against the placebo, so we didn't really prepare that part for the discussion today, but I am glad Dr. Benowitz brought it up.

There is no gold standard. It would really require people who got new shoes, maybe went

to the International Space Station where there is no dermatophytes on the floor, and they were watched over an entire year to see whether or not the fungus came back. So, that is a little on the epistemology, if you will, of what we really do know.

The second part, I would like to say is about do antifungals get to the site of action. I think it is true that you can scrape skin, you can lift it off with tape strips, and you can find that the active is there, but we all know that it needs to be in solution before it is really going to be active.

The other thing is Robert Jackson has got a really nice paper, and Dr. Elewski probably knows the exact citation, but it is the one where dermatophytes move in a centrifugal manner, I mean they move out, so that the leading edge, when you were looking at the very nice picture of between the fourth and fifth toe, that center part that everyone was focused on, that is probably gram-negative bacteria in that location.

The actual dermatophyte is out in what looks like normal-appearing skin out at the edge, and I think it is really very difficult to get these large chemicals to that location down through that very thick stratum corneum, so I don't think we have seen at FDA really good data to tell us that these products are in solution at the site of action, at that location, and it is a 1 to 1 relationship.

I guess I will stop at that.

DR. CANTILENA: Thank you.

Did you have a comment on this question, Dr. Ghannoum?

DR. GHANNOUM: Which question?

DR. CANTILENA: On the comment that was raised over here by Dr. Benowitz.

DR. GHANNOUM: I just wanted to comment about a couple of things. Number one is about how really do we determine the vehicle or the dose. A lot of the time, I know our Center gets studies in guinea pig model, which was mentioned, and that guinea pig model we look at different vehicles and

say which one, let's say, caused this erythema, and the same applies for the doses. We really do, let's say, three, four doses, and then select the best one.

I think industry at that time, then, they take it, that's one thing.

I want also to comment about the International Space Station. In actual fact, there is Trichophyton there, they found.

[Laughter.]

DR. GHANNOUM: There was a study, and it was there. So, I don't know where it came from, but it was there.

The last point is about the calcofluor and the KOH, the difficulty in that. I think really it is very important to use, not just regular KOH, use the calcofluor, because you can improve the sensitivity because this dye is specific for it, and I think a lot of the studies, like from 53 percent, you can improve it up to 80 percent.

DR. CANTILENA: Thank you.

Dr. Wilkerson.

DR. WILKERSON: Dr. Elewski, one question. There has been a lot of talk over the years about yeast and bacteria, and I haven't heard much about that today. Some of these compounds are more effective from what I understand from what people say, which isn't always true.

Overall, do yeast and gram-negative bacteria, one thing and another, play, and how important is it that the agents that you are treating with have activity against those also?

DR. ELEWSKI: That would be called, if you had a yeast or bacteria in the toe web, we could call that toe-web intertrigo. It could have started with a dermatophyte. I think one of the speakers talked about how Dr. Layden and Kligman described this, and they described it as a syndrome of dermatophytosis complex, where the dermatophyte, which is able to digest the keratin, damages the keratin, destroys the barrier function, and allow bacteria to enter.

Then, you may get a weeping, macerated toe web in that scenario. I actually did a study

looking at this, and we found that topical azole family category, and we were using Econazole cream as an example, and we published this and found that it had a lot of antibacterial activity, because we culture people beforehand and treated them with Econazole, and they did very well.

We can extrapolate from that and from others who have written about this that the azole family Econazole, clotrimazole, and so forth, have some antibacterial activity, and also anti-yeast activity.

Now, candida can also be a pathogen in the toe web, but it is extremely rare, and it generally would be a secondary problem, and probably I would think if it is there, it probably came riding on the back of a dermatophyte, so if you killed the dermatophyte, then, you would eradicate everything that was there because of the dermatophyte, and the same thing you could also say with this dermatophytosis complex. If you kill the dermatophyte, well, the dermatophyte was the way that the bacteria could get a hold in the foot, so

if you kill it, there is nothing left for the bacteria to do but leave.

DR. WILKERSON: Well, I think where this is important is particularly when we are talking about diabetics and other immunocompromised situations where it may be more important. My understanding is that allylamines do not have much of this activity towards yeast, and I don't know what their activity towards bacteria is.

DR. ELEWSKI: The allylamines have less activity for yeast and less activity for bacteria than the azoles, however, we are talking about now a topical antifungal, so if you were to take a drug, such as oral terbinafine orally, it is not going to be very effective for cutaneous candida, again because terbinafine would have to get absorbed, get into the skin, and it wouldn't get into the skin in high enough concentration to kill Candida albicans.

It might kill Candida parapsilosis, but not Candida albicans, but applying it topically, it is a very effective drug for Candida.

Another example could be another yeast Pityrosporon. Terbinafine doesn't get into the skin in high enough concentrations orally to kill Pityrosporon, but you can apply it topically to kill Pityrosporon, because it is exceeding the yeast.

So, when using these drugs topically, they generally, because you are applying to the skin in high enough levels, are going to exceed the MICs of the dermatophytes, of Candida, and of some, but not all, bacteria.

The bacteria that I still see a problem in my patients who have bacterial infections, some of which are diabetic, most of whom, though, have an anatomical occlusion causing a deformity, which leads to maceration because of the deformity, and they may have pseudomonas, and that can be a problem.

I have seen a few, a handful of patients with chronic pseudomonas in the toe web, that the only thing that I have been able to do to eradicate that is topical gentamicin, garamycin product or

oral products that are appropriate, but that is very, very rare, but nonetheless, I have seen.

DR. CANTILENA: Thank you.

DR. WILKERSON: One other part of my question was to the Schering-Plough representatives. My understanding is Lotramin Ultra is a different compound than Lotramin AF, is that correct?

DR. CLAYTON: Yes, Lotramin Ultra uses butenafine hydrochloride, whereas, Lotramin AF is clotrimazole.

DR. WILKERSON: Outside of playing on brand names, don't you consider that to be really confusing to consumers?

DR. CLAYTON: We have tried to communicate the difference. We have tried to communicate it both through packaging and advertising, and we have been challenged by Dr. Ganley and his Division to test this with consumers, which we have done through actual label comprehension and understanding, but we have tried to make them happy, quite different in appearance and the

communication piece also.

DR. WILKERSON: It was obviously done to play off of your brand name, correct?

DR. CLAYTON: It was done to establish credibility that existed in the marketplace, but there was the full intent to make sure that consumers could distinguish between the two.

DR. CANTILENA: That was a very good answer, by the way.

Dr. Fincham.

DR. FINCHAM: I have a question for Doug Bierer.

You mentioned in one of your slides, three hoped-for additions to labeling, and you mentioned a hope for increase in compliance. I was just curious from your data, what is the baseline rate of compliance and what do you hope to gain as far as an increase in compliance by your proposal?

DR. BIERER: I don't actually have data on the baseline for compliance with these products. That would depend upon the individual product. We don't collect that as an association. I think you

would have to talk with the individual companies.

But I hope that we would see consumers understanding from this proposed labeling, which I think you have heard from both companies that they would understand that they should complete the full course of therapy even if their symptoms improve. I think that is the message that we want to communicate to consumers.

DR. FINCHAM: But nowhere did I hear anybody talk about specific compliance rates, unless I missed it.

DR. BIERER: No.

DR. CLAYTON: The only thing we had was consumer survey, which indicated that they were using it on average 7.3 days, and a high percentage was using it less--

DR. FINCHAM: I guess I am talking about both duration, as well as intensity, and nobody talked about specific intensity, just the duration.

DR. CLAYTON: You mean numbers of applications per day? Some of the products are once-a-day application, some of them are twice a

day.

DR. CANTILENA: Final question. Dr. Wood.

DR. WOOD: I have two comments rather than questions. The first one is the techniques, the laboratory techniques that are used to establish the diagnosis. We are here to give advice, and it seems to me that the techniques that are being used are antiquated.

We no longer use cultures to identify tuberculosis for lots of good reasons. There are much better molecular biology techniques that could be used to identify these organisms. The fact that we are still using KOH seems to me just mind-boggling, so I would recommend that if we are going to start thinking about how we identify the organisms in the future, we ought to use the 21st century techniques, and not techniques from I guess almost the 19th century.

The second part is I think it shouldn't go unchallenged that concentrations in skin are necessarily higher by topical administration than by systemic administration, and I haven't heard

data to support that, nor have I heard data that say what these concentrations need to be at the site that kills the organism, because presumably, the site that kills the organism is not necessarily the one that you are sampling from when you scrape the skin.

So, I think we need to be careful about that. I am particularly concerned with the way that has been offered given that the data seem to suggest that systemic administration is at least, and probably substantially more, effective in terms of a cure rate than topical administration, so the assumption that the topical administration gives you higher concentrations and, hence, greater efficacy, doesn't seem to be borne out by the facts.

DR. CANTILENA: Any comments from the speakers to Dr. Wood?

DR. ELEWSKI: I don't have a comment on that, but we did do once a tape stripping study with an antifungal called Econazole, and did find that it was viable in the skin doing it

sequentially over a long period of time after someone applied it and tape stripping it off to see if you could still get fungus.

It was an in vivo kind of test, but I am not aware of any other data on that.

DR. ALBRECHT: I might just add to the study I referred to in my presentation. We did a skin stripping study using the nesmith [ph] method, and five weeks after initiation of treatment, you could still find drug at effective levels, you know, representing superpotent MIC values, if you will. I don't know whether that satisfied you.

DR. WOOD: Oral administration?

DR. ALBRECHT: We haven't done oral administration.

DR. CANTILENA: Dr. Ganley has one comment and then we will go to a break.

DR. GANLEY: I just wanted to follow up on something that Dr. Benowitz asked, and I am going to direct it to Dr. Elewski, because you had made the recommendation that there not be dose response studies done.

I think from a regulatory point of view, I think when we look at the data for the negative mycology, that Dr. Fritsch reported on today, it was her Slide 15, if you look at the negative mycology, at the primary timepoint, it runs from 55 percent to 88 percent.

If you look at her Slide 17, where you actually look at effective treatment, the effective treatment is 38 to 69 percent. So, it seems that there is a lot of room for improvement there.

In a slide that Dr. Albrecht showed, which was his Slide 13, which showed that there is a 1-week treatment of clotrimazole and a 4-week treatment of clotrimazole, there seemed to be difference. It may not have been powered to show a difference, there seems to be a difference on the treatment in obtaining a negative mycology.

So, I would like some information on how you could recommend that there not be a dose response, or that we shouldn't request that because our situation is we have folks coming in wanting to do 3-day treatments and 1-day treatments just to

establish that they beat placebo. It seems that if you come in with the right chemical, you can beat placebo, but then that may not be the best treatment for someone.

It would be concentration or numbers of applications per day or duration. Your statement is a very important statement if that is your position, and I would like to understand, because in my discussions with industry, when I have asked for data on a study where it has looked at multiple different regimens or doses within the same study, there is not much data.

I mean it is very important from a regulatory point of view as to what the hurdle is that someone has to get over, because otherwise you will see 3-day and 1-day treatment simply because they have beaten placebo.

DR. ELEWSKI: I guess I am not totally sure what you want, but I know with terbinafine, there have been data showing that 1 week of treatment may be as effective as 4 weeks of treatment for tinea pedis, so that dose response

has already been done.

DR. GANLEY: Within the same study.

DR. ELEWSKI: Within the same study.

DR. GANLEY: But I am thinking as a blanket statement, you know, you are saying that there is not a need for it, and that has a profound impact.

DR. ELEWSKI: I guess I was getting at that we have drugs that are effective, that are working to kill the dermatophyte, and I wasn't sure that further gathering more data is going to help the patient.

DR. GANLEY: But if someone comes in a 70 percent mycologic cure rate and an effective treatment rate of 50 percent, there is a lot of room there for improvement, it seems. I mean your blanket statement is--

DR. ELEWSKI: I don't have her slides in front of me, but 70 percent mycological cure, it probably isn't higher because there is some persistent scale there, which is causing the KOH to be positive. I think that is part of the problem

with that.

DR. ALBRECHT: May I comment on that?

DR. CANTILENA: Yes, one quick comment, please.

DR. ALBRECHT: I think Dr. Elewski made the point 1 and 4 weeks, there is no difference, established dose differences, there is lack of dose differences for this compound.

Another study that we have done, and I can't say a whole lot, because it's a developmental project, but we have actually done a study, a properly designed, adequately well controlled, randomized, placebo-controlled study with three different concentrations, 1, 5, and 10 percent for a proper treatment course of tinea pedis. We did not find any difference in the response.

So, again, I think dose ranging doesn't seem, with these kind of compounds, doesn't seem to really gain a whole lot once you have established enough drug in the skin. That is really the point I was trying to make before.

DR. GANLEY: The other question I have for

you, Dr. Albrecht, is you achieve approximately, I think 88 percent negative mycologic cultures, so that seems to suggest that the 12 percent or so would have had positive cultures.

DR. ALBRECHT: Not so, Dr. Ganley, because mind you, mycological response is the combination of culture negative and KOH negative, and I think we just discussed that KOH is a very fickle, if I may so, kind of instrument, so we may have had--I don't know the number right now--but we may have had 95 percent negative cultures, but the people failed because the KOH was positive, and that just means nonviable structures may have been found in the skin.

DR. GANLEY: So, you have 100 percent of the cultures are negative, is that what you are saying?

DR. ALBRECHT: I am not saying that, and I would have to look that up, but I submit to you, and I think even as we heard earlier from the FDA statistician, that a number of cases fail based on positive KOH.

DR. GANLEY: My question is has anyone ever looked at those where the culture has failed to see, are those the MICs for the organism growing there different from what we have seen throughout today, is it something that that is a resistant organism, or it just turns out that this is a compliance issue possibly with the individual.

I am directing it, are there outlier organisms there that require higher MICs.

DR. ALBRECHT: I can't speak to that, but may be Dr. Ghannoum or Dr. Elewski.

DR. ELEWSKI: Dr. Ghannoum and I did a study two years ago looking at onychomycosis. It was a huge study to see--and we did MICs on the organism against all the antifungals, and there was really no issue of resistance including people who failed, which made you wonder, and this data has been published, what does failure mean and why does someone fail. It's a very complicated process. It may be compliance issues, it may be the extent of the infection, and it may very likely be the patient's immune system may be doing something.

DR. CANTILENA: Are there questions for the speakers? We had a show of hands over here, Dr. Benowitz, Dr. Whitmore, and Dr. Wilkin. Are they for the speakers or are they general comments?

DR. WILKIN: Mine is actually just a response to Dr. Wood's query this morning on the effectiveness of systemic agents.

DR. CANTILENA: How about if we hold that until after the break.

Dr. Benowitz, do you have a comment or a question?

DR. BENOWITZ: I wanted to ask Dr. Ghannoum, who made the comment that he had done some animal studies on dose response, which I think would be quite interesting to know what the nature of the dose response is, do they really flatten out and do they flatten out at the same concentrations as these products are used clinically in people.

DR. GHANNOUM: We have an animal model which is coming out, also published, for dermatophytosis, and we use this model for different biotech companies, as well as pharma, to

look at the different concentration. Once you see something works in OIC, then, we say, look, does it work in vivo. So, we move into this animal model and to find the appropriate concentration, we always use at least three different groups, 1, 5, and, let's say, 10 percent.

When we look at that model, we look at efficacy as well as is there a clinical, let's say, redness to see whether there is irritation with higher concentrations and whatever.

Based on this, you will recommend or you call and suggest to the manufacturer, look, this is the concentration which is efficacious, as well as we don't see redness, scaling, and this sort of thing in that animal model.

Then, the manufacturer will sometimes take that concentration and try other vehicles because again to know, to improve it, will it improve or not, and then after that, they plan their clinical trial.

We found, at least with Lamisil, I know at an early time when they were trying to test it,

that 1, 5, and 10, there is really no difference, I mean they reached the maximum with 1, at least in that class of compounds.

DR. WOOD: What about duration of effect?

DR. GHANNOUM: Because the animal model itself, it is really self-healing, so you have only about 10 days where you can look, and we look only a 1-week treatment, but in that 1-week treatment, we compare once a day or twice a day, but only 1 week, and then we do after that, 9 days, we do the evaluation.

DR. CANTILENA: Dr. Whitmore, did you have a question or a comment?

DR. WHITMORE: Are we going to be talking about the consumer educational brochure for patients in the packaging?

DR. CANTILENA: Yes, that will be actually part of our discussion at the end of the day on labeling.

Any more questions or comments?

Let's go ahead and take a 15-minute break and return at 3:05.

[Break.]

Committee Discussion

DR. CANTILENA: The plan for the rest of this afternoon and possibly tomorrow morning, depending on time, is to discuss the issues before the committee. They are outlined for you, some in the form of questions, in the handout that you were given.

What I have done on this PowerPoint is to sort of partition our discussion, if you will, so that we are on track, by topic. We are first going to talk about the issues that actually come up in Questions 4 and 5 with microbiology.

We will have that discussion, we will focus on those issues, and then we will actually go through Questions 4 and 5. After that, drug development issues will be discussed, you know, dose response issues, lowest acceptable cure rate, et cetera, as outlined.

For that discussion, we will answer Question 2, and we will give our comments as requested in Issue No. 1, so we will comment on

Issue 1 and answer yes/no Question 2 under drug development, under the broad category of drug development.

Finally, under labeling issues, we will talk about the existing label and then the possible modifications or additions, deletions to the future labels. In that discussion, we will answer Question 6, as well as Questions 3(a) and 3(b).

So, that is the plan. If you can click on Clinical Microbiology, what I would like to do is try to focus the discussion sort of as requested by FDA, drug resistance issues and also the use of MICs in drug development.

I will just start by saying that what I heard this morning and also this afternoon was resistance is really a rare finding and does not seem to be an issue. What I thought possibly for MICs, and I would obviously love to hear everybody's comment on this, is that perhaps in the case of treatment failures, that could be part of the drug application file.

So, those are sort of my initial thoughts,

but I would like to open it up to the committee, again sort of in this topic, and let's hear what you all think about this, clinical microbiology issues as they relate to Items 4 and 5.

General discussion. One is we ran out of coffee and people are sagging, or the other is that there are no issue.

Go ahead, Dr. Wilkerson.

DR. WILKERSON: To assume that drug resistance is not going to occur, or is going to occur infrequently is probably relatively naive. I think part of the problem is we don't look for it, we don't have laboratory methods at least on a clinical level to evaluate for drug resistance.

If someone is treated with a topical or oral course of antifungal, and it doesn't work, the decision of the clinician is to just move forward generally with another drug or tell the patient to live with it.

So, I am not sure that we don't have drug resistance here already. It may be just the fact that we don't recognize it because we don't have

any means for screening for it like we do bacterial resistance, and we don't look for it. The techniques that were described this morning aren't available on a clinical basis for general use.

As far as the MICs, I am assuming we are talking about new drugs, new chemical compounds. I mean I would think that would be essential for any NDA type of application, that we need to know the pharmacology, we need to know when we put it into a particular vehicle or incipient, does it, in fact, deliver the compound, or does it sit there, you know, what are the pharmacodynamics that drive the compound out of the incipient and into the target organism or cell.

Just assuming that a 1 percent concentration does this and that we can strip it off the tape later, you know, for all we know, you know, the compound is sitting on top of the stratum corneum and doing absolutely nothing, yet, by the crude tape stripping methods that we use to evaluate this, one thing and another, it would still show up in the chemical analysis.

I think, going forward, you know, since these techniques are available, these are things that should be looked at for new compounds, new applications.

DR. CANTILENA: Thank you.

Any other comments in general? Dr. Benowitz.

DR. BENOWITZ: It seems to me we still have a lot to learn about mechanisms of fungal resistance. It looked pretty convincing from what I heard today that there is not much of a problem with the current drugs, and the question is with new drugs, would resistance be different. We need to know more about how the fungus works.

I think laboratory in the U.S., like is being done now, should follow this, but I don't know yet that it needs to be done as part of every new drug evaluation. It is just a big vacuum in terms of mechanisms.

DR. CANTILENA: Dr. Ghannoum.

DR. GHANNOUM: Just a comment about this number. I think I agree with you if we think

resistance is not going to develop, it's not right, which could be rare I agree, because we already saw at least one patient, which is very well characterized, so I think it will happen.

The fact that the method is just developed, we have the paper coming out in July issue of Journal of Clinical Microbiology, and the method will be adopted and available to the other laboratories in January of 2005. So, we are there as far as availability.

As far as measuring the MIC, from the clinical point of view, I think if we look at how we use MICs in the systemic agents, where we have methods available, what we do, we don't do it routinely, we do it for patients who fail therapy, and then you do it, and they say, okay, this is resistant, so you can switch drugs.

That is well documented and it is one of the IDSA guidelines, Infectious Disease Society of America, that it should be for those who fail therapy.

Now, as far as part of drug development, I

think it is very important that we have a baseline, I mean otherwise how are you going to know whether a drug works, not work, and once you have that available, it is going to help you in the long run whether there will be a change in MIC or not as you are monitoring patients, so that is what I can say.

DR. CANTILENA: Thank you.

Other comments? Okay. If there are no objections and no further discussion on this topic, why don't we actually go to Question 4.

Given the efficacy rates observed in the clinical trials, should antifungal drug resistance be a concern?

Actually, what I would like to do, Dr. Ganley and Dr. Wilkin, if this is acceptable, is to do this as a yes/no vote and then ask the individual to say what the concern is, so that you will know what is going on.

Why don't we start voting over on this side. Actually, before we start the voting, I would like to ask the non-voting members if they would like to comment on Question 4, first of all,

so I don't omit that as I have done in the past.

So, I will start over here, Mr. Kresel, and then Dr. Alfano.

MR. KRESEL: Based on the data that we saw this morning, I agree, as a microbiologist, that ultimately, you will see some resistance, but based on the tons of these products literally that are used every year, and for the number of years they have been used, I don't see that it creates a concern, the difference between whether it will happen and whether it's a concern.

So, yes, I agree it will happen, but, no, I don't think it is really a concern at this point.

DR. CANTILENA: Dr. Alfano.

DR. ALFANO: I agree that I don't think it is a concern. It is difficult when the efficacy rates are linked to resistance, because in this particular condition, as we have heard, the efficacy can be playing off of other parameters, i.e., the anatomical deformities, and so forth, that exist, but I didn't hear any data of any significance that drug resistance is a problem.

DR. CANTILENA: Thank you.

Why don't we continue here and we will just go around this way.

Dr. Ten Have.

DR. TEN HAVE: You want a yes/no to what question?

DR. CANTILENA: Question No. 4, yes/no, and if you are concerned, if you can explain your concerns.

DR. TEN HAVE: Given I have no knowledge in this area, I am going to approach it from a slightly different point of view. I agree that the efficacy rates probably could be higher, but, of course, there are other reasons in addition to the other parameters that Dr. Alfano just mentioned.

We haven't really looked at other factors, such as non-adherence, which could be a big factor in the lack of efficacy, if there is a lack of efficacy, so I would say given my lack of knowledge in this area, no.

DR. CANTILENA: Thank you.

Dr. Wood.

DR. WOOD: No, but, of course, our tense is in some way future tense, and there is no way of telling that for drugs that are under development or might appear in the future.

DR. CANTILENA: We are not going to let you two vote.

Dr. Bisno.

DR. BISNO: No. In a word.

DR. CANTILENA: That was Dr. Bisno. In a word, he said no.

Yes, Dr. Ghannoum.

DR. GHANNOUM: No.

DR. CANTILENA: Dr. Katz.

DR. KATZ: No.

DR. SCHMIDT: No.

DR. CANTILENA: That was Dr. Schmidt.

Dr. Davidoff.

DR. DAVIDOFF: I am not entirely clear what we are voting on, because it seems to me there are two concerns. One of them is a biological concern, and the other one is a regulatory concern, and I am not sure which one this is really

referring to.

DR. CANTILENA: You can answer it actually both ways.

DR. DAVIDOFF: I think that there is a biological concern. I mean it took many years before the pneumococcus became resistant to penicillin, 30, 40 years of exposure. So, I think that there could very well be biological and clinical concerns over time for resistance with these organisms, so I would vote yes, that is a clinical concern.

Is it a regulatory concern? I would say no.

DR. CANTILENA: Thank you.

Dr. Whitmore.

DR. WHITMORE: No.

DR. CANTILENA: Dr. Fincham.

DR. FINCHAM: It is difficult to answer yes or no, everybody knows that, but I think it is a concern. I guess my concern relates to I don't think we really know, as Dr. Benowitz pointed out, a lot about a lot of things here, one of which is

how many of these infections, so to speak, are repeat infections, multiple, multiple, multiple cases, time after time after time, and is that due to non-adherence, is it due to misunderstanding of what the drug is, is it related to something else.

So, I think it is a concern.

DR. CANTILENA: Dr. Ringel.

DR. RINGEL: Basically, no for now, yes for eventually. I do think that it would make sense for new NDAs to include minimal inhibitory concentrations because you really don't know how to interpret the future if you don't know what is there in the present.

DR. CANTILENA: That is actually Question 5, so you will have an opportunity to say that again in a minute.

Dr. Lam.

DR. LAM: I agree. Right now based on the data that has been presented today, I don't think it is a concern at this moment, but we know fungus are pretty smart and it may be a concern down the road.

DR. CANTILENA: Dr. Patten.

DR. PATTEN: I join Dr. Davidoff in a split vote. I will vote no from a regulatory point of view, but yes in terms of the future. I mean theoretically, yes, it is going to happen. Fungi have been around for a long time, undergoing natural selective pressures, no reason to think they won't respond to this.

DR. CANTILENA: Dr. Wilkerson.

DR. WILKERSON: As far as for the present, no, but looking forward, so we don't get the flesh-eating Tinea rubrum, and be blamed 15 years from now that we didn't stop the epidemic when we could have, I think we need to be aware and monitoring for that, but it is not an issue with the current drugs.

DR. CANTILENA: Dr. Raimer.

DR. RAIMER: I agree, no for now, but possibly yes in the future.

DR. CANTILENA: Dr. Epps.

DR. EPPS: I concur on no at this time. I guess a comment about some of my patients.

Certainly, a lot of them, as a subspecialist, have already used products when they come, and I certainly have faith that quite a few of them are compliant. As a parent who applies medication to their child, I think a lot of them do. I guess the difficulty is proving the resistance.

DR. CANTILENA: Dr. Clapp.

DR. CLAPP: No for now, yes for a concern for the future.

DR. CANTILENA: Dr. Benowitz.

DR. BENOWITZ: I sort of have a split vote, but my concern is actually regulatory for new drugs. I would say no for the current classes of antifungal drugs because resistance is rare, but I think when there are new drugs that come out, there are going to be new mechanisms of resistance, and I think that we should look at the potential for developing resistance when there are new classes of drugs that are introduced.

DR. CANTILENA: Thank you.

Ms. Knudson.

MS. KNUDSON: My vote is exactly the same,

no for right now, but yes for the future.

DR. CANTILENA: Thank you.

My vote is from a regulatory standpoint, no, at this time; from a clinical standpoint, yes.

Now that we have given you all those options, Dornette is going to give us the vote tally.

LCDR SPELL-LeSANE: 18 no and 1 yes.

DR. CANTILENA: With all the qualifications that are fortunately on the transcript. Okay. Very good.

Let's go to Question 5. Should antifungal MICs be determined for clinical isolates during drug development and submitted with the NDA?

I think we have some of your answers, but we have to have anyway for the transcript, so let's start on this side over here.

Ms. Knudson.

MS. KNUDSON: I will have to pass. I can't answer that.

DR. CANTILENA: Okay. Dr. Benowitz.

DR. BENOWITZ: I would say yes, now that

we can do this, I don't see any reason why we shouldn't do it, and it might be very informative. I would say yes.

DR. CANTILENA: Dr. Clapp.

DR. CLAPP: I would say. I think that helps address our concern about the resistance for the future drugs.

DR. CANTILENA: Dr. Epps.

DR. EPPS: I certainly think it could be helpful and informative. I have met some infectious disease people who wonder about MICs and the relevance, and that sort of thing, but perhaps it would help us look forward to know with more data what is pertinent and whether it's relevant.

DR. CANTILENA: Dr. Raimer.

DR. RAIMER: Yes.

DR. CANTILENA: Dr. Wilkerson.

DR. WILKERSON: I am assuming this was referring to in vitro or in vivo MICs?

DR. CANTILENA: In vitro on the isolates.

DR. WILKERSON: In vitro?

DR. CANTILENA: On the isolates.

DR. WILKERSON: I think it is part of an investigative process, it is absolutely essential.

DR. CANTILENA: Dr. Patten.

DR. PATTEN: I vote yes.

DR. CANTILENA: Dr. Lam.

DR. LAM: Yes, and it would allow us to learn more about may drug resistance and fungal resistance, and help us to devise strategies to prevent them down the road.

DR. CANTILENA: Thank you.

Dr. Ringel.

DR. RINGEL: Yes.

DR. CANTILENA: Dr. Fincham.

DR. FINCHAM: Yes.

DR. CANTILENA: Dr. Whitmore.

DR. WHITMORE: Yes.

DR. CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: Yes, although I assume that it's not just the drug developers who are going to be studying MICs, it's clearly a wider problem.

DR. SCHMIDT: Yes.

DR. CANTILENA: That was Dr. Schmidt.

Dr. Katz is yes?

DR. KATZ: Yes.

DR. CANTILENA: Dr. Ghannoum, yes.

Dr. Bisno?

DR. BISNO: First, to go back to 4 for just a second, we didn't discuss really in any detail what the reasons are for the lower efficacy rates when using drugs that are obviously very potent.

Some things came up about hammertoes and local factors and everything, but it seems to me that there needs to be more emphasis on what the factors are that make failure when you are using highly potent drugs, because if we don't identify those, then, we are going to be doomed to wasting all these drugs, because we will be doomed to fail.

So, I would like to see more interest in that anyway.

Now, to go on to 5, yes, it is true that, as an infectious disease person, we do believe in MICs, but we don't believe in them absolutely, but I think the fact is that if someone presented an

NDA that showed a tremendous clinical potency for a particular drug against particular isolates, and yet it was resistant by MICs, we would all scratch our heads and have to go back to the drawing boards a bit, so I definitely think this should be part of drug development and submitted with the NDA.

DR. CANTILENA: Thank you.

Dr. Wood.

DR. WOOD: Yes.

DR. CANTILENA: Dr. Ten Have.

DR. TEN HAVE: Yes.

DR. CANTILENA: Comments from Dr. Alfano and Mr. Kresel.

MR. KRESEL: I agree and I think in order for that to be meaningful, you would also want to do MICs on clinical failures, because you want to see if there has been any change in the MIC. If you start out susceptible and end up resistant, which is highly unlikely given the data that we saw today, but nevertheless, an MIC at the beginning and a failure at the end is really not very compelling data.

DR. CANTILENA: Thank you.

I also vote yes. I think it would be especially helpful in explaining treatment failures if they should occur.

I am sorry, have you commented? I thought you passed, Dr. Alfano.

DR. ALFANO: Pass.

DR. CANTILENA: So, you did pass.

DR. ALFANO: Yes.

DR. CANTILENA: You have sensitized me now forever for skipping you, so I am going to ask you at least five times every vote.

We will go to the next slide which changes topics now. Now, we are actually specifically talking about drug development. Basically, I would like to center the initial discussion on, first, Question 2, which has to do with drug response.

Dose response studies are not conducted in the development programs of antifungal products for the treatment of tinea pedis. Given the efficacy of products currently marketed, should they include dose response, you know, specifically, they

evaluate safety and efficacy at different concentrations, dosing durations, and dosing frequencies?

Let's initially sort of focus our discussion, if you will, on the whole issue of including exposure response type of information in drug development for new antifungals for this indication.

I guess we will just open up the floor.

Dr. Wilkin.

DR. WILKIN: Would you still want the efficacy information on the systemic agent that Dr. Wood requested?

DR. CANTILENA: Yes, we do. We have to have that because that was a homework assignment that we gave you.

DR. WILKIN: That was a homework assignment. The systemic antifungals are in a different division, so it took us a few moments to find out, and I will describe--and this ought to be available through Freedom of Information, and I assume this is so old, this is the ketoconazole

oral.

Protocol 009, patients were eligible if they had dermatophyte infections: one, which had been resistant to prior topical antifungals; two, if topical treatment were contraindicated due to the extent of the fungal infection; three, if the infection had failed to respond or had recurred after griseofulvin therapy; or, four, if patients requiring griseofulvin could not tolerate the drug. So, those are the entry criteria.

There were 47 evaluable subjects. There were 3 separate study centers. The patients who were in the negative KOH and culture group, that was 70 percent. We call that the mycologically negative. You have also earlier heard the phrase "mycological cure."

Then, the clinical and mycological cure was 62 percent, and that is above, well above actually, the rates that we saw in the topicals earlier.

DR. CANTILENA: And that was what dose of ketoconazole, and how long was the treatment?

DR. WILKIN: Patients were treated with either 200 or 400 milligrams a day for a minimum of 28 days and a maximum of 60 days.

DR. WOOD: Just for clarification, that would be the equivalent of Slide 19 in Dr. Fritsch's presentation, is that what we are saying? The clinical and mycological cure would be the equivalent of a complete cure on her slide, is that right?

DR. WILKIN: No, this is an older review, and it is really not that clear whether this would fit most with effective treatment and allow for some or not, because they say global clinical assessment was recorded as cured, markedly improved, moderately or slightly improved, unchanged, or deteriorated, and, as healed, mild, residual lesion or considerable residual lesion, unchanged or deteriorated in 9, and 9 is the one we are talking about.

So, it is not quite clear as I read this whether it fits with one or the other.

DR. WOOD: But the 62 percent is that

clinical endpoint plus mycological cure?

DR. WILKIN: Exactly so.

DR. CANTILENA: Thank you. That was the fastest Freedom of Information response I have ever heard of. Same day service. Thank you very much.

Comments, concerns looking at dose response, safety and efficacy at various sort of exposure responses for drug development of future agents? Dr. Katz.

DR. KATZ: I am a bit confused. Are we talking about issues for the committee now?

DR. CANTILENA: Yes, this is sort of like Issue No. 2 for the committee as it relates to drug development programs.

Should sponsors be doing exposure response for dried development for new products for over-the-counter? I think you have heard earlier about the exposures in either changing the concentrations or the application frequency or the length of application, and that is really what we are talking about.

Comment, Dr. Whitmore?

DR. WHITMORE: I guess we can't ask Novartis to do this, so this would of their own accord. It would be nice, as has been said here, to know if 3 days of therapy is the same as 7 days of therapy, but for future companies coming forth with the antifungals, it would be nice to have comparator days of dosing.

I think, more importantly, at least with the antifungal chemicals that we know of right now, in that the MICs are such that you are going to be killing them, you are above the MIC and everything else, but with those drugs, as far as different dosing regimens, if they could come up with a dosing regimen that has whatever acceptable percent clearance, we are talking about 70 or 80 percent or whatever of clearance, and then have a level of dosing somewhere below that where it's a lesser clearance rate.

Thus, to kind of restate that, when they are doing studies, come up with a dose response based on the number of days of dosing, so we know we are at the minimum number of days to get 80

percent clearance or whatever.

DR. CANTILENA: Very good.

Dr. Schmidt.

DR. SCHMIDT: Don't the drug companies do this already? I mean this seems awful simple, you know, that even before they would even approach or when they come to the committee or the FDA, they would have some evaluation of, say, different concentrations or some idea of the dosing and dosing frequencies.

Maybe I just don't understand how we are supposed to present this to them. This just seems like it's a given.

DR. WHITMORE: Can I just say it's kind of a new area because we have just gotten down to 7 days of dosing, and we have never talked about anything less than that to clear up tinea pedis, so that is kind of a new thing as far as asking drug companies to look at 2 days and 3 days.

DR. CANTILENA: I think I could say that I have heard that in terms of dose response, there are some companies that had animal data that we

have heard about, but I think what I have heard from FDA is in terms of clinical studies, you know, it's almost unheard of.

So, it isn't available from the actual studies, and they are asking us if we think it is a good idea for that to be included in the NDA.

DR. SCHMIDT: Well, I think definitely, it is a good idea, but it just seems like a no-brainer in the sense that the people would do it from the start to present that data. It is just a point of order of how these studies are done, but no, I agree definitely we should.

DR. CANTILENA: Comments from FDA to help clarify the issue?

DR. WILKIN: If I could just make a comment on the guinea pig model, I mean that is one where, quite literally, you have to hurry up and treat it before it goes away. I mean it is going to go away on its own, so there are limited days. I am not sure that the skin of the guinea pig really reflects the skin between the toes or on the plantar surface of the foot. So, there are many

relevant aspects of that model that really would be dissimilar and maybe not predictive.

DR. GHANNOUM: If I might comment on this. I agree with you, we are not guinea pigs, so we are not going to have the same data you will see in a patient exactly, but I can tell you from our experience with all the different classes of compounds that are now, whether topical or oral, that the guinea pig can predict whether the drug works or not.

You can see, for example, we have--not to bias, to be on anybody's side--but we have a positive control in the guinea pig, and it works beautifully, and when you compare it to other drugs, which does not work as well, although it is marketed, you will see the same.

I agree with you, the caveats which you mentioned are very important, because if you leave it up to 17 days, then, it is not good, but if you have that window of 9 days to do the whole experiment, then, I think it's predictive. The drugs that have been approved were tested in this

in the preclinical setting, and I really believe it is a very useful way to tell you whether, when you move from the in vitro to the in vivo, that things are going to work, number one, and number two, you can see the dosing also predictive, but eventually, you have to go into patients obviously.

DR. CANTILENA: Dr. Wilkin.

DR. WILKIN: Dr. Ganley earlier mentioned the "cures most" and the thinking that went into those words and how the original hope was that most would qualify the cure in a positive direction. Perhaps one of the unintended consequences of that is it is actually this incentivized competition for more effective products.

If that is going to be on the labeling for virtually all these over-the-counter topical antifungals, then, when the marketing groups at the different industries try to decide whether there is a place where they can make a profit with the new medication, and incidentally, that is how we get all the new and important drugs that are helpful to the public health, is someone, somewhere is going

to make some money.

I mean that is the American way, and I think it has a lot of positive aspects to it, so I am certainly not going to give any negative side.

But the one place that currently I think, if they look at these products and look at the labeling, is make it quicker, make it less time.

I walked by the microwave the other day. We have a microwave at FDA out at the corporate, and I was going in there to do something, and someone was standing by the microwave going "hurry up, hurry up," and I think that is one of the great things that patients want with products also, is they want something that is faster.

So, that is where the incentive today is, and maybe part of this plays into the labeling, maybe it cures most. If that gets modified, we can then encourage sort of moving towards higher concentrations, maybe somewhat longer durations in an effort to get better efficacy.

DR. CANTILENA: Thank you.

Dr. Wood.

DR. WOOD: Seeing that just came up, the most again, I don't think the Agency should allow labels that say "most," unless it is based on comparison. "Most" is a word that has a clear meaning. It means that it cures more than any other something. You know, it is not more, it is not a comparison, it is most, so it implies that this is better than anything else, and that is clearly not true, so it shouldn't be on the label.

But that wasn't what I wanted to say. It seems to me that you should insist on exposure response, and that is better I think than dose response, because my fear would be that somebody will do a study that beats placebo with one dose, and that doesn't mean that 7 days wouldn't have cured a lot more people.

Consumers will assume that the drug has been evaluated in a way that tested it and gave them the most--I will use that word--effective therapy, and not just any old therapy.

So, I think there is a real need to ensure that exposure is evaluated, to make sure that you

are not forced constantly into the least effective dose, even if it only cures, you know, fill in the percentage.

So, I think it is absolutely essentially that you know where you are on the exposure response, not the dose response, and that you have some understanding that you are at the plateau level of what is being produced and before you approve it.

DR. CANTILENA: Yes, Dr. Ten Have.

DR. TEN HAVE: Following up on Dr. Wood's comment, and I think I am interpreting it correctly, but correct me if I am wrong, so with exposure, you are talking about duration times dose, the total.

DR. WOOD: Correct, or some combination, yes, and it might be number of times per day or some variable.

DR. TEN HAVE: So, following up on that comment and also Dr. Wilkin's comment about increasing dose, but shortening the duration, it seems to me that the companies are interested in

shortening duration, but not necessarily increasing dose, and I may have that wrong, too, but increasing dose obviously increases efficacy, but may work against safety, so you have two competing criteria there.

I presume that the interest in increasing dose is to get at the non-responders. I know in other areas of medicine, there is sort of a stepped-up approach where if you don't respond at a certain dose, you step up the dose if you don't respond, so you can get a higher response rate for the non-responders.

I am wondering if that is feasible in this situation, or is it just not clinically feasible?

DR. CANTILENA: Dr Whitmore.

DR. WHITMORE: Pass.

DR. CANTILENA: Mr. Kresel.

MR. KRESEL: I was just going to comment on the classic anti-infective drug development paradigm as it relates to this, because what we usually look at as we are determining the dose is the half-life, the area under the curve, MICs when

they are available, bioavailability of the formulation, and tolerability to the patient.

So, I think that there is not likely to be the need to test multiple concentrations when you have done that preliminary work. Then, you get to dosing frequency, and dosing frequency has a very limited number of options, as I think somebody commented on earlier.

You can do once a day, you can do twice a day, patients are going to carry their medication with them to work and take their shoes and socks off in the middle of the day and do another dose.

So, you can dose something three times a day, and you can get labeling for three times a day, but you won't get any compliance to three times a day, so that it becomes kind of a moot point.

So, I think dosing duration becomes the one that probably ought to be thought about, and I think that FDA probably should determine what the "gold standard" is. That is, if four weeks is the gold standard, then, people should have to compare

to four weeks, are you better than or worse than four weeks, or as good as four weeks, you know, are you as good at three days as you are at four weeks, or if the gold standard is one week, then, the comparison should be that, but I don't know that there is a lot of value to be gained at looking at multiple concentrations if the preclinical work is done adequately, and certainly I don't think dosing frequency helps.

DR. CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: I agree with and extend a little bit what has just been said. It seems to me that the assumption that has been expressed a number of times is that the concentrations that are generally implemented are high enough, so that they are essentially nuking the bugs in terms of the concentration.

The issue, though, does seem to be primarily duration of exposure. Judging from the data on clotrimazole, there was a fairly clear difference between one week and four weeks of exposure, minimal or maybe zero difference between

one and four weeks for terbinafine, so I think it is not a fair assumption that one week is as good as four weeks for all drugs, and it does seem entirely reasonable to look for exposure-response relationship.

Otherwise, both the committees, the Agency, and clinicians are essentially flying blind, and five years from now or 10 years from now, they will still be in the dark as to how to make the decisions if they don't have the data.

DR. CANTILENA: Dr. Lam.

DR. LAM: I actually concur with Dr. Schmidt in that I thought dose-response studies are given in drug development, and I was surprised to see that this group of drugs is not required to do that.

Given the difference in response rate between one-week regimen and four-week regimen, I would imagine that there has to be some sort of an exposure-response relationship, and I would like to kind of turn the question into the opposite direction in terms of is there any historical

reason or scientific reason that this group of drugs should be exempt from doing that.

DR. CANTILENA: Historically, you heard sort of how they got here, but I think in terms of the Rx to OTC switches, I don't have that history.

Would you like to comment on that, Dr. Wilkin?

DR. WILKIN: Well, actually, requesting dose-response studies, you know, the Code of Federal Regulations is pretty good in giving us information on how to seek efficacy and safety information, but it is somewhat edentulous when it comes to going after dose ranging, and there is a ICHE.4 document that talks about dose ranging and exposure response, and interestingly enough, the last part of that is devoted to Phase IV dose ranging.

When I first heard that, I thought, you know, that might be some regulatory humor, but it really does exist, you know, that you can look for this after something has already been approved, and generally, that is in the circumstance of where

there is a safety issue and one might be trying to find a lower dose that might be just as effective.

But, no, we really are often at the mercy of the sponsors to whether they find it something that they want to do.

DR. CANTILENA: Dr. Ringel.

DR. RINGEL: Many of these antifungals have been around, I don't know, I can't imagine, probably since the turn of the century, 1920, some of the older ones like heliprogen [ph], I think it is high time that we stop testing these drugs against placebo and start testing them against the known drugs, the drugs that we have that we know work, that at least another monograph system have been approved since 1982.

If you think about it, the competition right now is how infrequent and how short a duration can you give these medications and still have them work. Theoretically, you could have a drug that has a very steep response curve, so that you could get a maximal response in a very short duration, but the ultimate cure rate could still be

very low.

I mean you could get to a 20 percent cure rate very quickly, but maybe all you will get is a 20 percent cure rate, and if you are only going to test them against placebos, you may actually be approving drugs that are less efficacious than the ones that are already out there.

So, I think at this point, you know, 2004, I think it's time that we stop testing against placebo and start testing against known agents.

DR. CANTILENA: Thank you.

Dr. Katz.

DR. KATZ: The point of necessity of new drugs getting dose-response studies, as brought out by Mr. Kresel's comment of comparing to gold standard, the problem is we have no gold standard. I mean our gold standard is, over placebo, 30 percent efficacy, or if you see Dr. Fritsch's page 9, page 10 cure rates of 20 percent over placebo, so we do need dose response.

There may be drugs that we know with the oral antifungals, they can use one week a month and

get equal effect, so it may be topical preparations would be in development that have to be used much less frequently or better cure rates if they use more frequently, so dose response I think would be very important because we have no gold standard.

DR. CANTILENA: Thank you.

Dr. Wilkerson.

DR. WILKERSON: I just wanted to say I did my homework before I came, and went to the grocery store, you know, a drugstore, and looked at the over-the-counter antifungal products that were there. Even as someone who I think is relatively sophisticated as far as these things, I was confused by everything that was out there.

I thought part of the gist or thrust to this was to maybe bring some comparative value for the consumer to the table, such that the consumer could be guided on something beyond packaging and advertising claims as to which agent to pick, because when you go in there to look, I like the question a while ago, even using the same brand name, you are talking about two totally different

antifungal agents, it is very, very confusing.

My recommendation would be a simple analog scale, much like what we have done with the psoriasis drugs with the biologic compounds, is that we set a minimal efficacy level and allow that to be used as the standard, whatever it be, 60 percent or whatever, so that consumers can actually compare between different products.

If I pay X dollars for this, I will get this level of potential cure versus paying $3.00 for this generic that will give me this potential level of cure.

I think there has to be some, you know, and even amongst physicians, most physicians' choices are based upon who the last rep was that was in their office, that they remember their name. There is very little science that goes into picking these antifungals on the consumer or on the physician level.

As far as the basic pharmacology, to me, this is just a slam dunk. I mean if you are going to put a drug on the market, you need to know the

pharmacology of it.

DR. CANTILENA: Dr. Benowitz.

DR. BENOWITZ: I would say first that I am sympathetic to the idea that if you have a good animal model, and you know pharmacokinetics and mechanism of action, that you can simplify the process and reduce the need to do dose response studies.

However, I don't think we are there, but I think we should try to get there. So, some of the things that I would suggest, for example, is that guinea pig data really be analyzed in a systematic way and brought to FDA to see how predictive it really is based on what we know from a whole variety of current agents, and see how good that test is.

I think we need PK data including things like both concentrations in skin and also persistence. It was of interest to me that terbinafine, I guess is the one persistent in the skin for up to 5 weeks after the end of administration. I think that is what I heard, and

other drugs don't do that, and that obviously is a key factor when you are dosing something, how long it stays in the skin.

It is going to influence what level you build up. So, I think it's a potential in the future, if we really got good PK data, good skin concentration data, good persistence data, and good animal model, but until we do that, I think we need to have dose response data.

DR. CANTILENA: Dr. Wood.

DR. WOOD: Could I just add to Neal's comment, and I think we need to be pretty careful of the animal model. The animal model, from what I have heard, is, by definition, fundamentally different from the human model.

The animal model is self-curing, the human model is not, so mechanisms of action that might be effective in the animal model, that would accelerate the self-cure, and would probably not be effective in humans, so I think the confidence in the animal model is, from what I have heard, grossly overstated right now.

We know that it does not reproduce what we see in humans, and that is something we need to be careful about.

DR. CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: That really needs a point of clarification, and that is, are we talking about clinical dose ranging studies or animal dose ranging studies, or both.

DR. CANTILENA: Clinical.

DR. DAVIDOFF: Okay.

DR. CANTILENA: Dr. Bisno.

DR. BISNO: Help me out as a non-dermatologist, because I am not sure what we are talking about in terms of the endpoints here. Are we talking about negative mycology, effective treatment, or complete cure?

Particularly, I don't understand complete cure when you have eradicated the fungus, you have effectively improved the patient's symptomatology, and there is a tremendous gap between that and complete cure, what is in that area, are those just some residual scaling and flaking, and things like

that, that are maybe of no clinical significance at all.

So, if some of my dermatologic colleagues, who understand this a lot better than I, can explain what that big gap is and is it worthwhile to shoot for complete cure when even the best stuff that we have now is getting 20 percent cure, and we seem to be curing it mycologically and in terms of symptomatology, is that a reasonable standard to set.

DR. CANTILENA: Comments from the dermatologists?

DR. KATZ: Well, simply the difference there is clinically improved, in plain English, improved, or completely clear, and improved is very subjective and it is less of an endpoint, because it is subject to the investigator, who may be biased since he is doing the study for the drug company, and it is compared to placebo, which is a necessity, but in plain English, what they call "effective" is improved, which is important, and it may be important enough to some people.

In fact, in real life, I check patients back, and, well, how is that doing, that topical treatment doing, oh, that is fine, that cleared me up, and to go along with what Dr. Elewski said, I said, well, let's have a look, and you look and it's 50 percent better. I wouldn't have thought it was that great. So, that is the difference.

DR. CANTILENA: Dr. Schmidt.

DR. SCHMIDT: I think that these funguses itch like the devil, and they are almost like an insect bite, like a mosquito bite, and most people, and I think these medications work very, very well and very, very fast for the most part, and most of my patients, I don't want to see them back and look at their feet again.

So, what I do is I usually tell them to use one of these things, and when I see them again, what they do is use it for four or five days and then they stop, but I don't even wish to cure them, I don't think I can. I think that every six months, or when it gets hot every summer, I tell them you are going to have to use this stuff again.

So, I think it's a pipedream, you know, that basically, at least in Houston and the Gulf Coast, you know, maybe up here in Yankeeland, you know, that you are going to do it, but I don't think so down where we come from.

DR. CANTILENA: Thanks for clarifying that.

DR. GHANNOUM: I just would like to clarify something of the animal model and put it into perspective. I think what our colleague said is very true. It is a good idea to bring all the data together and see how predictive is this model, number one.

Number two is this is not a model which is going to replace any clinical data. It is a part of the puzzle. A lot of the time, in the preclinical stage, you take a compound, you test it in vitro. It works great.

You go move into the animal model, whether it is for systemic infections or whether it is superficial infections, and the drug does not do anything. So, I think it is a method of another

stage for screening of the compound to determine whether it works or not.

Now, once that is clarified, and then also it is going to help the manufacturers to test a number of things, to allow them to have some basis for moving into humans. Once they move into humans, obviously, they have to look at, you know, again, a lot of the drugs fail once you move from animals to human, so that is really where I would like to clarify.

DR. CANTILENA: All right. Dr. Epps.

DR. EPPS: I think it would be useful, not only for dose response, but also for efficacy, to have that kind of information. I like the head-to-head studies, I think that is interesting to compare drugs. I agree there is no real standard, and I think individual response can vary.

As far as guinea pigs, you know, we are not talking about IV or oral medication, we are talking about cream on feet, and I think it is pretty straightforward and easy. Obviously, we go through the phases that we should, but I think the

hazards are fewer when we are talking about feet.

DR. CANTILENA: Comments? Over here, Dr. Alfano.

DR. ALFANO: I think Dr. Bisno hit on one of the key issues, maybe the pivotal issue, and that is what are we expecting in complete cure. I think it is, in some ways artificial and potentially misleading.

As I think through OTC categories and try to design what would be a complete cure, you think of acne, you think of psoriasis, gingivitis, dandruff. You know, for the most part, we don't achieve complete cures in any of those conditions--

DR. CANTILENA: How about headache?

DR. ALFANO: --whether they are managed Rx or OTC. So, it seems to be an artificial constraint that is compromised, his point about, you know, if the symptoms are mitigated and the organism is gone, what are we talking about.

I think there should be a more appropriate way to view how we see this category going forward.

The second comment I had is actually a

question to the dermatologists. I mean is there something in between an animal model and to full in vivo use studies. I am thinking going back to the Layden chambers or even organ culture in which skin can be obtained in cultured foreskin, for example, which would be perhaps a more relevant model and allow for some of the type of analysis that FDA is looking for to help with the dose ranging, and so forth.

I haven't heard it mentioned at all today, and I don't know if it has fallen into disfavor or whatever, but there was a time when I mean you can do permeability studies and find out about dermis penetration.

I know, for example, a cadaver skin actually behaves very much like live human skin, so there do seem to be other mechanisms that could be brought to bear on this problem.

DR. CANTILENA: Any comments from the dermatologists? Dr. Wilkin, do you have any experience with those other models?

DR. WILKIN: I think this bears on the

notion of bioavailability for topical products and bioequivalence. When one is doing a comparison of bioavailability of, say, a new product versus a reference listed product in the setting of a 505(j) Ananda [ph], a generic, or perhaps a 505(b)(2), the relevant part of our regs is 320.24(b)(4), which says that it is a topical trial, that is, it is a regular clinical trial, and you look at regular clinical endpoints.

The rationale for why that is different from the drugs that are given systemically is there you have systemically, you have the blood, which may not be perfectly mixed, but is, if you will, well mixed, and it's in equilibrium at some point with the organ site.

There is no comparable sampling site, no compartment, if you will, in the skin, and often the way the drug is extracted from different levels in the stratum corneum, it is not even clear whether it was in solution at the time it was extracted, and we know that drugs are not active unless they actually are in solution.

So, we haven't figured out a really good way, but when we do, that is going to dramatically lower the current burden that is out there right now for all the generic topical drug products. So, we are keen on hearing a good way to approach that.

DR. CANTILENA: Thank you.

Mr. Kresel.

MR. KRESEL: I just wanted to comment on Dr. Katz's comment about bias, because for one thing, we really don't encourage bias, we are quite adamant about not wanting bias, and there really isn't an incentive on the part of an investigator to be biased, financially or otherwise, since they get paid whether the study fails or not.

However, it is one of the reasons why we do placebo-controlled studies, because they are double-blind and placebo controlled, and if everybody gets better, then, in fact, you didn't beat placebo and your drug just failed.

So, I think it is one of the reasons why we don't like to introduce active controls, because if, in fact, your control is active and everybody

gets better, then, your drug does get approved.

DR. KATZ: I didn't mean that in a pejorative way. We are all biased. I just mean that in a normal way, that is why we have placebos in the first place.

DR. KRESEL: If everybody gets better, then, you didn't beat placebo, your study fails anyway, your product doesn't get approved.

DR. KATZ: I understand that, but that is why we have placebos in the first place, and my comment was only in response to the fact that this intermediate state of effective can mean different things to different people, so if we have placebos, like we do, we can see the true effectiveness of the medication. I was just meaning that in contrast to complete cure. I didn't mean it in a negative manner.

DR. CANTILENA: Yes.

DR. WILKIN: I was going to make a comment about the active comparator. There is also a document signed by President Clinton, Vice President Gore, 1997. It is called Reinventing

Government.

There is a section regarding drugs. On page 27 of that, it points out those circumstances where we would use an active comparator, and that would be for indications which are severely debilitating or life-threatening. So, that would be the setting.

In other settings, it is clear-cut. It said generally in other settings, an active comparator would not have to be in the mix.

DR. CANTILENA: And that is on what page again? No. All right. It's very impressive.

Why don't we go to Item No. 2 then, Issue 2, in the form of a question for the committee then, under Clinical Efficacy.

Given the efficacy of products currently marketed, should topical antifungal drug development programs for tinea pedis evaluate safety and efficacy at different concentrations, dosing durations, and dosing frequencies?

Basically, exposure, you know, response, which is what we have been talking about.

We will start over here if non-voting members would like to comment, and then we will head around, and if you can justify your answer or just yes or no, and I voted that way because, that would be fine.

MR. KRESEL: In order to be consistent with what I have said before, dosing duration I think is the one area that we could probably look at and get some data that would be useful to clinicians, so I would vote yes for dosing duration, but not dosing frequency or dosing concentration.

DR. CANTILENA: Dr. Alfano.

DR. ALFANO: I don't vote. I would certainly agree with the comment, and I am glad Dr. Wilkin clarified, because I was sitting here all morning wondering why FDA can't get this information that they are asking for.

Many years ago, when I used to be in the industry, it seemed to me FDA got whatever they wanted, so I now understand why some of this data is not available to you.

DR. CANTILENA: Dr Ten Have.

DR. TEN HAVE: Yes, especially with respect to non-responders.

DR. CANTILENA: Dr. Wood.

DR. WOOD: Yes.

DR. CANTILENA: Dr. Bisno.

DR. BISNO: Yes.

DR. CANTILENA: Dr. Ghannoum.

DR. GHANNOUM: I agree with dose duration.

DR. CANTILENA: Dr. Katz.

DR. KATZ: Yes.

DR. CANTILENA: Dr. Schmidt.

DR. SCHMIDT: Yes with the dose duration.

DR. CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: Also yes, and also with the main focus on duration.

DR. CANTILENA: Dr. Whitmore.

DR. WHITMORE: Yes with the dose duration and frequency, and with regard to concentrations, if we are requiring MICs to be done, I guess we don't need the different concentrations, like, for instance, if something like tea tree oil gets

proposed for a treatment, I think in that case, you would need if they came up with it, I don't know, but I think with products that are not established antifungal chemicals like the current ones we have, you would need different testing with different concentrations.

DR. CANTILENA: Thank you.

Dr. Fincham.

DR. FINCHAM: Yes for all, and while I have the mike, it's a naive question or statement, but when you talk about these FDA regulations, and you throw out these numbers and the letters, I don't have a clue what you are talking about. You are intimately involved with this on a day-to-day basis, but if you could just give us a simple explanation of what those are, it would help me immensely, and thank you very much for allowing me to say that.

DR. CANTILENA: Well, actually, you didn't ask me if you could say that.

[Laughter.]

DR. CANTILENA: That was actually in the

orientation packet that you got for the advisory committee, it's all the regulations and all the numbers.

DR. WHITMORE: I think all the numbers were just citations of the locations. They don't mean anything to us, but they are just citations of where this is.

DR. FINCHAM: My comment still stands.

DR. WILKIN: I may have said CFR. It is true, we tend to talk in a lot of alphabets. Code of Federal Regulations is basically what Congress has given us, how to actually interpret the '38 Act, and it does have a lot of interesting nuggets.

It is available electronically on the FDA web site. If you jot those down or I could mention them to you afterwards, there are some good places to look, because the exact wording is pivotal to industry. I know they really read those lines very carefully, and we do, as well, and they have enormous constraints ultimately on the information set that comes into FDA, so they are not trivial.

ICH, I may not have mentioned that, I

think it is International Conference on Harmonisation. It is Harmonisation with an "s" at the end, so it's not totally harmonized with American English, but it is Japan and Europe, and I think Canada is involved, and it involved academics, government regulators, and industry all coming to the table and deciding what were some of the common ways that everyone can look at it in different geographic regions with the idea that someday we might be able to have NDAs that are submitted simultaneously in different countries, so I think it is a positive sort of step, and I apologize.

DR. CANTILENA: Dr. Ringel.

DR. RINGEL: I would say yes. Just one further comment that if, in fact, we can't get an active control group when doing these studies, I would think that at the very least we should be able to have some minimal standard of efficacy. Perhaps that would be allowed by the regulations. I think it's CFR 43.154.

[Laughter.]

DR. CANTILENA: I think you just quoted the Drug Enforcement Agency, but I am not sure.

Dr. Lam.

DR. LAM: Yes for duration and frequency.

DR. CANTILENA: Dr. Patten.

DR. PATTEN: Yes for all three.

DR. CANTILENA: Dr. Wilkerson.

DR. WILKERSON: Yes.

DR. CANTILENA: For all three?

DR. WILKERSON: For all three.

DR. CANTILENA: Dr. Raimer.

DR. RAIMER: I wouldn't care too much about concentrations as long as we had good, reliable MICs. I think dosing duration is very important. Dosing frequencies, I agree, it is probably going to be once or twice a day unless the company wanted to go for something like once a week for a month or thought they had something they could market. I don't think it matters whether you put it on once or twice a day to most patients.

DR. CANTILENA: Dr. Epps.

DR. EPPS: Yes for all three, and I guess

as a point of information, and thanks to CDER, under Tab 6 are some of the CFR and definitions.

DR. CANTILENA: Dr. Clapp.

DR. CLAPP: Yes for all, but my concern is about standardization of efficacy.

DR. CANTILENA: Dr. Benowitz.

DR. BENOWITZ: Yes for all three, but I would just emphasize that the concentration issue, which many members felt did not have to be tested, I think in theory, that could be defended, but I am not convinced that the data presented to date adequately defend not testing different concentrations.

I think it is possible, but I don't think it is done, and I think it is the obligation of a sponsor to do that before we accept not testing different doses.

DR. CANTILENA: Thank you.

Ms. Knudson.

MS. KNUDSON: I will say yes to all three, and I would like to say that as a consumer, I would certainly like to see comparative trials done, and

I don't care whether a tube of this medication only cost $8.00, to some people, that is really a very important figure.

DR. CANTILENA: Thank you.

My vote is yes to all three. I think exposure response is important, and it just improves the overall use of the product.

The tally, please?

LCDR SPELL-LeSANE: To Question No. 2, 19 yes, all yes, no "no."

DR. CANTILENA: Thank you.

I think really what I would like to do is you didn't ask us a question per se for clinical efficacy, lowest acceptable rate of care, so what I would like to do is just open this for discussion and see if we can drive toward a consensus. If not, then, we can do a vote on this, but this would be Item No. 1, where we are looking for the lowest acceptable rate of cure, clinically meaningful, for a topical OTC drug product for the treatment of tinea pedis, using the complete clinical and mycological clearance as definition of "cure."

Really, what is the lowest that you would be comfortable with for a cure rate, you have something that is effective.

I will just open it up for discussion.

Dr. Lam.

DR. LAM: Are we lumping 1-week regimen and 4-week regimen together into our consideration and deliberation?

DR. CANTILENA: I was, but we will ask Dr. Ganley or Dr. Wilkin, can we lump the 1- and the 4-week for acceptable cure rate? Are you looking for a cure rate irregardless of duration of treatment? Yes, okay, so we are lumping.

So, what is a number that meets your definition of an acceptable cure rate in this setting? Dr. Wood.

DR. WOOD: I am not going to give you a number, but let me raise an issue that came up from the homework.

It seems to me that if you are a consumer and you are about to make the decision as to whether you should buy a product to treat some

disease, you want to know what the likelihood that you are going to respond is, but you also want to know what other options are out there.

Now, in an Rx situation, you expect your physician to do that, you expect your physician to look at you, make the diagnosis, and decide what the optimal therapy is.

In an over-the-counter situation, it seems to me that the consumer ought to have information on the cure rates which are substantially higher, and with systemic therapy that are available with these.

I think that should be in the package labeling, because that seems to me a critical piece of information that people ought to know.

Somebody said a minute ago, you know, if you are buying $8.00 tubes of something, and you are getting nowhere, for many patients, the decision to go to a dermatologist would be a huge decision for them, and their loins would be girded if they knew that there was a likelihood that the doctor could provide the therapy that would be more

effective.

DR. CANTILENA: Dr. Bisno.

DR. BISNO: Again, i want to make sure that I understand what we are discussing here. Are we discussing the complete cure for which the general data are about 20 percent, because it says "complete clinical and mycologic cure," so you are asking what is the lowest acceptable rate for complete cure in which the general data are about 20 percent?

DR. CANTILENA: I think that is what they are asking, yes.

DR. BISNO: I am a little bit blown away by that, because the only colleagues I have that think that 20 percent is a great rate are my oncologic colleagues, who really have to deal with some very, very life-threatening infections.

If the best we can do is 20 percent, I am not sure that we should be sitting around here in this room, I am not sure what we are accomplishing. My personal view, and again I am reluctant to express this, since I don't have the requisite

dermatologic expertise, but I do see a lot of inflammatory conditions and I know that after you have cured the infection, and after you have eradicated the organism, it takes a long time for the physical manifestations of inflammation to go away.

Therefore, I wonder, you know, if somebody came up with something that was a combination of terbinafine and then used the last week, steroids, that he might really get a much higher clinical cure rate because would inflammation would subside and it would look great, but I am not sure it is something we would want to be doing on a routine basis, maybe we would.

Anyway, I just have difficulty with setting a lowest acceptable range for complete cure when we know that the bar right now is set at only 20 percent, and is it possible that we can talk about lowest acceptable cure rate for mycologically and symptomatically improved, or is that not an acceptable thing to be discussing?

DR. CANTILENA: I will ask Dr. Wilkin

because it's advice for him and Dr. Ganley.

DR. WILKIN: I think it can be approached in multiple ways. The truth is that we do not know which patients who are effective treatment meaning KOH-negative and culture-negative, but having a 1-plus erythema or 1-plus scale, or maybe both of those, how many of those really that scale and erythema is due to residual tinea and how much is due to some other condition, maybe just inadequate epidermal turnover.

Our thought was that while it may be conservative, and I think it is conservative, looking at the complete cure population, it still may not be complete cure, because there may be some KOH's that they couldn't find it, and some cultures that they couldn't find it, so people still get into the complete cure, and still have--I mean these are all very imperfect ways of looking at it, but I think Dr. Bisno makes an important point. You probably wouldn't want to be going for 100 percent.

I think that is the essential point, is

100 percent is not the target, because it is probably going to be hard to get there. Another example of what you are describing is if you look 3 weeks after treating a pneumonia, at the chest x-ray, you would still see, you know, maybe what it looked like at the beginning.

So, I think that is the way it is with the foot, the epidermis is not going to turn over, but the idea of the complete cure at least is something that is--it is somewhat artificial, but it is a very clear endpoint.

DR. BISNO: First of all, just finding mycologic elements, again, I mean the clinical situation may have been completely resolved, but, you know, fungi are universal and it may be difficult to completely eradicate even if you have eradicated a clinical--but I am getting beyond my own area of expertise by far.

But what I am saying is if we set 25 percent or 30 percent as an acceptable cure rate, then, we don't have anything on the market right now that meets our executive cure rate, is that

correct?

DR. WILKIN: Well, you have Dr. Fritsch's example. What page is that on?

DR. CANTILENA: It's Tab 4, page 2, for the complete cure rates.

DR. WILKIN: The complete cure at the time. This is now, again, Week 6 to 9, so in 6 weeks it has allowed for substantial epidermal turnover. This is like waiting for many months before you get the chest x-ray.

DR. WHITMORE: I have a question. This addresses labeling, and not what we are saying the FDA should be approving, right?

DR. CANTILENA: I think actually we have on sort of the next category, we will be talking about the labeling. Here, I think they are asking for really, you know, in terms of a complete cure rate, what is something that is meaningful from our standpoint for an approvable drug.

So, like if you had a new drug under development, what would you like to see, and I think the ideas earlier about the active control

are important.

I think that sort of gives you a reference, you can have vehicle only and an active control, and that really sort of tells you exactly where you are, but are you able to ask for those, active control, and placebo, is that something that is feasible, or is that advice that really couldn't be followed?

DR. WILKIN: Again, if it's for an indication that is not life-threatening or severe debilitating, typically, it's against the vehicle or the placebo, and not against an active. I mean that just has been the standard.

I think I missed a response to one of Dr. Bisno's points, and that is, you know, what should the committee be looking at. It would be I think acceptable to look at maybe something that is less conservative, the effective treatment, realizing that some of the people who have effective treatment are clearly going to have some fungus remaining.

None of these are perfect ways of looking

at it, but if the committee felt more comfortable characterizing the endpoint, the lowest acceptable in terms of effective treatment, we would be happy to hear it either way.

DR. BISNO: Well, I would certainly bow to the expertise of my dermatologic colleagues on this one. I am out of my depth.

DR. CANTILENA: We actually have a list going here. We have Epps, Katz, Fincham, Wood, and Davidoff.

Dr. Epps.

DR. EPPS: I guess speaking clinically, the patients, we don't see the ones who do well, the ones who go to the drugstore, they get the cream, they are treated, and it works well. The ones who are referred to me, and when we say "fail," I mean it looks like baseline. It is still raw, it is still macerated, they are still fissuring, it is not like it is just a little pink, otherwise, they wouldn't come to the dermatologist.

If it is getting better with the over-the-counter, they keep using it, oh, it's

getting better, I am just going to keep going. How long that is varies by the patient. Percentagewise, I tell a lot of people it's zero or 100, it works or it doesn't. I mean ideally, across the board, I guess I tend to be tough, like I would like 75, 80 percent, I mean we want it to work, that is what I would call most.

I don't think "most" is equivalent to better, because we are not comparing drug to drug, but certainly it should be better than vehicle, it should be better than placebo, obviously, that is proven.

As far as culturing, by the time we get to the subspecialist, you know, they are partially treated, it's not very useful, you may still get a KOH, sometimes that can be helpful, but a lot of the ones that don't work tend to be weeded out.

I mean you use if three or four times, it is not working, you just don't use that drug anymore, and fortunately, we have a lot of options, but a lot of the patients, if you ask them--and I guess that goes to reporting--what was the cream

that you used before, well, it was white, and that's all you can get. They don't remember the name, they don't remember, you know, well, it was my friend's, you know, you get a lot of answers, so that clearly affects the reporting of failures, as well.

DR. CANTILENA: Dr. Katz.

DR. KATZ: Well, the question is what should we accept as the lowest acceptable rate. Now, it was my understanding from a previous meeting at the FDA that the FDA approves medication if the safety profile was such that it shows some effectiveness, even the slightest statistically significant effectiveness in the face of pretty complete safety.

If that is the case, and you can correct me, Dr. Wilkin, if that is not correct, that is why things like Penlac, which is almost tantamount to useless, but it is completely safe, and it did show a slight, after a year, 15 percent of people got better, so that is why it was approved. I wasn't involved in that. So that was my understanding.

Now, if that is the case, then, the answer to this question should be the lowest acceptable rate in the face of pretty complete safety, should be good effect over placebo even if it's 20 percent.

That, seeming somewhat ludicrous, we get into the situation, which we are not answering the question on labeling now, but in answer to Dr. Wood's comment, I don't know that we have to set a certain percentage here if there is truth in labeling.

That is going to be another issue, but rather than arbitrarily set the lowest acceptable rate, if something is on the label that says 15 percent of patients can expect complete clearing, but that 50 percent of patients can expect significant improvement, that tells the consumer quite a bit.

I know you don't want to get into labeling, but that would be my argument against setting a lowest acceptable rate, if my feeling of the charge at the FDA is correct.

DR. CANTILENA: Yes, Dr. Bull.

DR. BULL: I would like to bring your attention to the other part of that statement, which is that the lowest acceptable rate of cure that is clinically meaningful, and I think certainly we want to be in the business on behalf of public health of approving drugs that provide something clinically meaningful for the patients, who are either prescribed a drug or the ones for over-the-counter products, purchase them on the basis of self-diagnosis and self-management.

So, I think it is very important to attend to the qualifier that is part of this Question 1, which is what is clinically meaningful, and that what we want your input on is to attend to what is the lowest acceptable rate that addresses this concern of what is clinically meaningful and patients having a reasonable expectation of having a positive effect, a benefit relative to the risk for their condition.

DR. KATZ: Then, perhaps on the basis of that and Dr. Bisno's comments, this question should

be altered, rather than saying our definition of cure, rather that we should use the definition of effectiveness, which means significant clinical improvement and mycologic cure. Maybe the question should be changed.

DR. CANTILENA: As we go around, you can qualify your answer in that way. I think that is perfectly reasonable.

Dr. Fincham.

DR. FINCHAM: I guess just looking at this from a consumers' perspective, if you have something on the label that says "cures most," I think it would behoove everybody involved, and certainly people are making excellent points about definitions and rates and whatnot, but I think we need to be specific or suggest that it be specific as far as what those words mean, so the consumer can make an informed decision in order to be empowered about his or her health.

To get to what Dr. Epps said, you know, we saw slide, several times curiously, from different people, about presentation of interdigital tinea

pedis, and it looked one way on the screen, but if you look at the photo, page 4 of the Novartis handout, I would doubt that this patient just appeared at the pharmacy to get this fixed.

I mean I would say that there are some serious involvement here. It looks like there is some nail involvement. What I am trying to say is a person like this or a person with a less severe case of tinea pedis should have an informed ability to empower themselves to make a decision based upon what the labeling says relative to "cures most," what does cure mean, what does most mean.

Again, we are back to semantics. We are back probably to 3(b), but it is hard to separate these out and look at them one question at a time, and I just think that the more specific that you can be, the better it is going to be for the most important person in this whole equation. It is not us in the room, it's the patient that is going to use it or try to use it to get better.

DR. CANTILENA: Dr. Wood.

DR. WOOD: Well, I am a great believer in

letting the marketplace shake these things out. I mean I think the way to handle this is to have people put on the label the efficacy found from that product, defined in whatever common way you want to define that, and that should have on the label and the comparison that can be achieved from an Rx product.

The reason I like that is going back to the comment that was just made, is what is the minimally clinically significant effect is a moving target. You know, the minimally clinically significant effect for a diuretic was different when it was a mercurial diuretic from when furosemide came along.

So, as therapy improves, what is minimally acceptable, and hopefully improves with it, minimally acceptable, to me, seems different today with systemic and the drugs that have been given systemically produce 70 percent cure in patients who have been defined as resistant to treatment.

So, I agree with what was just said by Jack, I mean I think the consumer should know what

they are likely to see with the efficacy, and that when Dr. Whitmore, or whoever it was, goes into the pharmacy and picks up these packets and looks at them, he should be able to see the different response rates for the different products, and have some concept of how that fits with alternatives.

DR. DAVIDOFF: I want to be sure I am clear on exactly why this question is being asked. I mean I am assuming that it is being asked because the Agency is trying to decide whether they should set a threshold level before a drug is approved. Am I correct? That makes some difference as to the way I would answer the question.

DR. CANTILENA: Dr. Wilkin, would you like to answer?

DR. WILKIN: Again, I think there is a marketing pressure for faster, and faster may mean it still beats vehicle, but there may be a drop in the efficacy whether you look at it as complete cure or effective treatment.

We are wondering if there ought to be some base rate below which even if you have a product

that has no major safety issues in the safety profile, whether still there should be that baseline.

DR. DAVIDOFF: So, it is an approval decision question. My thoughts in that connection are that if it is an approval question, it seems to me it would be difficult to justify accepting a new product unless the efficacy rate, whether it is defined on the basis of complete cure or effective cure, that is less than what is on the market.

That just seems reasonable to me. I realize the marketplace maybe speaks otherwise, but in terms of regulatory decisions, that seems reasonable.

I also recognize, though, that there are other approaches to making the decision. I mean one would be to look at what is the absolute risk reduction for other drugs or other classes that is considered acceptable, sometimes expressed as number needed to treat, and number needed to treats in the range of 5, which is what I understand the complete cure rate here would translate into, are

considered terrific. I mean a lot of drugs on the market that have NNTs of 100 or whatever.

So, I think that you could take that approach and say that at least it ought to be doing as well as most other drugs in terms of NNT, and it clearly would be, I think.

The final thought in connection with rationale would be that I agree with Alastair Wood that it is hard to give a single answer, because a lot depends on the seriousness of the underlying condition.

I think you would accept efficacy of maybe 1 percent absolute risk reduction for something that was a fatal disease. I mean I would be happy to have a 1 percent chance of being protected or cured if I was otherwise going to die, but if I took the drug, I would have a small chance of survival.

If it is a matter of clearing up a rash on my feet, I might see it differently. I might be interested in complete cure rates that were In a different ballpark than maybe would have to be

higher--

DR. CANTILENA: But that is the question, Frank, is higher.

DR. DAVIDOFF: Yes, I understand, and I think that that is a reasonable way to go if the condition that you are treating is less than fatal.

DR. CANTILENA: We have Dr. Ringel.

DR. RINGEL: I have two comments. The first one addresses what everyone is talking about here. Basically, I kind of disagree. I think that the FDA should use as a standard mycologic cure rather than complete cure or even effective cure, and the reasons are threefold.

First, because at the very least, I think you should be able to say that you should kill the fungus to an optimal level. Whether or not the person gets better, I don't know, but at the very least, we should be able to say that the fungus dies. That is number one.

The second is that perhaps it is not quite as straightforward as complete cure, but it is certainly more straightforward than effective cure.

At least you can measure it, you could do a KOH, you could do a culture. I know they are not perfect, but it's doable.

The third reason is that I don't know any other antimicrobial agent that is being held to the standards that we are holding tinea pedis. When I treat a patient for scabies, the scabies' mites will be dead the next day or two days perhaps, but I tell the patient he is going to itch for another two weeks, and I don't call that ineffective treatment.

When someone has pneumonia, they cough for another month. That doesn't mean that they still have pneumococcus. When they have meningitis, they are going to feel lousy for the next two months. It doesn't mean that their CNS is still infected.

I think that for those reasons, mycologic cure is actually the better standard here, and I am going to go a little bit out on the limb.

I would say that if we are going to choose an efficacy level, I would choose that of the first modern antifungal, which at least in my mind has

always been miconazole, and that is very subjective, I realize, but, you know, trained when I did, I thought of the old antifungals and the new antifungals.

I have always thought of the new antifungals as starting with miconazole, so I would say that the efficacy for mycologic cure should be at least that of miconazole, and I supposed we could look that up. I know it is arbitrary, but that is what I would do. That is the first comment.

The second comment is I guess this is addressing Dr. Wood about whether or not we need to compare topical antifungals to oral antifungals, and I would I think argue against that for two reasons.

First of all, I think most normal consumers would assume that over-the-counter medications are not as effective as prescription medications. It may or may not be true, but I think that is what people assume.

For example, if they get an

over-the-counter antitopical, antibiotic that is not helping, they will go to their doctor and say, gee, that didn't help, what else do you have, assuming the doctor is going to have something that is stronger and better.

The other issue is that I think that you can't assume that the safety of a topical antibiotic is going to be the same as the safety of a systemic antibiotic.

I don't think that people should assume, well, I can just go the doctor and do better, because the systemic antibiotics have black box warnings for liver toxicity, for congestive heart failure, and also have significant hematologic toxicity, so I really don't want my patients going to the drugstore and say, hey, well, I can just get Sporonox.

I don't think that is good. I would rather have them approach it the way I think most people do, when you are first looking at over-the-counter, if that doesn't help, then, going to their physician for a prescription.

DR. CANTILENA: Dr. Schmidt.

DR. SCHMIDT: Looking at the data that has been presented today and thinking about skin diseases just in general, when I have patients come in with a lot of these skin diseases, like acne, I usually consider a good improvement, say, for acne, at about 20 percent per month, and usually, someone after about 3 months, I like to see about, say, 75 to 85 percent clearing.

To me, I think these antifungal agents are much more effective than some of the medications that we use for acne, so in looking at these graphs, I would say that what I would put down for this, if you want some hard data, is between 20 and 30 percent improvement in a week or two, and then I think the bar should be about 75 percent after a month for all these topical antifungals.

I think that, to me, you know, 75 percent, that is a magic number in my mind, maybe more in acne, eczema, but if you had to say from what you see in these studies, you know, with the 20 to 30 percent, and then it bounces up with some of the

others, that that is the bar that I would say if we are looking for numbers.

DR. BISNO: Do you mean symptomatic in mycologic, but not complete?

DR. SCHMIDT: Yes.

DR. CANTILENA: Dr. Ghannoum.

DR. GHANNOUM: I think the way, let's say, we look at other antifungals, like it was suggested it would be good to have a comparator, non-inferiority sort of cases. We don't have that because we don't have gold standard.

But I think we have what is available in the market, and I think that should be for complete cure, and if say like "assume," it is non-inferiority, it should be between 20 to 30 percent.

If we go into the effective cure, even if you look at the oral stuff, let's say Lamisil compared to Sporonox when they are compared for onychomycosis, it was 65 percent sort of cure, so I think that is reasonable for the effective cure.

DR. CANTILENA: Thank you.

Dr. Wood.

DR. WOOD: I think we should answer this question the way we are doing it. I think I understand now what Dr. Wilkin is asking us, and it seems to me that the question we are being asked is how we evaluate products, and everybody rushing to the bottom, and that everybody moves to the bottom of the pack and finds the lowest dose that they can give for the shortest period of time, anything that beats placebo.

Now, I think we answered that already, and I think we said that we should see exposure ranging, and I think you should only approve drugs, assuming they have no toxicity, that are given at the exposure that produces the maximum effect.

That gets you off the hook for the rush to the bottom, which is what I am hearing here, and having said that, maybe surprisingly, I am very opposed to introducing new hurdles that drugs have to leap to get approved.

So, the hurdle is you beat placebo right now, and the idea that we are going to sit around

here and kind of chew on our thumbs and come up with some arbitrary number that you have to beat to get approved is very disturbing to me, because that creates all kinds of issues for other drugs, as well, you know, what is it in heart failure, what is it in Alzheimer's, for God's sake, I mean the effects there are pretty trivial for most of the drugs on the market.

So, I think the answer to your problem is I am telling you that we should look at exposure ranging. I would expect that you would only approve a drug, assuming the drug has minimal toxicity, as these topical agents do, that you would approve the drug at the dose or exposure of the drug that produces the drug's maximum effect.

As a consumer, that is what I would think when I was standing in the drugstore. If you do that, then, you are not in this position of this rush to the bottom, because I think that is a very dangerous step to get into.

DR. CANTILENA: But how about if the drug overall is not very effective, it has just barely

beaten placebo?

DR. WOOD: Well, if the drug overall is not very effective, I think we should tell people what the efficacy is, and I think if you are standing in the drugstore and you have got three packets in front of you, and one says this is 20 percent effective, one says this is 60 percent effective, and one says it is something else, let people choose.

I mean if they like the prettier packet that's 20 percent effective or maybe it will be cheaper.

DR. CANTILENA: Dr. Epps.

DR. EPPS: Brief comments. Certainly when there is a discussion about the movement to decrease the duration, certainly, if we were talking about antibiotics, we would be certainly concerned about resistance. Does it apply to antifungals? I don't know.

Although tinea pedis may not be life or death, certainly, there are quality of life issues. I have patients who can't walk, they can't go to

work, they can't go to school because it is so severe. So, I certainly don't think it is trivial, but it is certainly not fatal and certainly, to piggyback on what Ms. Knudson said, I think if we are going to move to approve drugs or have antifungals approved, they should work.

Certainly, whether it's $8.00 or $15.00, or whatever the co-pay is, there should be some reasonable expectation that they are going to benefit from it.

DR. CANTILENA: Thank you.

I think what I would like to do is for anyone who has not expressed their opinion on this, I will give you an opportunity yet to do so, but I think we have heard from probably 90 percent, which is clinically significant, I believe, by anyone's definition.

Is there anyone else who would like to add to the discussion?

DR. TEN HAVE: Could we hear from the consumer representatives on what the consumers would think?

DR. CANTILENA: Good. We have Dr. Patten and Ms. Knudson.

MS. KNUDSON: I have an unrealistic expectation that we should have 100 percent effectiveness on anything that is on a shelf. I realize that is unrealistic. However, I do want to see some comparisons between anything that is on the shelf as to what the effectiveness rate is for most people.

DR. CANTILENA: Are you able to do that in terms of the current regulations, can you put efficacy rates, comparison to like other things that are generic?

DR. GANLEY: You wouldn't necessarily compare something else. You could be able to put in cure rates or efficacy rates. The company who does want to do two comparative studies, comparing it to another regimen of another drug, and show that they are better than them, they could achieve labeling by doing that.

I think that we would have to talk about it internally, there is some difficulties, because

we don't have, particularly for the monograph products, we don't have the consistent types of efficacy endpoints that we have for the NDA products, at least the most recent approvals.

DR. TEN HAVE: Then, how can you set a standard?

DR. GANLEY: We would have to go back and look at the data that was collected. Nothing is perfect here.

DR. TEN HAVE: In terms of defining the minimum rate, if the efficacy definitions differ across studies--

DR. GANLEY: Well, that is the potential down side, and that goes back to what Dr. Fritsch had said, is that in some of these studies, they may have included patients with onychomycosis, for example, which may lead to a lower efficacy rate.

So, it is like comparing apples and oranges in some cases. But it may be that you create categories of efficacy or something, I don't know, I think we would have to talk about it.

DR. TEN HAVE: So, is the implication,

though, that we need different thresholds, different minimum acceptable thresholds for different categories for these different definitions?

DR. GANLEY: No, I don't think so, but I think that it is what we do with the products we have now and what we decide we are going to do for the future, so I think that is where we have to really start from, and then set the standard of what we would like to do for the future and see what we can do for the other products that are on the market right now.

Nothing is going to be perfect here, because of that.

DR. CANTILENA: I think we also want to hear from Dr. Patten.

DR. PATTEN: I am going to agree with Dr. Ringel. I would say that, at a minimum, there needs to be negative mycology. If anything comes in without that, then, it seems to me it's an application for something that will manage the condition or decrease severity of symptoms, and the

concept of cure would be inappropriate.

My understanding of this is that this is the agent that causes the condition. If the agent is still there, the condition may recur, will recur.

DR. CANTILENA: Thank you.

Let's move to the last broad topic area, which has to do with the label. Actually, I would like to start with the safety issue, which is Question 6, and then we will do Question 3, (a) and (b).

I think what I heard this morning, and I apologize, Dr Bisno, if I didn't hear you correctly, but that with regard to safety, it really didn't seem to be a large problem, and from the AERS database, it doesn't show up in terms of cellulitis.

So, I think what the Question 6(a) basically talks about subpopulations, which I would like to hear from everyone. I am sure we all have an opinion on if there are specific subpopulations, because if so, then, we will sort of meld that into

the labeling.

I will open it up for general comments and talk about the risk of secondary infections, and then if there are any subpopulations who are at higher risk, and, if so, should that be in the label.

Yes, Dr. Bisno.

DR. BISNO: If I may say, I think the study that needs to be done, probably should be done, is to look at patients who have cellulitis and particularly those who have recurrent cellulitis, and to grade them on two different factors.

One is the severity of their tinea pedis, and the other is their coexistent comorbidities. I think if that study were ever done, we would see that there is probably a small subsegment of people with severe tinea and comorbidities who are probably at much risk of cellulitis and that the general population is not.

Lacking those data, my suggestion would be, what I had in my last slide, although I would

expand it just a little, I said tinea pedis is only one of a number of risk factors for the development of lower extremity cellulitis, but it is one of the most modifiable of such factors.

The committee might wish to add a caution about the importance of eradication of tinea pedis in patients with such risk factors as lymphedema, venous insufficiency, edema of the legs, marked obesity, saphenous venectomy for coronary artery bypass graft, or previous episodes of cellulitis.

It might be worthwhile to add immunosuppression there, too, immunosuppressed patients, and although the data on diabetes are not clear-cut, I wouldn't object if you wanted to add diabetes, too.

That would be my suggestion, to just have something on there that says that tinea pedis is a risk factor for cellulitis particularly in this group of patients, and they should take particular care to eradicate their condition.

DR. CANTILENA: Thank you.

Other comments? Dr. Benowitz.

DR. BENOWITZ: I think we need a clarification of what the issue is here. One issue, if tinea infection predisposes to cellulitis, then, we should treat them.

The question would be if you are at high risk of cellulitis, should you use oral instead of topical, because it is more effective. I mean that would be one question.

Or is there a concern that if you have cellulitis, you are not being treated for cellulitis adequately, because you think it's tinea, and you are being treated for that instead.

So. those are the problems, but I am not sure what the intent is of special labeling. We should effectively treat someone if they are infected, right?

So, my question is what is the purpose of the special label?

DR. BISNO: The question that was raised by the committee and to me specifically is what recommendation I could make regarding the issue of cellulitis and tinea pedis, and my feeling was that

there are certain subgroups of people who are at higher risk, and that it would be prudent and feasible to identify those.

We are not telling anybody not to treat tinea pedis, but we also know tinea pedis is extremely common and in many cases, go untreated unless they are highly symptomatic.

DR. BENOWITZ: I understand that, but in terms of the labeling for a product to treat tinea, the question is if you have this, make sure you take this product?

DR. WHITMORE: I think this is not a consumer information product. I think this is a physician education product, and those patients who do have these risk factors are being seen by a physician, so it actually is the responsibility of the physician to look for tinea pedis.

You can bet that the majority of the people with those predisposing factors probably have fungus on their feet, too.

DR. CANTILENA: Dr. Alfano.

DR. ALFANO: I am concerned about changing

the label for a potential effect that has occurred at such a low, ultra-low rate. I mean we learned this morning that we are really now talking about hundreds of million of doses, of treatments, and we have 13 cases reported, and as Dr. Bisno pointed out this morning when he reviewed those cases, most of them didn't seem to him to be cellulitis in any case, they seemed to be allergic reactions.

We have seen the industry propose to add some labeling that would encourage people to seek the advice of a physician if the condition worsens or changes in any way, which would be sort of the preamble to cellulitis, so there already is sort of a--I don't think we need a fix--but there already is I think a good one that has been proposed.

I am very concerned that as we make the label more complicated, it becomes less understandable and more intimidating, and we could actually be discouraging people from using this product, and it could have the unintended effect of decreasing use and increasing risk.

So, in the absence of any consumer

comprehension studies, label comprehension studies, I just wouldn't go near this particular one for such a seemingly inconsequential risk.

DR. CANTILENA: Dr. Schmidt.

DR. SCHMIDT: We are seeing more cardiac surgery and we are seeing a lot more stasis dermatitis, and a lot more lipodermatosclerosis, and I think even though these cellulitises of the lower extremities, I don't think they are rare, and I think that the cases that they presented were not cellulitis, they were contact dermatitis, but I would be interested to hear from the consumer reps because, to me, this does sound like a good idea, you know, we are doing something for these people.

A lot of these people just kind of bang around and then they finally come in with problems, and, to me, to have this on the labeling where someone comes in and they have a fungus, and they read this and they say wait a minute, I do have--I am wearing my support hose and I did have, you know, they have harvested my veins and now my legs are messed up, and I am going to start putting this

on, because it is a treatment that we can do something about it, whereas, this other stuff, it just happens.

So, I vote for this.

DR. CANTILENA: Dr. Wood.

DR. WOOD: I want to agree with what Neal and Dr. Alfano said. We can bog the label down with so much stuff, and I don't understand the problem we are addressing here. There is no evidence that these drugs produce cellulitis. This is not hepatic toxicity or some side effect we are trying to identify and tell people to go their doctor about.

These people are also at risk for having a heart attack. Why don't we put in the label, you know, if you get chest pain, be sure to go to see your doctor. These people are in danger of having a DVT, if you get calf pain, go and see your doctor and particularly if you get short of breath. I mean there is no end to this.

Unless there is some association between the drug and some adverse outcome, and that

informing the consumer will help prevent that adverse outcome, I don't think we should burden the label with a bunch of stuff, that I don't see that it helps them very much.

Maybe I am missing something here, but I have not heard some reason to believe that going to your drugstore, buying an antifungal, it makes you more at risk for cellulitis than you were five minutes before you did that.

DR. CANTILENA: It is just the complications if it is unsuccessfully treated, and I think that is what we don't know.

Dr. Davidoff.

DR. DAVIDOFF: I understand the kind of concerns that Alastair and others have had about unduly complicating things. The problem I have is not so much the concern of whether or not the drug is causing the infection, and so on, which it clearly isn't, the problem I have is that patients who are not clear whether they have a beginning cellulitis or tinea pedis, and if they have decided that it's tinea pedis and start treating it, when,

in fact, it really was cellulitis, and the continue treating it because they think if I wait 7 days or 4 weeks, or whatever, I am going to be okay, those are the people I am concerned about.

So, I think that the notion of adding some wording about if the condition worsens or if irritation occurs, and so on, it is more than reasonable, because of the issue of difficulty in people's minds in distinguishing what is going on in their foot, so that is my view on that particular subquestion.

I had some comments on some of the other subquestions, too. One of them was on this issue of cure rate, because it seems to me that the notion of adding data about cure rates for the different products--

DR. CANTILENA: Actually, that is going to be coming up.

DR. DAVIDOFF: I am sorry, okay, I will save it.

DR. CANTILENA: Dr Bisno.

DR. BISNO: I would like to say, first of

all, that I am not advocating for this change. I was asked to make a suggestion for the committee as what could be done about this very difficult and complex issue on which there is not a lot of data, and this was the best suggestion I could come up with. I am not advocating it one way or another.

But I would disagree, Dr. Wood, with your analysis or your comparison with other kinds of illnesses, because these are illnesses that are distinct risks for these cases of cellulitis, and some of these cases are severe and, at times, even life-threatening, and they are directly related, at least in part, not in total, but in part to the tinea pedis.

What is missing is we don't have tremendous great data to indicate--you said topical or oral--we don't have tremendous data to indicate that either of those would be actually effective in preventing it. It is only an assumption that if we are treating with something that is effective against the t. pedis, that we are going to therefore not be having a nidus for the bacteria,

and therefore we won't have the cellulitis, but that is a lot of speculation based on no firm data.

So, anyway, just to conclude, I am not advocating one way or another, I was asked to suggest what could possibly be said about this, and this is the best I could come up with.

DR. CANTILENA: We will have a comment here from FDA, and then we will actually go around the table with the vote.

DR. WILKIN: One of the things we learn in advisory committees is how to construct questions better. I think this has been expanded in a very useful way. I mean I think we have heard about some other areas other than what our original intent was, but I thought I would just share with you what the original intent was.

We did think that it would be helpful to have Dr. Bisno's experience given his writings in the literature, and, in part, we saw this paper by Morton Schwartz, Cellulitis. It is the Clinical Practice section in the New England Journal of Medicine.

He goes on to say the things to do in the management. You can imagine that the large part is devoted to antimicrobial therapy, but then when you get down under Ancillary Measures, he talks about the local care.

The second sentence is, "Interdigital dermatophytic infections should be treated with a topical antifungal agent until they have been cleared. Such lesions may provide ingress for infecting bacteria"--and then he goes on. "Observational data suggest that after the successful treatment of such dermatophytic infections, the subsequent prompt use of topical antifungal agents at the earliest evidence of recurrence or prophylaxis application once or twice per week will reduce the risk of recurrences of cellulitis."

That was the genesis of the question.

DR. CANTILENA: Would you have any objection if we slightly modify this to say, "Would you recommend that the current labeling be modified for subpopulations at risk for secondary

infections, yes or no, and if yes, which ones would you highlight?" Is that acceptable to you? Okay.

Is it a burning question, Dr. Benowitz?

DR. BENOWITZ: Yes, because there is still two things that are totally different that I don't understand what we are labeling.

One is a misdiagnosis question, so make sure that you don't have cellulitis before you take this stuff and it gets worse, and the second thing is if you have a predisposition to this, you should be treated more promptly. I don't see how either one is really relevant to the label, or the first one might be to diagnosis, but I still don't understand what you really want out of the label.

DR. CANTILENA: In that case, then, your answer would be no, because of those reasons, but if you have subpopulations, if you are concerned about the diabetics, for example, who would use the product, and it would fail for them, they would have a secondary infection that they still think is the slowly healing fungus, then, that is another issue.

DR. BENOWITZ: I guess I just need to know what specific label are you talking about, is it a diagnosis label or is it a treatment label? I just don't understand what the label would be.

DR. BISNO: Are you addressing that to me? The first issue that you raised was, let's see, it has nothing to do with if you have cellulitis, you should do something. That is not relevant.

The second issue is maybe it's not an appropriate place to put on a label, I am not saying it is, I am saying this is the best I can come up with if you want to give a caution to patients as part of the label as to what people are at particular risk of getting cellulitis related to t. pedis, and it may or may not be an appropriate thing to go on a label, that is for the committee to decide.

DR. CANTILENA: Would you like to vote yes or no on should we modify the label for subpopulations at risk for secondary infections like cellulitis? That would be a yes/no.

DR. GANLEY: Lou, I would just interject

here. I think it is probably better just to get comments from people, because there is a lot of caveats that have been thrown into this, and I think we can try to sort it out.

There is numerous ways to do things. Clearly, if we thought, for example, that people with lymphedema or venous insufficiency shouldn't even be starting a therapy on their own, you could include something in the label, such as ask a doctor before use if you have these conditions.

If there is no data here to support that, then, your answer would be no. Or you could decide that maybe we should put some package insert in there and include some information on some conditions that if you are not getting better, you should get better in this period of time, if you are not getting better, you should see a doctor immediately if you have these underlying conditions, and I think that is what Dr. Bisno was getting at.

I think there is a lot of ways to do it, and I think it is probably more fruitful to have

just a discussion as what people's biases are.

DR. CANTILENA: Okay.

DR. BISNO: Let me just say that one thing we wouldn't want to do is say go to your doctor before starting to treat this. I mean we don't want to discourage people with these risk factors from starting self-treatment.

DR. WOOD: But you want to encourage them surely.

DR. GANLEY: I think it comes out more in a discussion than in a vote.

DR. CANTILENA: How about if we just start over here, just go around the table and comment on your thoughts on this.

We will start over here. Ms. Knudson.

MS. KNUDSON: It seems to me that if diabetics are at higher risk for secondary infection or those who are immunocompromised, and certainly AIDS patients must get tinea pedis in great numbers, but I would like to see something in the label that indicates that if you have these conditions and you are not responding to the drug,

please see your physician or we recommend that you see your physician.

DR. CANTILENA: Dr. Benowitz.

DR. BENOWITZ: I would certainly agree with that as a label, and I think what the manufacturers suggested seemed like a reasonable label. If you want to do just extra education about people at risk of cellulitis, if there is room on the label, that's fine.

DR. CANTILENA: Dr. Clapp.

DR. CLAPP: It seems like the addition of a cautionary note on the outside of the box, that states if this is not getting better or gets worse, and give a specific time frame, that could be a clear general warning to anyone, and therefore give information that would make people stop and take note without giving a tedious list that might not be all-encompassing of the types of people who are at increased risk for problems secondary to cellulitis following or associated with the tinea pedis infection.

DR. CANTILENA: Thank you.

Dr. Epps.

DR. EPPS: Perhaps on both ends, one, you could say for uncomplicated cases of, you know, tinea pedis, interdigital, that sort of thing, and then follow with a sentence about if you X, Y, Z conditions, you consider asking your doctor about use.

DR. CANTILENA: Dr. Raimer.

DR. RAIMER: Logically, it does seem like people with lymphedema and obesity, and that sort of thing, certainly would have a higher risk of getting cellulitis if they did have a nidus or infection, so it seems logically like a reasonable thing to do, but I don't know if we should actually label, put things in labels when we don't have any scientific proof at this point in time.

So, I would like to see it done just because my opinion is that it is kind of logical that it would happen, but maybe it's too early, maybe we shouldn't do it without any real proof that it is happening.

DR. CANTILENA: Thank you.

Dr. Wilkerson.

DR. WILKERSON: I like the labeling that Novartis came up with. I think this is reasonable for consumer packaging. I think if you put too many things in there, list all these conditions, it just causes confusion.

I agree with Dr. Raimer. Teleologically, we believe that we are right about treating tinea pedis, but as far as I know, no one has done a large-scale study to show that if you put the stuff on once a day, twice a week, whatever, that we actually affect the outcome that we think we are going to affect here.

I think keep it simple, and their wording seems very good to me.

DR. CANTILENA: Dr. Patten.

DR. PATTEN: I would support indicating on the label if condition does not improve, condition worsens, or new symptoms develop, see your doctor. I would not support naming specific conditions.

If there is evidence to support increased risk of any kind coming from these conditions,

then, perhaps in insert, but not on the label.

DR. CANTILENA: Dr. Lam.

DR. LAM: I definitely agree with what Dr. Patten said, to make it simple.

DR. CANTILENA: Dr. Ringel.

DR. RINGEL: I would recommend putting a caution on the outside of the box, but simply have it refer to the medication guide inside the box, in other words, to say, you know, please see Caution Section of package insert or whatever, and then in the medication guide, then, have a discussion of specific issues.

I would think things on the label should have more to do with whether a person would buy the product or not, does he need to know that information at the time of purchase or does he not. I would say no, you don't need it at the time of purchase, you need to know it as you are using it.

So, I think it could go inside on the medication guide.

There is another issue that perhaps should be addressed, as well, having to do with diabetes,

not only as a risk factor possibly for cellulitis, but also in terms of poor wound healing. People with diabetes and peripheral vascular disease get ulcers on their feet if they are scratching at them all the time.

There are a number of issues that may come up that you might want to reference, and you can't possibly put all of that on the package.

DR. CANTILENA: Dr. Fincham.

DR. FINCHAM: I would vote to have the packaging be as inclusive as possible, and specifically because we are looking at a self-diagnosis in many cases and relying on the patient to make a decision without input from a health professional, so I think it needs to be inclusive.

I don't see this as any different than some of the things that are on pseudoephedrine labeling relative to hyperthyroidism, hypertension, prostate disorders, et cetera. I think the more inclusive you can be, you just give consumers a better chance to be better informed.

DR. CANTILENA: Dr. Whitmore.

DR. WHITMORE: I think the proposed packaging with back label information on the box by Novartis is good, and I think that is adequate.

DR. CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: I would tend to the more conservative side, that is, trying to avoid overcrowding an already crowded label, on top of which I think it would kind of lead to endless discussions about what conditions should be and what shouldn't be on that complicating list.

I do like the notion of including information about those conditions or whatever subset in the package insert, however.

DR. CANTILENA: Dr. Schmidt.

DR. SCHMIDT: I agree with Dr. Raimer and Dr. Davidoff. I think it sounds good, that it makes sense to be inclusive with some of these things, but it is going to crowd this package insert, and until we really know just how many times we have, you know, these cellulitises, I think it probably is best left out.

I agree, I think that the package insert that Novartis, they have pretty well covered everything.

DR. CANTILENA: Dr. Katz.

DR. KATZ: I would say no to the overinclusive listing of each subpopulation, and just a general comment if you don't get better, see your doctor, which I assume is on all the other over-the-counter things, so one sentence would be fine without listing all of the other subpopulations.

DR. CANTILENA: Dr. Ghannoum.

DR. GHANNOUM: I think make it simple, and I agree with the other members that just provide information as mentioned by Novartis.

DR. CANTILENA: Dr. Bisno.

DR. BISNO: I think after listening to the discussion, I would agree that this is probably inappropriate to put on the package label, and don't think it should be put on.

If there is a decision to add such a caution anywhere else, on the box or anywhere else,

I would advocate that the conditions that I mentioned in my slide be put on, because they are established risk factors, and I would diabetes on general grounds and also immunosuppression, which is also an established risk factor, if there is a decision to do that, but I would certain agree that it doesn't belong on the package labeling.

DR. CANTILENA: Dr. Wood.

DR. WOOD: I agree with what was just said about presumably, every over-the-counter product should probably have some disclaimer that says if you are not getting better or you are getting worse, see your doctor.

I am comfortable with putting lists on the label that are actually lists of things that should encourage you to take the drug rather than lists of things that can go wrong when you take the drug, and these are very different issues. I think most consumers would interpret a list on the label as something that should encourage them to avoid taking the drug rather than the other way around.

In fact, in Dr. Bisno's risk factors, it

would seem to me to be indications for rushing out today and buying these drugs, and the idea that consumers will read this label and be discouraged from taking it seems to me a major public health hazard actually.

DR. CANTILENA: Thank you.

Dr. Ten Have.

DR. TEN HAVE: Support a simple general statement, cautionary statement.

DR. CANTILENA: Dr. Alfano.

DR. ALFANO: Same comment I made earlier, simple statement as has been propose by both Novartis and CHPA, essentially, the same statement.

DR. CANTILENA: Thank you.

Mr. Kresel.

MR. KRESEL: I support a simple statement. I think the first rule of label writing is keep it simple. People don't read beyond that, or they just get so confused they give up.

DR. CANTILENA: I would agree with generally what has been said, that we should not add specifics at this point until we have the data

to support that, but we do need to strengthen the other warnings, which have already been talked about, and I would support those changes.

Okay. I think we have all talked about the shortcomings of the existing label, so I am confident that this group can go right to 3(b), are there claims on the current labeling that may mislead consumers to have greater expectations.

We can start here and we will do an actual yes or no on this. If there are claims, then, if you would specify which ones trouble you the most about misleading consumers.

Tab 7, Table 2 tells you the choices for the monograph, and Table 3 has some samples of information from some of the OTC NDA drugs. We had sort of touched on these earlier today.

Some people have significant trouble with some of the wording and whatnot, and the qualifiers or lack thereof, so I think maybe we can just say whether or not you do have a problem with the existing label in terms of it being misleading to consumers, and if you do, which are the things that

trouble you the most.

Go ahead, Mr. Kresel.

MR. KRESEL: I think the one that we have talked about the most is "cures most," which I don't think anybody really had any understanding of anyway, it doesn't seem to have any meaning, so it ought to go away. I think "cures most" being replaced with "treats" makes a lot of sense to me.

DR. CANTILENA: Dr. Alfano.

DR. ALFANO: I think back to what Dr. Bull said, what is clinically meaningful to the consumer, and if you think of the data that was presented by Schering-Plough, most consumers buy these products for sort of symptomatic relief, they are not treating hyperkeratosis.

So, under that basis, just to clear up the issue on cures, I would agree that "treats" would be a better word as proposed by Novartis.

DR. CANTILENA: Dr. Ten Have.

DR. TEN HAVE: I agree that "treats" is better.

DR. CANTILENA: How about in terms of the

other items in the current OTC labeling? Let me find a good example of that. Attachment 2?

DR. FINCHAM: It is Tab 7, Attachment 2, not Table 2.

DR. CANTILENA: Attachment 2 in Tab 7. Yes, we are going to go all the way around.

Dr. Wood. I think I know what your most important concern is.

DR. WOOD: My biggest concern is most, but seriously, I think there are other questions that are in here that we should address, on page 6, for example, that are specifically addressed, at least I imagine are specifically addressed to the committee.

I like the idea on page 5 of including specific efficacy data, which would not have to rely on comparative studies. Does that make sense? So, the data that came from the studies, if that exists; if it doesn't exist, then, tough luck. I mean if it doesn't exist, you don't get to put anything on, and people should draw their own conclusions from that. Maybe you should say there

are no data to say how effective this is, if that is what it is, and if the other products that says it is X percent effective--

DR. CANTILENA: I think perhaps you are crossing over into 3(a) with additions. I am actually sort of looking for problems that you have with the current label.

DR. WOOD: Then, I will pass.

DR. CANTILENA: We will have an opportunity to come back to all the items that we would like to add.

Dr. Bisno.

DR. BISNO: I don't have any comment.

DR. CANTILENA: Dr. Ghannoum.

DR. GHANNOUM: I agree "treat" is better.

DR. CANTILENA: Dr. Katz, any problems with the current label?

DR. KATZ: There is a lot of problems here because as Dr. Wood said initially, "cures most," it clearly doesn't cure most, so that is wrong, it is deceptive. It is not even effective in most, so using that word is very deceptive. The effective

treatment in Dr. Fritsch's discussion on page 8, Table 16, even effective treatment, if you subtract the effective improvement from the placebo, in none of them does it even reach 50 percent. That is not considering cure, it is just effective.

So, using that word, I agree with Dr. Wood adamantly that that is deceptive. Even treating most, what does that mean, "treating most?" I don't understand that. If I am a consumer and I go to the store, and I see it "treats most," what does that mean, that it helps most? So, that is another word that shouldn't be there.

The most clear-cut situation would be clear symptoms in whatever the number that the FDA and company agree upon improves symptoms in 48 percent of patients, or if you take a few studies, in anywhere between 35 and 48 percent of patients. That means something. Most consumers know what that percentage means.

So, I would be very specific with that without getting too tedious, and that should be for each drug.

That's all the comments I had.

DR. CANTILENA: Dr. Schmidt. Problems with the existing label.

DR. SCHMIDT: I agree. I think put "treats athlete's foot," and then I agree with Dr. Wood that there should be some percentage, if it's available.

DR. CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: I also have a concern with the "cures most," phrasing, but for a somewhat different reason. It seemed to me that we have been looking at this from a rather narrow point of view, namely, sort of a bug in the skin, and it seems to me that the actual situation is more complicated than that in the sense that there is bugs in the skin and in the surrounding environment, and that unless you take that ecological view, it's I think not fair to be talking about cure, because unless you treat all parts of the situation, you are not really dealing with the whole situation.

It would be a little bit like talking about preventing surgical infections because you

have given pre-op antibiotics, but surgeons don't have to wash their hands. I mean the ecological view would include the surgeons' hands.

So, having said that, I think it is also fair to say that the word "cure" is appropriate for many patients. The organism is eliminated, the symptoms either disappear or get much better, and what is residual may not be related to the infection. So, I think "cure" actually is not an unreasonable term.

So, putting that all together, it seems to me that the word "cure" might be appropriately retained, that the word "most" should go, agree, but I think there are other words that could be used, for example, I know you may not want to get into wordsmithing, but even saying "cures many" would be not be unreasonable. That is not I think false advertising.

Finally, if you take the ecological point of view, you might want to include a word like "helps," so "helps cure many tinea pedis infections" might be useful in the same sense that

fluoride in toothpaste, the claim for it is included in the context, you know, the ADA's statement about fluoride is that fluoride helps prevent cavities as part of a program.

I wondered if from the dermatologists' point of view, having a word like "helps" might be useful in the sense that it would allow or encourage patients to at least find out what else they could be doing like the other things that dermatologists do talk to their patients about, like how they should deal with their socks and shoes and their shower, their avoidance of swimming pools, or whatever else.

So, I would summarize it by suggesting that "helps cure many" might be the way to go.

DR. CANTILENA: Dr. Whitmore.

DR. WHITMORE: I agree with what has been said about the current labeling and then if I could say something about the proposed label. On the front of the Lamisil box, they talk about "eliminating fungal infection," and I would not say that, I would say "treat fungal infection." The

same is true for the Desenex.

DR. CANTILENA: We will talk about the additions that you would like in the next question, but thank you.

Dr. Fincham.

DR. FINCHAM: I have troubles with the wording of "cures" and "most," and an appropriate replacement needs to be made. One of the problems with advisory committees is they give you advice, and I appreciate your patience listening to us today.

DR. CANTILENA: Dr. Ringel.

DR. RINGEL: I think that the label should reflect exactly what the product does, and I think what this product does is that it kills athlete's foot fungus, and I think that the label should say "kills most athlete's foot fungus." If, then, the symptoms don't go away, the person should have assumed that either he has persistent inflammation or some other disease that is not athlete's foot, or perhaps a resistant organism, but that is as honest as I can think of, it kills athlete's foot

fungus.

DR. CANTILENA: Dr. Lam.

DR. LAM: I actually think that the word "most" should go just because it's misleading, and leave out "cure athlete's foot." To me, the consumer will actually think that it takes care of the problem, and when you look at the response rate, it doesn't.

So, I think it should just state what it is supposed to be used for, which is treatment of athlete's foot, and that, in a sense, make an implication that there is not guarantee that it will take care of that condition in every single patient.

DR. CANTILENA: Dr. Patten.

DR. PATTEN: Certainly, the word "most" should go, and I even wonder about the word "treatment." I wonder if, in the general usage of that word, or the way it is conceptualized, treatment does not imply the goal of cure.

I just raise that question. I am operating on the assumption that it does, so I would favor

information that tells people that it improves symptoms or alleviates symptoms, or something like this.

Also, I am looking farther back in this Section 7, and I am seeing some samples on prescription drug labels, and I am seeing the word dermatologic and dermal crop up several places, and I think when that is for consumption of the purchasing public, the word "skin" should be used rather than dermal or dermatologic.

DR. CANTILENA: Thank you.

Dr. Wilkerson.

DR. WILKERSON: The only thing I have to add, I have seen on some packaging, there is a warning on there to the effect of do not use on nails, and I don't see that in any of our materials. I just wondered if Dr. Ganley could--I mean many times we don't want to treat patients with systemic antifungals, and we tell them to go get something, and they read this warning on the box not to use this on their nails, thinking that some harm is going to come to them outside of the

fact that it may not work.

Dr. Ganley, I was wondering, it is not in our materials, but I know it is on consumer items, I have seen it in the last few weeks. Maybe it is in there.

DR. CANTILENA: Dr. Ganley, do you know?

DR. GANLEY: Yes, I am looking on page 18 of Tab 7. Do not use on nails or scalp.

DR. WILKERSON: A lot of people interpret that to mean that--I mean is this the standard wording every time, or are there variations on this wording?

DR. CANTILENA: This is for the NDA version, right?

DR. GANLEY: It's on some of the products, I believe, not all of them.

DR. WILKERSON: Would there be other wording that would actually warn against using it on hair or nails?

DR. GANLEY: I think the point would be is whether this would be effective in treating a nail infection like onychomycosis, and it may be that it

may have to be stated differently, but I think it is a point well taken.

DR. WHITMORE: I think it might be helpful to say do not use to treat infection of the scalp or nails, because patients will come in and say I got some on my nails, am I going to die.

DR. CANTILENA: So, you have a problem with that in the NDA version.

Dr. Raimer.

DR. RAIMER: I don't really have much to add either. I don't like the most cures obviously, as everyone else has stated, but what we should replace it with exactly, I think we have had several good suggestions, I don't have any strong feelings about any of them.

DR. CANTILENA: Dr. Epps.

DR. EPPS: Well, if someone wanted to use cures, that would be a nice time to put in your percentage cures, or a little asterisk referring to the bottom, in our trials 50 percent or 20 percent or 60 percent or whatever, that might be helpful.

Are we commenting on all the label or just

that part? I like relieves, for relief of, as well.

DR. CANTILENA: Dr. Clapp, problems with the existing label and what you don't like.

DR. CLAPP: Problems with the existing label certainly are "cures most," because I haven't seen any evidence of that. "Most" and "cures" is a standard that I don't think most of them can live up to within the time frame that is expected. I think if we take it out to 6 to 9 weeks, then, we see more relationship to actual cure.

But I think that the efficacy endpoint are interesting, and negative mycology certainly would be among our standards for expectation with patients, but I think the patients are more interested in a symptomatic cure or to symptomatic relief, so I like the concept of effective treatment as being the standard for us to consider as opposed to actual cure, complete cure, but I think it could also be something that consumers could conceptualize better than cure, and that if they have a relapse or recrudescence or just

incomplete treatment, they can say, well, it didn't say it was going to cure me and just didn't effectively treat me.

Perhaps that is a middle ground that makes patients more willing to try again.

The other things on the label that I am concerned about are the warnings for children, because I am not sure--I know that this is getting into a different scope, but I think we have to consider always reasons that we are limiting use for children under 2 if there is not a legitimate reason, or whether or not there is.

Also, we are talking about the monograph labels, are we?

DR. CANTILENA: Actually, either one. There is NDA, OTC, and the monograph.

DR. CLAPP: Some say don't use in children under 2, some say use only in children over 12, and I think we have to have a good reason for the use specific to the medications that are being used.

The other interesting thing that I find , the Novartis label is interesting, the graphics are

nice, but I am concerned about the claim that is must be used twice daily for full 7 days to eliminate fungal infection, when, in fact, on the indications that we have for usage was the moccasin type tinea pedis, is that it must be used for 2 weeks, so there is an ambiguity here that I think perhaps patients are not, when they grab the box and read it, and if they think that they have tinea, and it is the moccasin type, I don't think they are distinguishing between moccasin versus intertriginous, and they would perhaps expect, leave with the expectation that they are fully cured in one week, so I think that ambiguity should be addressed.

The other part that I see in some of these labels are where we are demanding of the patient to make the diagnosis of not only tinea, but intertriginous versus moccasin type, and I think it puts quite burden on the patient, and when you read the attached labels, some of the labels you have say cures between the toes, and others say but not on the bottom of the feet or only for use between

the toes, and I want to make sure there is some consistency between the use and indication, and the actual reality of whether or not patients should then think that they should not use it if they have it on their feet or whether they can only use it if it is between the toes.

The instructions to the patient has to be consistent with the type of tinea that we are advising them or the location of the tinea that we are advising that they could treat.

Oh, and one last thing about the Novartis. If we are talking about the last question about indications or warnings for patients, many stated that they liked their label in terms of the warnings to ask a doctor if the symptoms worsen or new symptoms develop, but then it also has a precautionary note especially if you have diabetes, and I haven't heard that we have a clear link between diabetes as being worse than anything else. I like the caution, but not specifying diabetes and not listing lymphedema and CABG patients and everything else.

DR. CANTILENA: Thank you.

Dr. Benowitz.

DR. BENOWITZ: For the first part, I am happy to say "treats athlete's foot." One thing which I just noticed in this Novartis ad which is a problem because it's not true, although it is not a bad idea to encourage people, but it says, "Must be used to eliminate."

According to these guidelines, to eliminate fungal infection, that's not true. Most people don't use it according to the way it is supposed to be used, and in many cases, it still works. I think we should encourage people, but not say that it must be used according to guidelines in order to kill fungi.

DR. CANTILENA: Ms. Knudson.

MS. KNUDSON: Well, everything I was going to say has been said. I really do not like the word "most," I don't like the word "cure," and I am not crazy about the word "treatment" either.

I like Dr. Ringel's idea about "kills athlete's foot fungus." I think that is a pretty

clear statement and there is enough information to back that up.

I would also like to see something that says something about when you could expect your symptoms to clear.

DR. CANTILENA: Well, that will be coming up actually. We will make it unanimous in terms of nobody likes "cures most," and I think you should obviously fix that, and then strengthening the warnings is something that we will talk about now.

That was unanimous for 3(b).

Let's conclude. I don't think you all want to come back tomorrow morning just for one part of one question, so although we are past the hour, I apologize, but I think we will be finished.

3(a) is the last thing we need to deal with, and basically, in addition to what has already been said, I would like to get everyone's opinions, and we will go around the room this way looking for specific additions that should be made with regard to the three things that were suggested. Cure rate, should that be there.

Expectation of symptom relief, you know, delay in response, and anything else that you need, that you think should be added to the label to help consumers select this and use this class of products.

Ms. Knudson, would you like to talk about things that you would like to see added to the label of existing and future?

MS. KNUDSON: I would like to see what the effective treatment rate is. I think that is more important for consumers than cure rate, because they are going to think that it is has really gone forever.

I would like to see certainly expectation of symptom relief. That is something that I think is terribly important. I think that since it has been pointed out repeatedly in the material that we have received, that there is a delay in response. I think that should be noted, so that consumers can expect that and will continue with the drug or wait to see what happens for the full 7 days or however many days it's appropriate.

DR. CANTILENA: Thank you.

Dr. Benowitz.

DR. BENOWITZ: I agree with Paula's comments.

DR. CANTILENA: So, everything that was in the question, you are in favor of.

DR. BENOWITZ: Yes.

DR. CANTILENA: Dr. Clapp.

DR. CLAPP: Oops, I think I gave my answer already.

DR. CANTILENA: Well, that's all right. I just wanted to come back to see if you had any additional comments. You were on such a roll there, I didn't want to interrupt you.

Dr. Epps.

DR. EPPS: Yes, I agree with 3(a) and all its parts.

DR. CANTILENA: Dr. Raimer.

DR. RAIMER: I like the idea of effective treatment rates also rather than cure rates.

DR. CANTILENA: Dr. Wilkerson.

DR. WILKERSON: I like effective rates,

too, much like what we are doing with psoriasis. Instead of calling this the PASI index, we are going to call it the FASI index. That's the Fungal Area Severity Index, and we will put a 12-week marker, at which time they have to be mycologically negative culture, after a course of therapy, develop a score, and then classify it on an easy scheme.

I think this is something we need to cross all drugs right now for comparability is we don't have standards to really compare whatever we are comparing to each other.

DR. CANTILENA: So, how would you express that information on a label for consumers?

DR. WILKERSON: I would develop a very short analog scale 1 to 4 or some kind of classification, very effective or ultra effective, or something, but behind the scenes, we would score these to some standard, 75 percent mycologic cure at 12 weeks or whatever our standard.

This thing about the erythema and the scaling, and all that, I agree is nothing, and what

really counts in the end is once you are treated, does your infection come back, and there is a lot of reasons to have red feet and one thing and another, but in the end, at a reasonable period of time, 3 months out, it could be arbitrary, is your infection still gone, or are your symptoms of your infection still gone.

If it is, then, as a consumer, I would probably be very happy. I think we need some standardized scoring, something that is standardized, easily scored, and to give consumers an idea of which one of these, because as a physician, I have no objective evidence outside of clinical experience to tell me which one I think works better.

DR. CANTILENA: Dr. Patten, specific additions to the label.

DR. PATTEN: I support all three. I think telling the consumers something about effective treatment is particularly important, but I think you also need to tell the consumer what effective treatment means, so they don't conflate it or

confuse it with complete cure.

DR. CANTILENA: Dr. Lam.

DR. LAM: Some sort of a measure of effective treatment by whatever means that we agree later. I think definitely, the consumer should be notified on the label regarding the time course of response relative to the duration of treatment, as well as the time course of resolution of symptoms, so that they know that they have to continuously take the medication as directed.

DR. CANTILENA: Dr Ringel.

DR. RINGEL: I agree that there should be labeling that addresses all three of these issues, however, I think it needs to be pretty general unless we can do one head-to-head study of every antifungal on the market and then update that study every time a new antifungal comes on the market, there is going to be unrealistic competition and unrealistic claims for every product that comes along.

So, I think what you need to do is stay pretty general and say something like resolution of

symptoms may take weeks, not all symptoms may resolve, you know, reinfection is possible, and just leave it at that.

DR. CANTILENA: Dr. Fincham.

DR. FINCHAM: I think to reduce costs on the part of the sponsor, which, in turn, will reduce costs for patients hopefully, I think we need to be general relative to the effective treatment and what that means, but I think something needs to be referenced to that point, and I think expectation of symptom relief, as well as delay in response are perfectly appropriate to have on there.

DR. CANTILENA: Dr. Whitmore.

DR. WHITMORE: I second all that, and I wonder if you could cut down on physician visits for tinea pedis not responding to topicals by adding to the labeling that if after one month, you still have some symptoms, you can repeat it, but that is another issue.

DR. CANTILENA: You would probably have to study that in order to put that in your label.

Dr. Davidoff.

DR. DAVIDOFF: Yes, I agree that Nos. 2 and 3, there should be additional information about the delay in response, and so on. No. 1, I am not comfortable with, the notion of putting cure rates for several reasons, one being that there aren't head-to-head studies and therefore if you are asking consumers to compare one box to another, they are really comparing data that is not very comparable, and I don't think that is fair or appropriate, on top of which, we can't even decide, I think for good reasons, whether cure rate or effective treatment is the appropriate endpoint to be talking about.

Finally, Tom Ten Have and his colleagues have convinced me that relying on point estimates as a way of conveying information alone is very chancy, and I think that putting down cure rates doesn't take into account the measures of uncertainty of the data, and without that, it is actually misleading.

DR. CANTILENA: So, how would you

communicate that information to the consumer?

DR. DAVIDOFF: I wouldn't try to quantitate it.

DR. CANTILENA: Dr. Schmidt.

DR. SCHMIDT: I agree. The one thing I would mention, though, as putting information on the labeling, and it is already on this one on page 19, is about proper foot care. I think that is very important.

DR. CANTILENA: Dr. Katz.

DR. KATZ: I think it would be more informative for the consumer to know whether it's effective in 20 percent or 40 percent or 90 percent, and a range. It wouldn't be head-to-head comparison if it was just comparison against placebo.

I think also it is very important when you say 80 percent clear, that the consumer know that 50 percent of the placebo may be clear in that study, so the effective clearing rate is really 30 percent, so I think it is important that we not be deceptive in that degree, but it is more specific

to let somebody know when they are picking up a tube of medication whether they have a 30 percent chance of stopping itching or 90 percent.

I would say also as an aside, that when people say that it's negative mycology completely in 90 percent of patients, things of that sort on page 7, Dr. Fritsch's comment, even negative mycology, if you subtract placebo, you are talking about 23 percent to 67 percent with different drugs giving clearing KOH and culture. That is on page 7.

DR. CANTILENA: Thank you.

Dr. Ghannoum.

DR. GHANNOUM: Although I agree with Dr. Davidoff about really it is no comparative, I think it will be helpful to add for the effective treatment, the percentage, clarifying that is relative to the placebo, and I agree with the other two that we should add information as far as symptom relief, that the response may take longer, may be delayed.

DR. CANTILENA: Dr. Bisno.

DR. BISNO: No additional comments.

DR. CANTILENA: Dr. Wood.

DR. WOOD: I think we should add efficacy data and although I am very sympathetic to Frank's comments about point estimates, and so on, I think one of the issues here is that we want to encourage people to develop more effective therapy, and the only way we are going to do that is to give them the right to promote on that.

So, I think allowing people to put efficacy data on the label encourages better and more effective therapy to be developed, because people will have a commercial advantage.

I am very much against putting wording on the label that requires interpretation, like very effective, partially effective, and so on, because the FDA will end up in interminable arguments about where these cutpoints are, and they will appear to have credibility that don't exist, so I mean if you are going to put it on, you put it on the way the studies came out, and you don't try and squeeze them into boxes, because everybody will be trying

to move the box line to catch their product.

DR. CANTILENA: Dr. Ten Have.

DR. TEN HAVE: As a statistician, I would take Dr. Davidoff's bait and say confidence intervals, of course, but as a consumer with athlete's foot, I can understand both sides of the issue in terms of whether or not you report, say, effective treatment rates.

It's a difficult issue and as a scientist, I would say yes, even though the rates are based on different types of responses, it is still the more information and caveat emptor, so, I would have to say report confidence intervals, but I know that is not plausible.

DR. CANTILENA: The comprehension study on that would be interesting.

Dr. Alfano.

DR. ALFANO: I would agree with (a) ii and iii, and I think there have been adequate proposals from the industry to enrich those two claim areas.

I strongly disagree with any specific statement of cure rates or effective treatment

rates or whatever. Dr. Ringel just said it brilliantly, I think. I mean we will have initiated an insane horsepower race that will only confuse the consumers. The studies are done at different times in different ways.

The newer studies could be penalized because they have more rigorous controls and the response rates might not look as good, and we have already seen how this becomes a slippery slope. We now have charts, now we are talking about confidence intervals on some package labels. The consumers are going to need Ph.D.'s to understand these things.

I thought we were going the other way. I thought we were going to simple icons to make it easier for people to do this, and you apply this to other categories, analgesics. Do you put on headaches, do you put on toothaches, third molar extraction, episiotomy? I mean it's insane.

I understand we want to inform the consumers, but this is I think wasteful information that will only confuse them.

DR. CANTILENA: Thank you.

Mr. Kresel.

MR. KRESEL: I think meaningful data is the only thing that helps the consumer, and I absolutely agree with Dr. Ringel and Dr. Davidoff. You are just comparing apples and oranges, studies that were done over a 40-year period, conducted different ways, and try to compare them to today's standards.

I don't think that gives any meaningful data to consumers. We here today couldn't agree on whether it should be a complete cure and effective treatment, so we don't even know where that number would start.

I think what the consumer really wants to know is when can I expect to start to feel relief, so onset of activity is really important for a consumer, and the fact that after I stop treatment, can I expect to continue improvement and for how long.

So, I think those are things that consumers really want to know, need to know, and I

think it really helps them.

DR. CANTILENA: Dr. Alfano, did you want to add one thing?

DR. ALFANO: One follow-up comment. I think it's a justifiable concern that the Agency has about improving drugs in this therapy, so I can understand the concern, but there is a mechanism, Dr. Ganley pointed out earlier, and that is, two, well-controlled trials will get you a claim.

You can advertise that claim, and you can drive sales in that fashion, and I think that is the mechanism that will drive this category to further improvements. We have seen it driven that way already without all these other tools brought to bear.

DR. CANTILENA: I would just like to add that I certainly understand what has been said and the concerns about confidence intervals and flooding the label, but I think as it stands now, the consumer is not given enough information for them to select the most efficacious product.

There obviously is information available

because we have seen it today and we will hear the Code in our closed session tomorrow in terms of who is A, B, C, and D. So, at least you, as a committee member, will be able to go buy the most effective treatment for athlete's foot.

So, Tom, if you can just hold on another day, relief is on the way.

But I think the other things, what is on the slide, I think would inform the consumer. I think the current label is inadequate in those areas and I agree with what has been suggested as possible additions. I don't know the right way to handle the effect of treatment, but you have to give them some information that is quantitative in some respects.

So, having almost the last word, we have an issue for tomorrow. Since we basically accomplished the morning agenda for tomorrow this afternoon, we will start the closed session--the Nonprescription Advisory Committee will meet here at 8 o'clock. Everyone will meet here and we will split up.

DR. GANLEY: Jon and I talked and I think we could probably meet here at 8:30. We have to have the Open Session at 11 o'clock. I think both of us have probably two hours' worth of information to go over with the committees.

DR. CANTILENA: Just to summarize for those of you who didn't hear all that, all of us back here at 8:30 tomorrow morning. The other committee is escorted over to the Parklawn. We will have another class outing with your chaperons. Then we are all back here together for the Open Public Hearing at 11 o'clock.

With that, we will close today's meeting. Thank you very much, members of the committee and members of FDA.

(Whereupon, at 6:00 p.m., the meeting was recessed to be resumed at 8:30 a.m., Friday, May 7, 2004.)

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