FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

Thursday,
November 4, 1999

Ballroom
Hilton Hotel
620 Perry Parkway
Gaithersburg, Maryland

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C O N T E N T S

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P R O C E E D I N G S (8:35 a.m.)

DR. DRAKE: Good morning. I would like to call the 51st meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee meeting to order. One of the first things I would like to do is have our distinguished table introduce themselves, but as part of that, may I please remind everybody to speak directly into the mike. These meetings are recorded. The agency uses the comments carefully and reviews them, and so they want to have an accurate transcript that reflects the sense of the meeting.

My name is Lynn Drake. I'm professor and chairman of the Department of Dermatology at the University of Oklahoma Health Sciences Center, and I'm a senior lecturer at Harvard Medical School in the Department of Dermatology.

With that, I would like to introduce first our executive secretary. Tracy, would you like to start? Then we'll start down there.

MS. RILEY: Thank you. Good morning. My name is Tracy Riley. I'm the executive secretary of the Dermatologic and Ophthalmic Drugs Advisory Committee.

DR. KILPATRICK: Good morning. Jim Kilpatrick, biostatistics, Medical College of Virginia.

DR. MINDEL: Joel Mindel, Departments of Ophthalmology and Pharmacology, Mt. Sinai Medical School, New York.

DR. ABEL: Elizabeth Abel, clinical professor of dermatology at Stanford, and in private practice of dermatology in Mountain View, California.

DR. JORDON: Robert Jordon, chairman of the Department of Dermatology, University of Texas Medical School, Houston.

MR. THOMSON: Steve Thomson, Division of Biometrics III, FDA.

DR. SRINIVASAN: Dr. Srinivasan, biostatistics team leader, Division of Biometrics III.

DR. VAUGHAN: Brenda Vaughan, Division of Dermatologic and Dental Drug Products, FDA.

DR. WALKER: Susan Walker, clinical team leader, Division of Dermatologic and Dental Drug Products.

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

DR. DeLAP: Robert DeLap, Director, Office of Drug Evaluation V, FDA.

DR. DRAKE: And then I would like to move -- I'm going to interrupt and go this way. I wanted to introduce our distinguished panelist, my predecessor, Dr. McGuire, who chaired this committee just prior to me, and then we'll go that way.

DR. McGUIRE: I'm Joe McGuire, Dermatology and Pediatrics, Stanford.

DR. LIM: I'm Henry Lim, chairman of dermatology at Henry Ford Hospital, Detroit, Michigan.

MS. GOLDBERG: Jackie Goldberg, consumer representative.

DR. DiGIOVANNA: John DiGiovanna. I'm director of the Division of Dermatopharmacology at Brown University School of Medicine, and an adjunct investigator at NIH.

DR. MILLER: Fred Miller, Director of Dermatology, Geisinger Clinic, Danville, Pennsylvania.

DR. STERN: I'm Rob Stern. I'm professor of dermatology at Harvard Medical School at the Beth Israel Deaconess Medical Center.

MS. COHEN: I'm Susan Cohen, and I'm a consumer member.

DR. DRAKE: Thank you very much.

I will now turn this over to Ms. Riley for our conflict of interest statement.

MS. RILEY: Thank you. The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting.

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

Dr. Philip Lavin has been excluded from participation in today's discussion and vote concerning Loprox. In addition, in accordance with 18 U.S. Code 208(b), a full waiver has been granted to Dr. Joel Mindel. A copy of this waiver statement may be obtained by submitting a written request to FDA's Freedom of

Information Office, located in Room 12A-30 of the Parklawn Building.

We would also like to disclose for the record that Dr. Lynn Drake has passed unrelated interests in Janssen and Novartis, which should not constitute financial interests within the meaning of 18 U.S. Code 208(a), but which could create the appearance of a conflict. In addition, Dr. Robert Stern has passed unrelated interests in Janssen which does not constitute financial interest within the meaning of 18 U.S. Code 208(a), but which could create the appearance of a conflict.

The agency has determined, notwithstanding these interests, that the interest of the government in their participation outweighs the concern that the integrity of the agent's programs and operations may be questioned. Therefore, Drs. Drake and Stern may participate in today's discussions with full voting privileges.

Further, several of our committee members have had interests relating to Loprox that we believe should be disclosed. FDA believes that it is important

to acknowledge these participants' involvement so that their participation can be objectively evaluated.

Dr. Lynn Drake's former employer was involved in a past study of Loprox. While Dr. Drake was listed as a subinvestigator on the study, she was not directly involved. Dr. Fred Miller served as principal investigator on Loprox Protocol Number 211.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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

Thank you.

DR. DRAKE: Thank you, Ms. Riley.

I'm going to ask Dr. Jonathan Wilkin to give us an overview of the issues regarding this meeting.

DR. WILKIN: Thank you, Dr. Drake.

Of course, crucial to the discussion today is ultimately the recommendation of the committee either for approval or against approval of the Loprox product, and in thinking about the risk/benefit relationship to help the committee to get to that decision, one can think about what the primary efficacy variable should be.

If we could look at the first slide, please.

The sponsor had a teleconference with the FDA on October 25th, 1993. This is the heading of, I believe, the sponsor's meeting minutes.

Next slide, please.

At the bottom of the first page, they captured the question that they posed to the FDA: "Will the FDA approve a drug which controls but does not necessarily cure toenail onychomycosis?" And the FDA response in 1993 was: "The FDA's defining treatment success for all topical and systemic agents is 100 percent clearing of the nail plate, absence of clinical signs. Complete cure is being defined as mycological cure, negative KOH and culture, and 100 percent clearing of clinical signs maintained for at least three to six

months post-treatment." Then they had in parentheses, "The division is leaning more toward six months. Control of disease -- that is, partial improvement -- is not an option."

So this was October of 1993, and those of us who are in the division now were not in the predecessor of our division in 1993, so it's hard for me to actually go through the thinking of the FDA group that gave this advice. But I do know folks that write about what should be the efficacy endpoint for onychomycosis today, and there are some folks who think of onychomycosis as an infectious disease, sort of the model of pneumonia, and the goal is one completely eradicates the pneumonia. Partially treating a pneumonia is probably not a great idea.

So we had a very nice meeting -- next slide, please -- of the Dermatologic Drugs Advisory Committee in 1994, and the focus of that meeting, the centerpiece of that meeting -- and the discussion lasted over two days -- we discussed regulatory issues and clinical trials for onychomycosis. We literally had nine pages of questions that we posed to the committee and received

answers back on.

Next slide, please.

One of the recommendations of the committee was that treatment success be measured by clinical parameters -- in other words, a clear nail bed -- that normal appearance of the nail is what patients want, and the clinical endpoint is a cleared nail. But I think it was very helpful for us before closing that meeting to ask another question.

Next slide, please.

We asked, is a lesser indication, namely clinical improvement without cure, acceptable for therapies without any significant risk? The committee generally agreed. The answer to that was yes. The longer statement is there should be measures of efficacy that are less rigid for products that are safer, and I think it embraced the view that onychomycosis is infectious, it's true, but it's not an infection in the same way that pneumococcal pneumonia is, where one has the chance for a complete eradication, that many of the patients who have toenail onychomycosis, it's going to be something that's with them on and off through life.

It's a very difficult entity to treat.

So these are the things that the committee will be thinking about in terms of risk/benefit today when you make your recommendation to us. In addition to the recommendation for approval or not approval, we'll be very interested in what you'll have to tell us regarding the labeling, and we have some specific areas that we would like some feedback on, and I would like to mention them now before the sponsor and the FDA give their presentations so you can actually be thinking about these topics while you hear the discussion.

Next slide, please.

We would like to have your input on the evidence for penetration of ciclopirox through the nail to the nail bed. Remember that this is a nail bed disorder. The use of systemic treatment for onychomycosis, would it be appropriate to combine this topical therapy with that, with one of those modalities? The sponsor excluded several groups from studies, and we'll list those. These include folks who had involvement back to the lunula, insulin-dependent diabetics, and others. We'll talk about those groups.

They provided for concomitant tinea pedis therapy. Over half of the patients in the active group and in the control group received concomitant antifungal therapy for tinea pedis at some time during the trial, and there was periodic trimming and debridement by the investigators, and emery boards and alcohol swabs were issued to the patients to remove material from the nail site. So these are the things that we'll be interested in hearing from the committee later this morning.

Thank you.

DR. DRAKE: Thank you, Dr. Wilkin.

We are now at the point of the meeting where we have time allocated for the open public hearing.

May I have the lights up a little bit, do you think? That would be helpful right now.

I would ask if there's anybody who has a comment that they wish to make. If so, they must approach the mike, identify themselves and any affiliation or financial interest or support that they might have in the products under consideration.

(No response.)

DR. DRAKE: Seeing none and hearing none,

we'll move then to the active part of the meeting. This meeting, of course, I may have neglected to identify this morning, the session is on NDA 21-022, Loprox, or otherwise known as ciclopirox nail lacquer for the treatment of onychomycosis.

I think we'll then move to the sponsor presentation, which is Hoechst Marion Roussel.

We actually have a little extra time that we can use either for presentation and/or discussion since the open public hearing was so brief. Do you suppose that's a comment on my chairmanship? We just saved 30 minutes.

Anyway, we will move to the sponsor, and I believe that Alberto -- is it Granola?

DR. GRIGNOLO: Grignolo.

DR. DRAKE: Grignolo. Dr. Grignolo, welcome.

DR. GRIGNOLO: Thank you very much.

Dr. Drake, members of the committee, Ms. Riley --

DR. DRAKE: I guess the mike is not working?

DR. GRIGNOLO: Thank you for your patience.

Dr. Drake, members of the committee, Ms.

Riley, Dr. Wilkin, members of the division, my name is Alberto Grignolo. I am Senior Vice President of Worldwide Regulatory Affairs at Parexel International Corporation, a contract research organization. Parexel is the agent for the sponsor, Hoechst Marion Roussel, for NDA 21-022, ciclopirox nail lacquer 8 percent. I will provide a very brief introduction to our presentation today and then turn the podium over to my colleagues.

We have previously provided to the committee a succinct briefing document for distribution to you and to the division. The purpose of our presentation today is to highlight the key elements of NDA 21-022, with emphasis on the clinical efficacy and safety of ciclopirox nail lacquer 8 percent. A copy of our presentation has been provided to the executive secretary for distribution to you.

Next slide.

Following my brief introduction, the sponsor's presenters will address the following topics: nail penetration studies; efficacy in U.S. clinical trials; clinical safety; and benefit/risk

considerations. We respectfully request that members of the committee hold substantive questions until the end of the sponsor's presentation, although we do welcome at any time your questions seeking clarification. Thank you.

Next slide.

Onychomycosis is a fungal disease of the nail mostly caused by dermatophytes. The most common form is distal subungual onychomycosis. Onychomycosis is not only a cosmetic problem but can impair social, professional, and recreational activity, and subjects frequently experience pain, discomfort, and problems with simple daily activities, such as walking. Even when asymptomatic, the onychomycotic nail constitutes a reservoir of fungus that can cause repeated infection of the skin.

Systemic prescription therapies for onychomycosis have been approved by the FDA and are marketed in the United States, but they do have certain limitations, mainly side effects and drug interactions. Therefore, a safe and effective topical treatment would fulfill an unmet medical need.

Next slide.

To assure successful topical therapy of the onychomycotic nail, a drug has to meet the following criteria, in our opinion: an antifungal agent that is highly effective against onychomycosis-causing strains -- for example, T. rubrum, T. mentagrophytes, and E. floccosum -- a vehicle that guarantees the adhesion of the formulation to the nail, and a system which provides a high concentration gradient and allows optimal reuse of the drug; a drug substance that penetrates the nail plate; and a fungicidal drug concentration at the site of infection.

Next slide.

Ciclopirox nail lacquer 8 percent meets these basic criteria, as the sponsor has demonstrated in the NDA. It is a synthetic broad-spectrum antifungal agent which is fungicidal against T. rubrum, T. mentagrophytes, and E. floccosum. It provides transungual delivery through proper adherence to the nail and release of the drug. It has been shown to penetrate human nails in vivo. It provides effective drug concentrations at all nail levels.

Next slide.

The sponsor's approach to the development program of ciclopirox nail lacquer 8 percent has focused primarily on clinical development, since several ciclopirox formulations are already approved for marketing in the United States for the treatment of a number of fungal infections. Specifically, the drug is marketed in the U.S. as a cream and a lotion, and, in addition, a gel formulation of ciclopirox has recently been approved by the FDA.

In addition, ciclopirox nail lacquer has been approved and is marketed in 41 countries around the world, including nine European countries.

Next slide.

The objective of the clinical development program has been to demonstrate that ciclopirox nail lacquer 8 percent is an effective and safe treatment of mild to moderate onychomycosis without lunula involvement due to T. rubrum, T. mentagrophytes, and E. floccosum. The clinical development program has comprised a series of Phase I, Phase II, and Phase III clinical trials conducted in the United States. In

addition, a number of clinical trials have been conducted in Europe and have provided a great deal of safety information. The data from these trials will be presented by my colleagues.

Next slide.

The sponsor believes and has documented in the New Drug Application that ciclopirox nail lacquer 8 percent is an effective topical treatment of onychomycosis compared to vehicle when administered over 48 weeks. The results presented in the NDA show that ciclopirox nail lacquer 8 percent has an excellent safety profile.

Ciclopirox nail lacquer 8 percent may be somewhat less effective than systemic therapies of onychomycosis, though no direct comparative trials have been conducted by the sponsor. But its excellent safety profile makes it an important alternative to systemic agents. This is especially true when physiological state -- for example, advanced age -- systemic diseases, interactions with commonly used drugs, and patient preference preclude the use of systemic antifungals.

Next slide.

In closing, today's presenters on behalf of the sponsor include Dr. Hans Donaubauer, head of General Toxicology, Hoechst Marion Roussel, Frankfurt, Germany; Dr. Richard Scher, Department of Dermatology, Columbia University, New York City; Dr. Philip Fleckman, Division of Dermatology, University of Washington in Seattle; and Dr. Aditya Gupta, Division of Dermatology, University of Toronto, Canada.

The sponsor believes that the data presented in the NDA are consistent with the expectations of the division and of this advisory committee, as well as with established criteria for the approval of antionychomycotic agents.

We thank the members of the committee for this opportunity to present NDA 21-022. I would now like to turn the podium over to Dr. Donaubauer for our first presentation. Thank you.

DR. DONAUBAUER: Good morning. My name is Hans Donaubauer. The title of my presentation has been changed, and it now reads: "Ciclopirox Nail Lacquer 8 Percent Nail Penetration."

Ciclopirox is an antifungal drug which is

already approved in three dermatologic products in the United States.

Next slide, please.

It is a broad spectrum antimicrotic which is fungicidal against pathogenic dermatophytes, yeasts and molds. For most of the organisms tested, including the dermatophytes causing onychomycosis, highlighted in this slide in yellow, the minimum inhibitory concentration is between 0.5 and 4 micrograms per milliliter. Ciclopirox is mycologically effective, but is it penetrating the nail plate?

Next slide, please.

After repeated application of ciclopirox nail lacquer 8 percent in vivo to toenails and fingernails of healthy volunteers, the nail was sectioned into four equal layers, and the concentration of ciclopirox in each of the layers was far above the efficacious concentration. Layer 1 is the outer surface layer, layer 4 the innermost layer. The application time was 7 to 45 days. Increased concentrations of ciclopirox occurred over time, and steady state was approached after approximately 30 days of continuous treatment. In

yellow are the concentrations in the innermost layer, which is a part of the nail bed.

Next slide, please.

For fingernails, a similar picture was obtained. Again, ciclopirox increased over time, and concentrations in all layers by far exceeded the minimum fungicidal concentrations. Thus, as shown, ciclopirox penetrates the healthy nail plate. But what about the diseased nail?

Next slide, please.

This was studied by the penetration of labeled ciclopirox applied once to 15 nails removed for onychomycosis. The nail plates were sectioned into four layers, and the concentrations measured were 29 micrograms per gram, which is approximately seven times the minimum fungicidal concentration in the innermost layer. This level was achieved even though measurements were made only 24 hours after a single application. As shown in the previous slides, much higher concentrations are reached with repeated applications. Ciclopirox penetrates the diseased nail. In addition, it is also known from in vitro studies that ciclopirox penetrates

epidermal keratin. Therefore, penetration can be expected to occur through the keratin which may be built up beneath the diseased nail.

Next slide, please.

As the drug clearly penetrates normal and diseased nails, systemic exposure of ciclopirox has been measured in clinical trials with nail lacquer 8 percent. In Study 111, all 20 nails, plus 5 millimeters of surrounding skin were treated. Only five patients were in this study, and in only one single patient a maximum level of 18 nanograms per milliliter was reached in serum. The median level was 16 nanograms per mL. In the pivotal studies 312 and 313, serum levels up to 25 nanograms per milliliter were found. In most subjects, the level was below 10, the level of quantification.

Next slide, please.

To summarize, ciclopirox applied as 8 percent nail lacquer penetrates the nail plates and concentrations are achieved exceeding minimum fungicidal concentrations in the nail bed. Systemic absorption of the drug is minimum.

The clinical efficacy data will now be

presented by Dr. Scher. Thank you.

DR. SCHER: Good morning. What I'd like to do this morning in 15 or 20 minutes is to summarize for you the U.S. clinical data with 8 percent ciclopirox nail lacquer.

Next, please.

This is the clinical development plan, Phase I, Phase II, and Phase III, and you see here all of the studies that were performed. I will concentrate on the Phase III studies.

Do we have a pointer?

I will concentrate on the Phase III studies, which you see here, Studies 312 and 313, which are the efficacy pivotal studies, which ran a timeframe of 48 weeks, and a safety follow-up period, Study 320, which ran a period of 24 weeks.

Next, please.

The objective of these studies, the two pivotal studies, which were identical, was to look at the efficacy and safety of the ciclopirox nail lacquer 8 percent for the treatment of distal subungual onychomycosis. This was a multi-center, randomized,

double-blind, vehicle-controlled, parallel-group study, and treatment consisted of ciclopirox 8 percent lacquer or the vehicle applied daily for a period of 48 weeks to all toenails, and affected fingernails as well.

Next, please.

The observation schedule. As you see here, visits were screening, baseline, every four weeks for 48 weeks. The evaluations included mycology, KOH and culture, done every 12 weeks; planimetry every 12 weeks; physician's global assessment every 4 weeks; laboratory evaluations every 12 weeks; and adverse event recording throughout the study.

Next, please.

The main inclusion criteria you see before you. Patients were between the ages of 18 and 70; mild to moderate onychomycosis defined arbitrarily as 25 to 60 percent involvement, distal subungual onychomycosis of at least one great toe; culture-proven disease at the screening visit, and the baseline visit was within 28 days; a positive KOH examination from the specimens taken from the target nail and at baseline.

Next, please.

Exclusion criteria. Patients with white superficial onychomycosis were excluded; patients with proximal subungual onychomycosis, which, as you know, is a marker often in immunosuppressed patients, particularly HIV infection; patients with the yellow spike. The yellow spike, by definition, is the extension of the fungal infection from the distal edge, where it originates, further back in a proximal direction and actually involves the nail matrix, otherwise known as total dystrophic onychomycosis.

Lateral disease was permitted, and this is very significant because we know that lateral disease nail infections are more difficult to treat, are less responsive to therapy, and even some systemic agents have difficulty clearing lateral disease.

No systemic antifungal treatments within 24 weeks. Topical treatment for flares of tinea pedis was permitted. No immunosuppressed patients or insulin-dependent diabetic patients were permitted in the study.

Next, please.

In regard to mycology, a positive culture for dermatophytes T. rubrum, T. mentagrophytes, E.

floccosum; KOH stain for fungal elements. For inclusion, patients must have had both positive culture at screening and a KOH stain at both screening and baseline.

Next, please.

The overview of the planimetric method. This included the investigator nail marking, standardized photography, and quantitative image analysis of the marked areas.

Next, please.

Here you see a demonstration of what the planimetric method includes. If we call this the healthy nail or the uninvolved nail, this would be the affected area, and the affected area, by definition, means that portion of the nail where the nail plate is still attached. If we look at this area here, where the nail plate is no longer attached, the nail plate is absent, that is referred to as the other area. Collectively, these two areas represent the involved area. This represents the uninvolved or healthy nail.

Next, please.

This is the physician's global assessment,

which is pretty standard and pretty self-explanatory in terms of the percentages of the clinical signs, as you see here, and this is simply the scale usually used to evaluate each of these areas of involvement.

Next, please.

The derived efficacy criteria included three parameters, and they are, number one, mycologic cure, which means negative KOH and negative culture; treatment success, primary treatment success means negative KOH, negative culture, and a planimetry at 10 percent or less of involvement; and finally, the treatment cure is defined as negative KOH, negative culture, and a physician or investigator global assessment of a cleared nail.

Next, please.

The primary efficacy analysis is time to first occurrence of treatment success.

Next, please.

The secondary efficacy analyses, the rates at endpoint, which would be 48 weeks or last observation, or mycologic cure, treatment success, treatment cure.

Next, please.

The demographics. Three-quarters of the patients were male. Approximately one-quarter of the patients were female. The mean age, as you can see, was 50. So you see that many of these patients had actually longstanding disease, from a minimum of 19 to a maximum of 70. The area of involvement was very significant. The mean area of involvement was close to 39 percent. So we are dealing with significant disease, and the duration of the disease was a mean of 11 years. So we are again talking about longstanding disease, with a minimum of less than a year, but as high as 50 years in some patients.

The causative organisms. As you might expect, overwhelmingly T. rubrum, 96 percent; T. mentagrophytes, 3 and 4 percent; and only one patient with the floccosum.

Next, please.

The graph that you see before you here, I show you this slide at the insistence of our statisticians, but basically there are two points that you may wish to take away from this slide. Number one, there is a very significant discrepancy. Let me say

that this is Study 312, 313, and these are the pooled studies. There's a significant discrepancy between the vehicle, which is in green, and the active ciclopirox, which is in blue. So you see a separation between the two. Everything that goes in this direction, from upwards to downwards, is good, is positive. So you can see that in terms of the active, there is a very nice range downward in time to first occurrence, which does not occur with the vehicle alone.

Next, please.

Now let's look at the graphs of some of the data. These are the rates at endpoint, and here you see the two studies presented separately, 312 and 313. I think it's important to note the differential between vehicle and active drug. Here you see the active drug, and the vehicle is very low. I also think it's important from this slide to note that there really is a very significant mycologic cure. We know that in treating toenails, it's very difficult to get a mycologic cure, which means negative KOH and negative culture. Here you see that there are significant numbers in terms of mycologic cure, and a definite

differential between vehicle and active drug.

Next, please.

This further shows the pooled data of 312 and 313, and again you see a very significant mycologic cure rate, and a definite differential between active and vehicle. Even when you look at treatment success and treatment cure, where the numbers are lower, there is still a differential between the active and the vehicle.

Next, please.

This slide I think is important because it compares two subpopulations that we are looking at here. It compares those nails on your right, where there is more than 40 percent involvement -- that's a lot of nail infection -- and it compares that with the less affected subpopulation where there is under 40 percent involvement. You can see I think very clearly that those patients who have over 40 percent involvement show a significant very definite response with the mycologic cure, which again is always difficult to obtain, and a marked differential between active and vehicle.

Next, please.

Now let us look at a few cases. I'm going to

present to you four patients. Two were treatment successes and two were treatment cures. I've chosen arbitrarily the better cases. The reason for choosing the better cases is not to make the drug look good. The reason for choosing the better cases is to show you that in some patients there is very definite efficacy, and I think this becomes very clear when you look at this.

Here you have a baseline of a patient with distal subungual onychomycosis. This nail is more than 52 percent involved, and you can see it's a very significantly affected nail. This is at baseline.

Next, please.

Here you see the patient at week 48. This patient is negative KOH and negative culture, and the global evaluation by the investigator is excellent improvement. So this is for the treatment success, meaning mycologically negative and 10 percent or less involvement on the planimetry. But I think even if you forget the numbers and you just look at the nail, there's no question that there is efficacy here.

Next, please.

This is a patient also with distal subungual

onychomycosis. Look at this nail. You have marked subungual hyperkeratosis. There is a lot of thickening in the nail bed. You have beginning lateral extension, which contributes to the resistance of the infection, and you have total involvement of about 32 percent.

Next, please.

Here you see the patient at week 36, mycologically negative, global evaluation of excellent improvement. But again, look at the nail and see the difference at week 36.

Next, please.

This is the patient at week 48, and you see the nail is still in excellent shape despite the fact that there has been somewhat of an increase in the planimetry. But it is still mycologically negative.

Next, please.

Those first two I showed you were treatment successes. I'd like to now show you treatment cures, which by definition means mycologically negative, and the investigator's assessment is a completely clear nail.

Here we have baseline involvement of about 28

percent. Notice again there is beginning lateral involvement.

Next, please.

Here we have at week 48. The patient is now mycologically negative, and clinical evaluation by the investigator is clear, and I don't think there is any question that there is marked improvement.

Next, please.

The final case that I will show you is a very significant case. In terms of percentage, you may say, well, it's 22 percent, and that's not a lot of involvement. But look at the type of involvement that you have here. You have very prominent lateral disease. This is an example of distal lateral subungual onychomycosis, one of the more difficult types to treat, even with systemic therapy. If you see the extension here, here is the lunula, here is the extension, and this is very close to total dystrophic onychomycosis, a case where the lunula, the nail matrix, the nail growth center is affected. So this is baseline.

Next, please.

Here you see this patient after 48 weeks.

It's very important to note that the lateral extensions are gone. So I think that this shows you a very significant response. KOH and culture are negative. The global evaluation of the investigator is that the nail is clear. This is, by definition, treatment cure.

Next, please.

This is 24 weeks post-treatment, and you can see the excellent response and appearance of the nail.

Next, please.

So, to summarize for you, you've seen some of the data from an 8 percent ciclopirox nail lacquer investigated in patients with mild to moderate distal subungual onychomycosis. Efficacy was evaluated by mycology, planimetry, and global assessment of the target great toenail.

Next, please.

The efficacy parameters were confirmed by two well-controlled Phase III studies based upon three main criteria: mycologic cure, which was KOH and culture negative; treatment success, which was mycologic cure and planimetry at 10 percent or less; and treatment cure represents mycologic cure plus the global assessment of

the investigator as cleared.

Next, please.

So we have a 48-week topical treatment with ciclopirox nail lacquer, which is definitely superior to the vehicle, and is certainly of benefit for patients with mild to moderate onychomycosis without lunula involvement.

That completes the sort of technical statistical presentation. I would like now to do a little philosophical observations.

Next slide, please.

I'd like to speak now as a clinician, as a clinical dermatologist who sees patients on a daily basis, lots and lots of nail patients. Many of you might think that that's quite boring, and it probably is to some, but to me it's very exciting. I would like just to speak to you now as a practicing dermatologist, and I would sort of speak for primary care physicians, the dermatologists, the podiatrists, and anyone who takes care of "cruddy looking" nails.

Next, please.

I feel strongly that no matter how effective

systemic therapy is, there will definitely always be a need for topical antifungals. Why is that?

Next, please.

Because there really is now in the U.S. an unmet need that patients should have. Oral therapy is often contraindicated in some patients. Some patients refuse oral therapy. In addition, it is my perception that perhaps -- and we don't have data for this yet -- perhaps combining topical therapy with systemic therapy will enable us to treat systemically for shorter duration periods. Lastly, it is also the perception of many of us who treat lots of males that a topical agent may eventually play a role in the post-therapy approach to the evaluation of onychomycosis.

So in total, in summary, I would just say to you that I think that this is an effective product, I think there's a need for it, and both our patients and our practicing physicians will be able to have such a drug in the near future.

Thank you very much.

DR. DRAKE: Dr. Scher, I believe we have a question from the panel on clarification.

DR. STERN: Could you please just describe to me in some detail what was mentioned by Dr. Wilkin? It was mentioned briefly also in the materials, exactly what went on in terms of nail care, in terms of trimming, in terms of once a month by the investigator, and in terms of the other things that might not be usual nail care in people with onychomycosis who we treat with oral agents, for example.

DR. SCHER: Well, patients were permitted to trim the nail and sort of superficially clean up the nail bed. I believe that that was the extent of what was permitted.

DR. STERN: I thought there was a once a month investigator trimming, or every four -- am I incorrect on that, reading the materials?

DR. SCHER: Dr. Fleckman?

DR. FLECKMAN: I'm Phil Fleckman. I'm the next speaker, but I also participated, as did Dick, in the Phase II and III studies. In the Phase III studies, the patients were instructed to file their nails once a week when they applied the lacquer. In addition, they were seen monthly during the blinded part, the 48-week

part of the study. At that time, the investigators were instructed to debride the nail to remove the onycholytic plate, take off as much of the plate as they could. This was done, at least in our center, with double-action nail clippers.

DR. STERN: So the kind of trimming a podiatrist might do to an onycholytic nail. So it wasn't just drug. There were some mechanical things on a monthly basis, for basically 12 months or 12 4-week periods.

DR. FLECKMAN: Right.

DR. STERN: Okay. Thank you.

DR. KILPATRICK: May I ask a clarifying question?

DR. DRAKE: Yes, please.

DR. KILPATRICK: I may be missing the point. Was this not done for both vehicle and Loprox?

DR. STERN: In terms of efficacy, but in terms of looking at how an agent might be used in real life, the efficacy data we have shows it's efficacy in conjunction essentially with 12 visits to a professional to trim your nails, which gives you the maximum

likelihood that this agent is going to work, not just at home with the file or with your nail clipper, but with someone going in once a month to see a professional who is going to trim your nails back.

In terms of the validity of the differences between placebo and drug for this protocol, it's absolutely correct. But in terms of what you think of, how well this is going to work in the real world, it may not present the most accurate picture.

DR. DRAKE: We're drifting very closely to discussion. I'd like to keep the questions focused, please, on clarification at this point.

Are there other questions for clarification?

DR. ABEL: I believe this is clarification. It's in regard to mycology.

DR. DRAKE: Would you please speak into the mike?

DR. ABEL: This is in regard to the mycology. Cultures were positive for three organisms, the majority due to T. rubrum. What percent of disease out there, mycotic disease, is due to other organisms, and is this mostly in immunosuppressed patients?

DR. SCHER: Do you mean nondermatophytes, Elizabeth? In the study, or in general?

DR. ABEL: In general.

DR. SCHER: Well, in general, there's controversy about this. Let me preface it by saying that. There are some who believe that the nondermatophyte is a rare pathogen in nail fungus, and that even if you isolate a nondermatophyte, it's probably not pathogenic. Particularly if you isolate a nondermatophyte and a dermatophyte together, the nondermatophyte is not the pathogen, it is only the dermatophyte.

There are others who feel that nondermatophytes, in fact, do play a role in onychomycosis. I believe that in a small but significant percentage of cases, they do in fact play a role. But I think it is probably safe to say that the percentage of patients with toenail onychomycosis where the etiologic agent is a dermatophyte is probably in the 90 percent range. This is not the same situation with immunosuppressed patients. As you know, in immunosuppressed patients, everything changes and you

get a wide range of organisms, and you can have almost any organism.

DR. ABEL: Thank you.

DR. DRAKE: Other questions pertaining to clarification?

(No response.)

DR. DRAKE: All right. Thank you.

DR. FLECKMAN: I'm Phil Fleckman. I'm a dermatologist, an academic dermatologist at the University of Washington. I also participated in both the Phase II and Phase III controlled clinical trials for this product.

You've seen that the ciclopirox nail lacquer penetrates both normal and diseased nails to the site of action, where the infection is. You've seen that it is effective for mild to moderate onychomycosis, distal subungual onychomycosis. I'd now like to present the safety data, which I think will show you that it's a very safe product.

Next slide, please.

The studies, as has been outlined briefly, included Phase I studies, and these are the U.S. trials,

two Phase I studies; Phase II studies, 211 and 212, which were parallel, identical, double-blind, placebo studies involving fingernail onychomycosis; two Phase III studies, which were again parallel, identical, double-blind, placebo-controlled studies for toenail onychomycosis or toe onychomycosis; and then a subsequent open-label study for safety in which some of these patients were enrolled. Safety data were captured from all of these studies.

Next slide, please.

The two Phase I studies involved a small pharmacokinetic study and a larger dermal safety study.

Next slide, please.

The pharmacokinetic study involved five patients with distal subungual onychomycosis of the fingernails. All fingernails were treated. They were treated daily for six months, and lacquer was applied not only to the nails but to the 5 millimeters of adjacent periungual skin. That's an important point, and it's true for all these studies.

Blood levels were determined for ciclopirox and its glucuronide metabolite at periodic intervals.

The maximum level determined, which was in one volunteer, was 80 nanograms per mL, which has a wide safety margin from that seen in animals, from the no-effect level in animals. This is, in fact, the most conservative estimate of that safety margin. So the blood levels are relatively low and quite safe. In fact, this 80 nanogram per mL value was a single very high value. The remainder of the values were in the range of 20 to 25 nanograms per mL, which were also the values seen in the Phase III studies.

Next slide, please.

The dermal safety study was a standard study determining irritation and sensitization -- that is, the allergic potential of the product used in a larger number of healthy subjects -- in which the active product in lacquer, the vehicle alone, and petrolatum were repeatedly applied under occlusion to these subjects over a period of three weeks. They were subsequently challenged with the same products. Mild irritation was seen, but no evidence of allergic sensitization was seen.

Next slide, please.

The adverse event information is pooled from the controlled Phase II and Phase III studies, the two fingernail studies, which were for 24 weeks, and the two toenail studies, which were 48 weeks. The data were compiled in terms of severity, in terms of relationship to treatment, and in terms of the time course of the adverse events.

Next slide, please.

Six hundred fifty-five patients with distal subungual onychomycosis were treated, approximately an equal number with the ciclopirox product or with the vehicle. Again, approximately two-thirds of these were male; 24-week exposure in the Phase II studies for fingernails, 48-week exposure in the Phase III studies for toenails.

Next slide, please.

Of the 655 enrolled, 80 percent completed the study. Those who dropped out were, for the most part, people who were lost to follow-up, who were noncompliant, or who lost interest. Six patients withdrew because of adverse events, one treated with ciclopirox, five with vehicle. The person treated with

ciclopirox withdrew for an unrelated adverse event. One of the five treated with vehicle withdrew because of a related adverse event. This was an individual who had bleeding and tenderness around the nail folds. Again, recall that the drug was applied not only to the nail plates but to also 5 millimeters of periungual tissue. So this is a worst-case estimate of side effects.

No deaths were encountered, nor were there treatment-related serious adverse events in any of these individuals.

Next slide, please.

As you might expect, because of the long-term nature of these studies, approximately three-quarters of the patients had adverse events of one nature or the other. Most of these were not related to the drug.

Next slide, please.

This table categorizes adverse events by frequency. These are both causal and non-causal events, and as you can see, upper respiratory infection, accidental injury, headache and so forth were commonly encountered.

Fungal dermatitis -- that is, dermatophytosis

-- was seen in a large number of individuals, as one might expect, because it's known that tinea pedis and tinea manuum are usually seen concomitant with onychomycosis.

I'd like to focus on the local adverse events that were seen in these individuals, rash and nail disorder.

Next slide, please.

These are possibly or probably related adverse events. Forty-one events in total were seen, roughly twice as many in the ciclopirox group as in the vehicle group. Most of these events were mild, a few moderate, none severe. Most were early and transient. All resolved during the study without further treatment -- that is, additional treatment -- and in the process of treating with the lacquer or with the vehicle alone. And again, these people are putting this material on the periungual skin. In all the cases, you will see that most of these side effects are mild, they occur early, they were transient, and they remit without treatment.

Next slide, please.

Under the category of rash, all of these were local erythema. This was the most common adverse event that was causally related. It was seen in more ciclopirox-treated individuals than in vehicle-treated individuals. Most of these were mild. Two or three were reported as moderate. Again, they were transient.

Next slide, please.

"Nail disorders" is a wastebasket term which includes irritation of the nails, ingrown nails, and shape changes in the nails, most of which were described as tinting. These were seen in a few of both ciclopirox- and vehicle-treated individuals, equal numbers. Again, these were almost exclusively mild and resolved quickly in the process of the study.

Next slide, please.

A few application site reactions were possibly related to the treatment. These included tingling, burning, stinging, paraesthesias. An equal number of ciclopirox and vehicle were seen. These were all mild, and again resolved quickly.

Next slide, please.

Standard clinical laboratory measurements

were obtained at baseline and throughout the study at specified times in both ciclopirox- and vehicle-treated individuals. Occasional values were found that were outside of the predetermined normal levels. They were seen in both ciclopirox- and vehicle-treated individuals. These showed no correlation with clinical signs or symptoms. They remitted spontaneously, they required no treatment, and they were felt to be random events.

Additionally, plasma levels of ciclopirox were obtained from both ciclopirox-treated and vehicle-treated individuals. It's recalled that a significant number of these individuals had dermatophytosis, and approximately 70 percent of the individuals in the study were treated with ciclopirox cream for their fungal dermatitis. This was both in the ciclopirox and in the vehicle group.

Determinations of ciclopirox level were made in the plasma of these individuals over time in the studies. These revealed occasional detectable but low levels of drug in both the vehicle- and ciclopirox-treated individuals. The levels were all low. I think

the highest level was 25 nanograms per mL. There seemed to be no correlation -- that is, there was no synergy between lacquer and cream. So the levels seen in individuals treated with vehicle were the same as levels seen in individuals with ciclopirox. Almost all of these were seen in those people treated with cream, certainly two-thirds in this group, and seven out of eight in this group.

Next slide, please.

The adverse events were evaluated in terms of subgroups. There were no major differences with respect to sex, age, or race, nor was there evidence of drug-drug interaction or drug-disease interaction.

Next slide, please.

Roughly half of the individuals treated either with ciclopirox or with vehicle in the double-blind placebo-controlled toe onychomycosis study rolled over into an open-label study for safety, which continued for an additional 48 weeks. The number of patients experiencing at least one adverse event during this 48-week period was roughly the same as that seen in individuals in the initial 48-week period. There was no

difference in the numbers of the adverse events seen in individuals who were treated with ciclopirox in the double-blinded study compared to those treated with vehicle in the double-blinded study.

Next slide, please.

The majority of these adverse events were again unrelated. They were accidental injury, flu, bronchitis, and so forth. A few local adverse events were seen, as was seen in the Phase II and Phase III studies. Two of these were mild periungual erythema. Four of these were so-called nail disorders, dysmorphia, or ingrown nails. All of these were mild and transient and resolved spontaneously during the study.

Next slide, please.

In addition, data has been captured from 22 worldwide non-U.S. studies involving over 6,500 individuals. The most frequently reported adverse events were in the body categories that are required for these kinds of studies as "body as a whole" or, as one might guess, "skin and appendages."

Next slide, please.

Additionally, a worldwide database is in

place in which spontaneous reporting for adverse events is recorded. One hundred fifty-two subjects have been reported with 186 adverse events in this database. These are individuals using all products containing ciclopirox. So this is cream, lotion, gel, and lacquer. The cream and lotion have been available for roughly 25 years worldwide and are available, I believe, in 41 countries. The lacquer has been available for about seven years now. It's estimated that approximately 8 million people, conservatively, have been treated with the lacquer.

Nine serious adverse events have been associated with products containing ciclopirox. Of these nine, one serious event was associated with the lacquer. The rest were associated with the other ciclopirox products. This involved an individual with paraesthesias and pain who applied lacquer to acute paronychia.

Next slide, please.

So to summarize, ciclopirox has been available worldwide in many forms for over 25 years. It's been available as the lacquer for approximately

seven years. It has low potential for systemic availability. There is minimal evidence of systemic toxicity. There is no evidence of drug-drug or drug-disease interaction.

Next slide, please.

The overall adverse event incidence in these studies -- that is, in the controlled U.S. studies -- was quite low, and the adverse events were similar in those treated with active drug as compared to those treated with vehicle. Those that were causally related were mild and transient, primarily local erythema. They resolved spontaneously without treatment as the study progressed. Therefore, one can assume that the ciclopirox nail lacquer is safe and it's well tolerated, and it's appropriate for use for chronic onychomycosis.

Thank you.

DR. DRAKE: Dr. Lim?

DR. LIM: Phil, I have a question for clarification on the CPK level. By my calculation, about 2 percent of the patients had elevated CPK, 16 out of the 600-some patients, between the control as well as the vehicle group if you put them together. How high is

the CPK elevation in those patients?

DR. FLECKMAN: The CPK -- and I will address this from a clinician standpoint. We have Dr. Roberts here, who is a cardiologist, who is here to address CPK specifically.

The CPK levels were all low. The CPKs were total CPK. If you break that down into the MB fraction, the MB fraction, although it was elevated in I think 14 individuals, it was not significantly elevated. So the assumption is that the increase in CPK that was seen was non-cardiac related.

Dr. Roberts, do you want to comment further on that?

DR. ROBERTS: Yes. I'm Rob Roberts, the chief of cardiology at Baylor College of Medicine in Houston. The CK values, I think the four comments I would make in response to your request is that they were equally distributed between the vehicle and the treated group. It was total CK, meaning that the MB/CK fraction never exceeded 3 percent of the total, indicating that the source of that MB/CK is not from the heart. Of course, it's almost always in skeletal muscle.

At no time did the elevations -- they were usually about 300. The upper limit of this was about 250. It did not correlate with any dose, it didn't correlate with any of the other adverse events, and there were no symptoms at any time. I think the key issue is that the MB/CK levels were in the normal range, therefore indicating it's not cardiac in origin.

DR. LIM: Thank you.

DR. DRAKE: Yes?

DR. KILPATRICK: A question for Dr. Fleckman. Dr. Fleckman, you will realize from my questions that I don't have the wealth of clinical background that my colleagues have, so some of these questions will reveal my ignorance.

In terms of the adverse effects based on worldwide data, were you comparing like with like? Somewhere I read or I have the impression that Loprox is a more concentrated form of this substance, 2 percent to 8 percent?

DR. FLECKMAN: That's correct. The worldwide data are gathered from all ciclopirox-containing materials, both cream, gel, and lotion and lacquer. The

lacquer contains more ciclopirox. It's more concentrated than those other products, but the lacquer has been available worldwide for over seven years now, and at least 8 million people have been treated with it. So those data do reflect that population to some extent.

I don't think it's fair to compare the worldwide data to the data from the controlled trials. The controlled trials, as you know, are designed to collect adverse events. So if you walk under a ladder and a can of paint falls on your head, and you happen to be in the ciclopirox study, it's an adverse event.

DR. KILPATRICK: That is the next question I wish to turn to. I'm struck by the prevalence of adverse effects in both the treated and untreated groups -- that is, the vehicle and Loprox group. Now here comes the dumb question. Is the vehicle inert? Is it known to be inert? Is there any possible causal relationship between the vehicle and some of these adverse effects? Or, as you said, is it simply a long-term -- people have spontaneous adverse effects irrespective of what's going on?

DR. FLECKMAN: I believe it's the latter, although I'll defer to Dr. Donaubauer. He's the expert. I'm sorry -- Dr. Bohn.

DR. DRAKE: Jim, I'm going to let him go ahead and answer the question. That's kind of discussion, but do go ahead and answer the question for the moment, please.

Is he here?

There's a microphone right there, sir.

DR. BOHN: The question regarding the placebo, I think it is containing alcohol and ester and a film-forming agent, and I cannot imagine that there are these reactions caused by placebo.

DR. LEVY: If I might just add to this conversation. I'm Sharon Levy with Dermik Laboratories. The agents that Dr. Bohn has mentioned are commonly occurring in many cosmetic products. They are considered inert in terms of these applications and generally regarded as safe.

DR. DRAKE: Thank you.

DR. KILPATRICK: This really leads to the question, do dermatologists here know that ladies

painting their toenails have some adverse effect? Is there a need for a controlled trial between the vehicle and some other inert substance? Because I'm struck by the three out of four vehicle-treated subjects who had some adverse effect, and that's all I'm responding to.

DR. FLECKMAN: I think the three out of four adverse effects only reflect the fact that this was a 48-week study, and having done these studies, if you take an aspirin, it is an adverse event. Anything that is different from baseline, by definition, has to be captured and recorded as an adverse event. So it is a major bug-a-boo concerning these studies. Obviously, the requirements for this are to try to elicit any possible adverse effect, but the ingredients are in nail polish, and the incidence of adverse events I think is not different from that which most investigators incur in such long-term studies.

DR. DRAKE: Okay. I'll remind the panel once again, please, we'll have time for discussion and general questions, but this is clarification questions only.

DR. KILPATRICK: Yes, madam.

DR. DRAKE: Thank you.

Any other clarification questions?

(No response.)

DR. DRAKE: All right.

DR. GUPTA: Good morning, Dr. Drake, ladies and gentlemen, Dr. Wilkin. As you heard, I am Aditya Gupta. I'm out of the University of Toronto.

Next, please.

The last several presentations we have heard on the effectiveness of ciclopirox nail lacquer and its safety. We should keep in mind that in the U.S. at the moment, there is no approved topical antifungal agent for the treatment of onychomycosis. If this drug does get approved, the lacquer, it will provide a treatment alternative to those that are currently out there.

Next, please.

Ciclopirox nail lacquer targets infected nails directly. You paint the drug onto the nail. It penetrates through the nail plate to the nail bed. It is fungicidal, and it has a low systemic bioavailability, which makes for a very safe drug.

Next, please.

You heard in the earlier presentations about the efficacy of this drug. This drug was significantly more effective than placebo for the treatment of dermatophyte toenail onychomycosis.

Next, please.

As one of the panel members alluded to, you also heard about dermatophytes. The study that was presented to you earlier did not speak of nondermatophytes, but we know that there is a certain percentage of individuals who will have nondermatophytes, and indeed, this drug, in studies conducted elsewhere, outside the studies you just heard about, has been shown to be effective for certain nondermatophyte molds.

This is of practical importance to us, because as dermatologists, as family physicians and internists, those of us who treat onychomycosis, we realize that in the U.S. many of us are not doing keragen cultures. We're also finding it's difficult to get culture results back in a timely manner. So, unfortunately, a lot of physicians out there are treating on spec. It is important, therefore, to have a

broad spectrum antifungal agent.

Next, please.

This drug is not metabolized to the cytochrome P450 system. There have been no identified drug interactions and no contrary indicated drugs. This is important. With oral agents, drug interactions are generally predictable and manageable. But we realize that in real life, patients are on several drugs, especially as they get older. They often go from physician to physician, specialist to specialist, and one hand does not often know what the other hand is doing. They often go to several pharmacists. Therefore, it is important to know that there are no identified drug interactions.

Next, please.

As we heard, the ciclopirox nail lacquer is well tolerated. The adverse events are localized and cutaneous and transient. There are no identified systemic toxicities attributable to this drug, and there's no need for lab monitoring. On a practical level, that is very important. It reduces the hassle factor for the patient, and for the physicians, who

don't have to go looking for lab work. It's nice to know that there's no requirement for lab monitoring.

Next, please.

As has been alluded to, there is considerable worldwide experience with this compound, 41 countries in all, and nine in Europe. The safety profile elsewhere is consistent with that in the U.S.

Next, please.

So, in summary, I think the ciclopirox nail lacquer provides significant benefits to patients with distal and lateral subungual onychomycosis. You heard in an earlier presentation about its effectiveness in dermatophyte toenail onychomycosis, and I also provided you with some evidence about its effectiveness in nondermatophyte. It has a high safety margin. It's convenient. There's no requirement for lab monitoring and no drug interactions.

I think this is a treatment choice for patients with onychomycosis and, if approved, will fulfill an unmet medical need, a void that is currently present, with no topical agent for onychomycosis in the U.S., unlike, say, in Europe and elsewhere in the world.

Finally, I think this drug has a high benefit-to-risk ratio. Where would I use it, on a very personal basis, as a physician with a keen interest in nails and fungus? I've looked at these clinical slides, and many patients have been cured, and you saw some examples that in substantial patients there has been improvement. So you would use it as first-line therapy.

Also, the patients who failed oral antifungal therapy, that's just the nature of the disease. They may fail one drug, the second drug, or both drugs.

The patients who are not candidates for oral antifungal therapy, and there may be patients who refuse to take oral antifungal therapy.

So I think there's a whole population of people who would benefit from a good topical antifungal agent that is safe.

Again, just to kind of go further, I think we dermatologists, we like to kind of take things one step further, and perhaps there is a place for combination therapy. This has been alluded to. And also perhaps it would be of help to prevent reinfection or relapse, because we know that despite what treatment we may use,

a fair number of patients tend to get the disease back in a year, in two years, and so on.

Thank you.

DR. DRAKE: Thank you.

Now I would ask for any additional questions from the panel for the sponsors, and I'll allow a little more latitude now since the presentation is complete.

Yes, Dr. DiGiovanna?

DR. DiGIOVANNA: I have a question that I believe is a clarification question, but I'm not certain. It's for Dr. Gupta, and it has to do with efficacy. I did read all the materials we were given and I saw that there were studies done in the U.S., and there's a large worldwide experience. Most of the worldwide experience information that was given to us had to do with safety, and the question that I have is that with the U.S. information, we have very specific criteria and information about efficacy, but there was really nothing mentioned about the efficacy in the larger population of 6,000-plus individuals.

I wonder if the European or worldwide experience with efficacy with the lacquer is similar or

if there are some differences.

DR. DRAKE: Would somebody please -- okay.

DR. LEVY: Sharon Levy again. We did not show the data from the non-U.S. experience because, as you might guess, there were differences in methodology. A number of the studies were open-label. There were controlled studies, including vehicle-controlled as well as positively controlled studies.

I would say on balance a number of the outcome measures that we normally look at may appear a bit higher in the European studies in terms of the actual numbers, but I would be a bit loathe to try to compare them to the U.S. experience where we had a very rigorous standard in these trials. We included a rather new methodology, the photographic planimetry, and I think that has a great impact on how one interprets the data.

DR. DRAKE: Dr. Lim?

DR. LIM: A question of clarification. I believe I read in the material that you treated not only toenails but also fingernails -- is that correct? -- in your study, or just toe? I'm talking about Studies 311

and 312.

DR. LEVY: The fingernails and infected nails were included in the study. I would say that it was a relatively small number of patients and nails.

DR. LIM: Was there any difference between the two groups, understanding that the number is small on the fingernails?

DR. LEVY: Right. Because the number was so small, and because that was not the prime focus of these studies, there were no planimetry measurements made, and, in fact, a different physician global rating. That data is not available in a format that we could show you.

DR. DRAKE: Other questions? Joel?

DR. MINDEL: Just a comment. These patients must be a little different than eye patients, because if you gave an eye patient a medication for 40 weeks that was a placebo and it didn't produce any result, I don't think you'd continue it for 48 weeks. I'm wondering how compliance -- there's no statement about how compliance was monitored in these two groups, the treatment and the control.

DR. LEVY: That's always a tough question, I think, in clinical trials. In these studies, as Dr. Scher mentioned, the patients did return on a monthly basis for visits, at which point they were queried as to their compliance with the product, and their deviations from the scheduled treatment were included if more than three applications were missed in a 4-week period. Additionally, there was a reconciling of the returned medication from all patients in the study, both active and vehicle.

DR. DRAKE: Dr. Stern?

DR. STERN: I think you're right, 80 percent compliance for a 48-week trial is a lot. One of the issues is were these patients paid, and how much, for return, because that is one thing that sometimes -- and I think it also addresses the issue of how great could the morbidity in these patients -- we've heard emphasis on how much morbidity is associated with these conditions, which is the case in some cases. But in these patients, how much more morbidity could there be if they waited 48 weeks for potential improvement? So if you could address those issues.

DR. FLECKMAN: Yes, the patients were paid. In addition, I can speak to our studies. I think there were two things unique about it. One is that there's a subset of people who really do want to help, and they've had this problem for as long as five decades, and they really would like some sort of an answer, and they're really very motivated.

The other is that I know Terry Kellings, the woman that ran our study for us, was an incredible cheerleader. She had birthday cakes. This was a social affair once a month where these people got together. So they really got into the spirit of the thing.

But you're right, the adverse effects were not that severe. No one really was afraid that they were being hurt. There was no evidence that that was the case. They were compensated, and they really just were into it.

DR. STERN: So am I interpreting you correctly that what one would expect in the clinical use, one might well expect a higher proportion of dropouts before --

DR. DRAKE: Rob, would you please speak into

the mike? I'm sorry.

DR. STERN: I'm sorry. So if I'm hearing you correctly, the 80 percent follow-through here is in a situation of cheerleading, economic compensation, and we have an agent where no one can guess whether it's working in them for at least six months. So if we're looking at a population treated, we might expect a substantially higher dropout rate than the general population before there's efficacy than we would in a trial where there's economic compensation and cheerleading.

DR. FLECKMAN: I think that's the case, although there are two other factors. One is that the people in real life are paying for this, and so that's some incentive. The other is that this is not unusual to this product. Anyone who has onychomycosis -- for example, if you treat them with terconazole or terbinafine systemically, you treat them for three months, but they're not going to see much response for a long time.

DR. DRAKE: Dr. Gupta?

DR. GUPTA: Can I just add to that? I think

for those of us who treat onychomycosis, it's important to note that a lot of patients do want to be treated. I've certainly spoken to a lot of my patients about the possibility of a longer duration therapy, and they seem to be willing to put up with it. I think if you can counsel the patient about possible expectations and the fact that they may not see significant improvement for about six months or so, as long as they understand that and they understand what's going to come to them, they'll be willing to put up with it.

DR. DRAKE: Dr. Wilkin?

DR. WILKIN: I think there's one additional factor that hasn't been mentioned, and it's a little different from the usual therapeutic setting where a clinician is treating a patient. Usually when the physician hands the prescription to the patient, they don't say, "This might work for you." They say, "This will work for you, this is something I think is going to be very helpful," or it will be phrased something along that line.

This is a blinded study where the participants realized going into the study that they had

a chance of getting something that wasn't active at all. So I think there's that component that needs to be weighed in.

DR. DRAKE: Yes, Dr. Lim?

DR. LIM: A question for the group. Specifically in terms of a cost/benefit analysis, I read in the folder that this treatment is as effective as systemic, and I heard from Dr. Scher that there are potentially other indications for this that are in combination with systemic medication or as post-systemic treatment management of the nail in these patients. I wonder if anybody could answer about the cost/benefit analysis of this treatment.

DR. DRAKE: Somebody from the sponsor? Then I'm going to allow two more questions after this, and then we'll break, and then we'll allow the FDA presentation. There will still be time for comments and questions.

I saw two hands I'll recognize before break, after this answer.

DR. LEVY: Regarding cost/benefit, I would just stress what I think the presenters mentioned

previously. These studies were all controlled trials versus vehicle. There were no direct comparisons to other therapies, including oral systemic treatments, which have their own track record. I think it would be inappropriate for us to directly compare them.

In terms of cost, again, I think that's a question for future availability of the product on the market. But I think that many of the panelists are aware that many of the therapy alternatives right now, oral systemics do have a considerable price tag, which I think does impact their use and choice by patients.

DR. DRAKE: I saw Dr. Miller, and then Dr. DiGiovanna.

Dr. Miller, please.

DR. MILLER: I have a couple of questions for the group. On follow-up to Dr. DiGiovanna's question, the techniques might have been different. Is there literature in those countries where the product has been used for several years in follow-up? What has been the efficacy in no recurrences, et cetera?

My other questions are the mycology data. Mycologic cure is significantly higher than either the

success or the cure percentages. Would you speculate on that, why might that be?

Finally, we saw the data for penetration of the nail plate, and then assuming that it would get into the keratin, but those studies have not been done. Was there any plan to do it? Has anything been looked at in the nail bed as far as concentration of the drug is concerned?

DR. DRAKE: Dr. Scher?

DR. SCHER: I'll answer Dr. Miller's middle question. Forty-eight weeks is not enough time for growth of a toenail. A toenail takes a minimum of one year to one and a half years to grow out completely. In addition, it has to do with the age of the patients. The older the patients, the more slowly the nail growth.

So if you can achieve a mycologic cure in 48 weeks, which means that there are no live fungi there, that is extremely significant, and the appearance of the nail becomes secondary at that point because the rationale would be that as the nail continues to grow, if the fungi are dead, and a negative culture would suggest that they are, if there is no reinfection at a

later time, that nail will be clinically normal. So the mycologic cure is extremely important at that point in time.

DR. DRAKE: Thank you.

Somebody else from the sponsor to answer the other two parts of that question?

DR. LEVY: Again, I'm not sure that I can shed more light on the first question about efficacy without the numbers at hand.

To the last question about penetration, if we could just show again I think Slide 12 in the primary presentation from Dr. Donaubauer. In his presentation he did review with the group here our experience with penetration in vivo in toenails, and as you'll see from the slide -- is this the correct slide? -- this is from a long-term study where the lacquer was applied over a 45-day period to toenails of healthy volunteers, and then samples from these toenails were obtained looking at the outer layer, layer 1, and the inner layer, which includes a portion of the nail bed.

You can see from this that, first of all, one starts to achieve a steady state level at around 30

days, and all of these levels, levels of ciclopirox, all layers of the nail, including that innermost layer that includes some of the nail bed, are far in excess of the maximum inhibitory and the maximum fungicidal concentration for the organisms that were looked at.

DR. DRAKE: Thank you.

Dr. Miller, are you okay?

DR. MILLER: Yes, but it actually did not look at the nail bed. We're assuming that it went more deeply.

DR. DRAKE: I believe in the presentation that they said that the yellow bar did penetrate into the nail bed. That included nail bed data, and that was in the original presentation, as I recall.

Dr. DiGiovanna?

DR. DiGIOVANNA: As I struggle with the meaning of these different categories and the efficacies that have been reported, the mycological cure and treatment success, there are a couple of issues that I don't know if the nail experts might be able to clarify for me in some way.

Basically, two. The first one is that I

think infectious diseases are sort of odd diseases. The presence of an organism doesn't equate with clinical disease. We see this commonly in dermatology. If someone is infected with staph and develops folliculitis and maybe keragen, other members of the family who have it, it doesn't represent disease. If a child develops tinea capitis, there may be other members, siblings, that have positive cultures but don't have the disease.

So thinking about that suggests to me that, for example, the pooled data of 30-some-odd percent mycologic cure might actually be an underrepresentation of the actual efficacy of the drug. When one looks at the treatment success of 10 or 12 percent, which seems very low, I also wonder if that might also not represent a gross underestimate, because those of us that see somewhat a fair number of nail disorders, certainly not to the extent that Dr. Scher does, but abnormal skin, abnormal nails, abnormal skin-nail units for various anatomical disruptions tend to be more likely to become infected, and once one clears that infection, the anatomical abnormality may remain for a persistent period of time, or forever.

So I wonder if these measurement techniques of planimetry have built into them a necessity for lower efficacy. Those people who have abnormal nails because of anatomical abnormality may be more likely to develop fungal infections, and then when you get a mycologic cure, you may have some of that residual which you will measure with your planimetry. What I would like to get a better sense of from those people who have done these studies and are experts is are these efficacy measures underestimates, and are there other nail abnormalities that are measured in this, and is there some way to get a sense as to what might happen in the real world with treatment?

DR. DRAKE: Dr. Scher?

DR. SCHER: Yes, I totally agree with Dr. DiGiovanna. In my view, the efficacy is underestimated. But we have here a very stringent study, and it was designed to be very stringent and very accurate, so that we could present as careful data as possible. But if one goes by perception, you're absolutely correct. There is nail dystrophy where there is no longer nail infection. So my sense would be in agreement with you

that the efficacy here is probably much better than, in fact, the data show.

DR. DRAKE: And I said no more questions, but I'm going to yield to our previous chair. He does have a question.

DR. McGUIRE: It's a very short question. Is the apparent mycologic cure in any way related to the Loprox that's carried over in the specimen for culture? Have you ruled out any influence of residual Loprox in the specimen?

DR. SCHER: That's a tough question, Joe. I would expect tough questions from you. I'm not sure that we can answer that. I'm not sure that we can answer that. Perhaps one of the others can. I think that is a conceivable possibility, but do one of the scientists want to address that question?

DR. NOACK: Hello. Good morning. My name is Herbert Noack. I'm project biometrician from HMR in Frankfurt. We have prepared back-up slides for this question. Because a very high proportion is using concomitant Loprox cream, the question arises could it be excluded that there isn't an effect on onychomycosis?

Ciclopirox is deactivated by glucuronidation immediately after absorption, and you also can see, due to PK rate reasons, that the Cmax is very small. So I think this will not have any impact on onychomycosis.

DR. DRAKE: Dr. Scher?

DR. SCHER: I don't think that was your question, Joe.

DR. SHUSTER: I wonder if I can answer the question. Sam Shuster, Emeritus Professor, dermatology, Newcastle.

Where it's not possible directly, it is extremely unlikely to be due to leaching after the chemical. The evidence for that is if there was leaching out, it would occur immediately on the culture; whereas the evidence is that there is a time course of inhibition which occurs gradually, long after the nail is saturated with drug. So if it's leaching out, there would be immediate inhibition. That's not the situation. There's a progressive increase in inhibition. In other words, it's not leaching out.

DR. STERN: Can I address Joe's issue? I think there are two issues, the one you raised, and the

other is I believe these were cultures from the distal nail, and certainly if you look at something that's being applied 5 millimeters beyond the edge of the nail and you look at something that's going to soak into that debris, there's more likelihood of mycologic cure distally than there is, perhaps, proximally. They didn't do, as far as I know, any drillings into the nail and culture the still-affected nails further back. Perhaps they did in a large number of patients.

DR. DRAKE: Dr. Scher?

DR. SCHER: Another point, Joe. Your question really addresses the culture but would not really address the KOH. Even if we assume that there is some residual there, it might give a false-negative culture but certainly would not give a false-negative KOH. So that's just a point that I think you have to take into account.

DR. FLECKMAN: Also, you're partially correct, Dr. Stern. The nail plates were debrided back before the subungual debris beneath the onycholytic plate was cultured, and the lacquer was removed before that. So if there was contamination, it would have been

drug that had penetrated through the nail plate into that material. So it wouldn't have been from the nail plate or material from the outside edge. But again, as Sam pointed out, the culture showed progressive increase in negative cultures over the first three months, not an abrupt increase as soon as the drug was applied. So it's unlikely that that's a leach out.

DR. DRAKE: All right. This discussion is interesting and I don't want to terminate it. It can continue later, but I do believe that people are ready for a break. To be delicate, I think people need a break right at this moment.

(Laughter.)

DR. DRAKE: Although I saved time early on, we've now lost some of that time. May I suggest we reconvene in 10 minutes, please, so that we do not get too far behind. Thank you.

(Recess.)

DR. DRAKE: If I could ask the panel members to please take their seats and to have the guests please be seated, because I'm reconvening the meeting effectively now.

I realize the break was slow, particularly for the ladies who had to stand in line so long, because we spent most of our time standing in line, and thanks to the courtesy of some other ladies, I'm here to actually help preside instead of still standing in line. But we will press on.

I want to, at this point in time, move to the FDA presentations, and I'll ask the sponsor to please -- I hope you and all your experts will please remain, because during the discussion I'm certain that other questions will arise.

But let us move now to the FDA presentations. Brenda Vaughan, I believe, is going to start this portion of the program.

DR. VAUGHAN: Good morning. I'm Brenda Vaughan, medical reviewer from the Division of Dermatologic and Dental Drug Products. This morning we're presenting to you NDA 21-022, Ciclopirox Topical Solution 8 Percent. It's being presented for your discussion and recommendations.

The proposed indication is for ciclopirox topical solution 8 percent in the treatment of mild to

moderate onychomycosis without lunula involvement of the fingernails and toenails due to T. rubrum, T. mentagrophytes, and E. floccosum.

The demonstration of outcomes for treatment of onychomycosis can be schematically represented by three regressing subsets. These subsets can be viewed as a target, with a center and two outer layers. Each layer from the center outward encompasses the innermost layer. In the center of the subset would be the completely clear nail with negative mycology, KOH, and culture. Moving out from the center is the almost clear nail, with equal to or less than 10 percent involvement, with negative mycology. The outermost subset is the negative mycology alone.

There are no standard terms for efficacy endpoints of the progressing subsets. Terminology varies from sponsor to sponsor, and terminology also varies between the sponsor and the Division. As the table displays, the regressing subsets, however, are the same; the terminology differs. Terminology should not imply a value judgment.

Results from Studies 312 and 313 were

submitted in support of safety and efficacy of ciclopirox topical solution 8 percent. The study designs were identical. They were multicenter, randomized, double-blind, vehicle-controlled, parallel-group studies, stratified by center and percent involvement. The objective was to compare the safety and efficacy of ciclopirox topical solution 8 percent with vehicle in the treatment of mild to moderate onychomycosis.

The study design. Eligible subjects with 20 to 65 percent involvement of at least one great toenail at baseline were randomized to either study treatment. Medication was applied daily for 48 weeks. Clinical assessments were made every four weeks. Mycological assessment, global assessment, and photographic planimetry were taken every three months.

In this study, patients with clinically clear and mycologically negative target toenails at the 48-week treatment period entered a post-treatment follow-up; or patients with clinically clear and mycologically negative target toenails at any time prior to the 48-week treatment period could also enter a post-treatment

follow-up. Subjects or patients without clinically clear target nails at 48 weeks were invited to enroll in Study 320, a safety extension study.

Patient instructions included that all toenails were to be treated; only infected fingernails were to be treated; applications were to be applied daily over the previous coat, to be removed every seven days with alcohol; the patients were provided with emery boards, instructed to file away loose material and to trim the nail as required.

The investigator instructions included removal of remaining material with acetone; the target nail was to be trimmed at least to the distal groove at all visits; and the target nail was also trimmed to remove unattached, infected nail.

The investigators also were permitted to use their own preferred method to clip the nail. They were permitted to file off excessive horny material from the remaining nail surface prior to retreatment and application.

The age, race, and gender were similar between treatment arms and between the two studies.

Steve Thomson, statistical reviewer, will address statistical issues.

MR. THOMSON: Thank you, Dr. Vaughan.

My name, again, is Steve Thomson. I was the statistical reviewer for this product.

Next slide, please.

Usually at the FDA, we evaluate drugs at a particular time point. Usually for this type of product, this would be at some point after completion of the study, or perhaps in some window of time after the completion of the study. Then we evaluate the efficacy at that particular time point compared across with the vehicle. This would seem to be particularly important with this type of product, where there may be some long-lasting effect due to remnants of the ciclopirox and the material that was taken for culture, these sorts of things.

This isn't any different than the sponsor's analysis. The sponsor is testing things over time. We believe that these things should be tested at a particular time point. One of the assumptions of the sponsor's analysis would be that the censoring

distribution -- that is, the distribution where the subject is lost -- is independent of the event distribution -- that is, whether it's success or clear or almost clear, or anything like this. I think we're not so sanguine that those are necessarily independent when you have 90 percent or more of the cases being censored. So we would prefer to evaluate this at a fixed time point.

Next slide, please.

To look at this again, referring to the regressing subsets, there are four variables that I want to start off with. One is the percent area from planimetry. It's a continuous measure. It's nice. We can have some nice pictures of it, and it would be the most general, broad one, theoretically. Then we can enter a variable of mycological cure, which has been pointed out that these things are sometimes measured in error, and so may be a little bit more misleading.

Then we come into a variable which would be almost clear, which was defined at our recommendation as an area less than or equal to 10 percent, plus a mycological cure. And then finally a complete cure of

the nail. That's the investigator evaluation of clear plus mycological cure.

Now, theoretically, these were supposed to be regressing subsets of the last three of them, at least. That is, everybody who was a clear was an almost clear, and so forth. Later on, the fact that that did not happen caused some questions at the FDA, and Dr. Vaughan will address some of that shortly.

Next slide.

Just to start talking about the planimetry measures, this is not stuff that I pulled out of an old hair brush or anything.

(Laughter.)

MR. THOMSON: These are the individual profiles of responses, the planimetric responses in the two different treatment groups. First off, I guess the thing to notice is that there is a lot of variation in responses. Some people are getting worse, some people are getting better. These people down here are the people who entered the post-treatment phase, and they're getting better. There's also a lot of very jagged going up and down in some of these subjects, and some of these

are quite extreme. This may be measuring a variation in the planimetric method, or it may be measuring the course of disease. I'm not sure.

But, nonetheless, it is interesting to observe that there is a lot of variation here. Again, the point I guess I'm trying to make with these is that in both ciclopirox and the vehicle, that some people are getting better, some people are getting worse.

Next slide, please.

This is something that might help indicate a little bit more the overall trends. These are LOWESS lines, which is sort of a smooth mean. The knots are the vehicle group, the crosses are the Loprox group. This is to give an illustration of the variation about the responses. But anyway, the ciclopirox tends to go like this, and the vehicle tends to go like that. That's all in the 312 study.

Another way to get a picture of this would be to see how subjects are going above and below certain limits and the way they behave.

Next slide.

These are just, then, in those people from

planimetry, what percent ever went below 10 percent, what percent went above 65 percent. Sixty percent was the admission to the study. So patients who go above 65 percent are presumably getting worse. Now, this is if they ever went below 10 percent or if they ever go above 65 percent. So it gives you some idea, again, that a number of patients are getting worse by that measure of getting worse, and some patients are getting better, a number of patients are getting better.

Again, these are just tests for homogeneity across the proportions of the treatment groups.

Next slide.

The last slide here is sort of a similar thing. We're now comparing at the end of the study; that is, those who were below 10 percent, those between 10 percent and 65 percent, and those at 65 percent. That is the last measurement that I have of their planimetry. Here again, we decided to test homogeneity across here, only using a Fisher exact test because of the low percentage there, and this would be the differences in the columns.

We have summary results for the 313 study.

Next slide, Frank.

Again, another one of the hair plots or spaghetti plots. Again, the same sort of thing, and it's curious whether all this jaggedness is due to the planimetry measurements or to natural course of the disease. The same sort of information, though, lots of variation, many people getting worse, many people getting better. It's hard to say. So we'll take a look at the same sort of proportions again.

Frank, next slide.

Oh, excuse me. I wanted to go over the LOWESS lines and compare them. That gives sort of an overall trend. Again, you'll notice in both of these that the ciclopirox LOWESS line is lower at the endpoint than the vehicle. I haven't provided a test of any differences yet or anything like that.

Next slide, Frank.

This is the number of subjects who at any time ever went below 10 percent, and the number of subjects at any time who ever went above 65 percent in the two different studies. So this study actually seems to have a little bit more variation when measured that

way than the previous study.

Next slide.

This is the same sort of thing at the end of study, where again we have significant difference. Again, there's some indication that comparing these numbers may or may not be some indication.

Next slide, Frank.

To provide some tests of differences of these at the various time points, these are from an analysis of variance of these, and here we have the mean comparisons. So now the question is, is the 5 or 6 percent here and the 7 or 8 percent here -- this is close to statistical significance, and it's debateable at this point. We are just barely at statistical significance for this difference right down there. And, of course, quite significant here. So this is at 48 weeks in our measurement. The LOCF at 48 weeks is all observations up to and terminating at 48 weeks.

If you look at some of the sponsor's tables and our tables, they do tend to differ a little bit due to some definitional differences.

Next slide, Frank.

In the following tables, I want to analyze some of the discrete variables. In particular here now, the significance that I'm providing you is from Fisher exact tests. These are exact tests and they are discrete, and that means there is some limitation on exactly reaching a 5 percent level. Another statistic that is useful is something I just found out about recently, and that's something called the number needed to treat. In particular, it's an estimate of the number of patients that you would have to treat for 48 weeks or so to get one success response. However, the success response is divided into individual tables.

There are, again, some differences between what the sponsor defines and what we define. For example, our week 48 is within 14 days of week 48. The sponsor's week 48 is within 28 days of week 48. That's how they define week 48. Those are all rational decisions, but it does need to make some difference in the way things are counted at some particular times.

The sponsor in at least one case did a carryover for -- if somebody had part of a missing value for one thing and they had to carry over from a previous

value to make the composite measure, we would not do that. We normally have not done that in any of our studies. But it does make sense to do it. So any difference between the sponsor's numbers and ours are just due to minor, quite rational, and really interpretable differences in definition.

Next slide.

Getting to the regressing subset idea that Dr. Vaughan was talking about, first I want to talk about the mycological cure. This is again at week 48, our week 48, not necessarily the sponsor's, and the yellow week 48, all subjects up to and including the week 48 endpoint. In all the studies, of course, there are statistically significant differences. The number needed to treat down here again is an estimate of the number of patients that you would have to treat to achieve that level of success in your practice, treat for one year.

This is primarily, I suppose, background information.

Next slide.

This and the next slide I would say are the

two key slides in my presentation, because this is where one is defining an almost clear response -- that is, a mycological cure -- and a 10 percent or less planimetry measure. We'll take a look at the differences here. Actually, this has passed through several times and I'm afraid there is a slight error. That should be a 7, and this should be a 0.035, but that's the difference between the way we're doing the computation and the sponsor. We agree here on these. They dropped two subjects from this group, and we dropped two subjects in, but basically the total numbers agree.

Overall, I think the results, the sponsor and we would agree on these particular values. Number needed to treat -- again, they are statistically significant differences.

Next slide.

Here we have for the clear response, this is sort of our gold standard. This would be the one that we would like to achieve if we could, and I think the sponsor and we would agree that while they achieved that fairly handily in the 313 study, statistical significance there, they don't achieve it in the 312

study. But there are still maybe, perhaps, some signs. Then here, these are maybe relevant, looking at the numbers in needed to treat. You get 90 out of the efficacy of treatment.

Thinking about these led to some questions about mycological cure. In particular, we were concerned, because we expected these all to be regressing subsets, there was some concern about why we have cases that were, or the sponsor had cases that were almost clear in their categorization and were not counted as clears. I think that's what Dr. Vaughan would like to address.

Thank you.

DR. DRAKE: Dr. DiGiovanna?

DR. DiGIOVANNA: One question?

DR. DRAKE: Yes.

DR. DiGIOVANNA: In reading through all the materials in here, I still haven't found a definition. What is "LOCF"?

MR. THOMSON: Last observation carried forward.

DR. DiGIOVANNA: Thank you.

DR. DRAKE: Yes?

DR. KILPATRICK: Steve, I want to compliment you as a fellow statistician for your presentation. I have one comment and one question.

Reading some of the material handed us this morning, it appears there was an earlier review of this sponsor's proposal, at which time it was recommended that they do an analysis of time to response. I completely agree with you that I would put more width on the incidence at a given point in time, but in defense of the Cox proportional hazard model, I think that was implicit in what was recommended at an earlier time.

MR. THOMSON: Actually, I'm not sure. I was at one of those meetings, and I recommended at that time a Cochran-Mantel-Haenszel test at a certain time point. We have that in some of our documentation. However, the problem with the Cochran-Mantel-Haenszel test for these sorts of situations is that when you have zero responses in both categories, it's dropped out. So here we have some of these response measures, but out of eight or nine centers, six of them had no responses in either group. So basically, then, the test is based on

the other three centers. So that's why we went to a Fisher exact test instead of that.

DR. KILPATRICK: I'm not questioning your analysis. I'm just trying to indicate that there may be some justification for what the sponsors did.

MR. THOMSON: Yes.

DR. KILPATRICK: Can you again tell us what a regressive subset is? I mean, I've got regression fixed in my mind. It's not the same as regression, no?

MR. THOMSON: It's a terminology that I guess we are using for increased -- think of this as the target where this is the most restrictive subset, and then layers inclusive of that. So these are nested sets, if you want to look at it in that terminology, where the smallest set is included in the next set, and included in the next set, and so forth on up.

DR. KILPATRICK: Thank you.

DR. DRAKE: Dr. Stern.

DR. STERN: I had a question about number needed to treat. In your analysis of number needed to treat, you're assuming dropouts at the rate in these clinical studies and not in practice?

MR. THOMSON: Yes.

DR. STERN: So if there's a higher dropout rate for a drug that had no predictability of efficacy at six months, as your data show, the number needed to treat per nail cleared of initially treated patients would go up in proportion to that higher dropout rate. Is that correct?

MR. THOMSON: Definitely true, yes.

DR. DRAKE: Thank you.

DR. VAUGHAN: Efficacy endpoints. The sponsor was successful in demonstrating almost clear at week 48, LOCF, for ciclopirox topical solution 8 percent in both Studies 312 and 313. As originally hoped for, the sponsor was not successful in demonstrating efficacy for complete cure in Study 312. However, the sponsor was successful in demonstrating complete cure at week 48, LOCF, in Study 313. However, the number of successes was small.

The sponsor defined global assessment of cleared as 100 percent clearance of clinical signs of disease, corroborated by absence of investigator markings on photographs.

During review of the NDA, there were interesting features noted of the data that was presented, in that there were inconsistencies in the sponsor's regressing subsets that we have referred to, and the planimetric values of the cleared subset. The sponsor's subsets do not regress as ours do. In other words, patients who are in the complete cleared group would also be included within the almost cleared group. Subjects with the global assessment of cleared had non-zero planimetric values.

For example, at 48 weeks the planimetric values for the category of cleared ranged from 7 percent to 11.8 percent for the cleared groups. These inconsistencies prompted evaluative photographs to elucidate the positive planimetry in the cleared patients. It became apparent that some patients with a global of cleared may have had a nail that we considered to appear clear with positive planimetry with non-planimetric values, and also that did not appear as clear as we thought that they may have been.

I'm going to show you four photographs. All of the photographs that are being shown, I will have to

say, showed substantial improvement over baseline. These photographs are only being presented to you to really demonstrate that cleared is not as clear-cut and objective as one might think. Cleared is subjective, and it's difficult sometimes to assess cleared. One investigator may think a photograph is clear and someone else may think it's not.

These were at 48 weeks. They were in the cleared group. This is one patient from Study 312. This is with the distal groove marked without additional, other than the notch shown.

Next.

This again is a patient from Study 313 at week 48 that was considered cleared.

Next.

Again, another patient from Study 313 that was called cleared.

Next.

This shows the difficulty in assessing cleared from a photograph. It's just subjective and it's difficult to assess.

MR. THOMSON: I have only a couple of slides

to discuss, sort of almost what we would like to have as our platinum standard if the other cleared is called a gold standard.

DR. DRAKE: Could you put the mike closer to you?

MR. THOMSON: Oh, sure.

DR. DRAKE: Thank you.

MR. THOMSON: This is a post-treatment response. It's just to give the successes post-treatment for the people who entered into the cleared group. Unfortunately, the way the study was designed, not all the subjects who entered post-treatment, and maintaining the blind and everything -- well, these particular subjects were maintaining a true post-treatment study with these particular subjects who had the clear nail. This sort of success was just whether they remained clear at the 12-week follow-up, which by my measure turns out to be a 16-week or an 8-week follow-up or something like that, and success at the 24-week could also be a 20-week.

So this compares the follow-up successes for this small group of people who were clear in the 312

study and entered the post-treatment period.

Next slide, Frank.

This indicates similar information from the other one. The solid lines there are merely an artifact of the processing of the data. These were all ciclopirox subjects. There were no vehicle subjects in this particular study who went into the post-treatment period. So this says if they were remaining clear. If they were not clear at 12-week follow-up, they were failure, a 24-week failure and this sort of thing. So this person remained clear, and these two subjects remained clear. The other ones were failures or no data.

DR. VAUGHAN: Safety assessment data was derived from seven U.S. clinical trials. Included in those were pharmacokinetic studies, which will be addressed by Dr. Bashaw, and sensitization and irritation potential study. Also, pooled safety data for the 22 non-U.S. studies.

Local safety was derived from three sources. Local skin assessments from Studies 211 and 212, which were with this product in the treatment of fingernails.

However, this study was for 24 weeks duration. Also, data were presented from treatment adverse events for the Studies 312 and 313, and probably causally related to the test material. However, we prefer just all adverse events reported, regardless of causality. But we also have that data in the skin and appendages table we submitted, irrespective of relationship to the study drug. This was included in your package.

Next.

Results from the topical safety study, the irritation and sensitization study, reveals that ciclopirox topical solution and vehicle appear to be mildly irritating. Based on the results of this study, ciclopirox topical solution 8 percent does not appear to be frequently sensitizing.

Clinical laboratory analysis was obtained from Phase II/III studies, and there were 327 subjects treated with ciclopirox and 328 subjects treated with vehicle. No clinically significant differences in the laboratory evaluations between the active and the vehicle groups were noted.

An overview of pharmacokinetics from

ciclopirox topical solution will be presented by Dr. Bashaw.

DR. KILPATRICK: Madam Chair?

DR. DRAKE: Yes, please.

DR. KILPATRICK: I would like to ask Steve Thomson what again NA means in effect, non-available or undefined. Can you give a little bit further with that?

MR. THOMSON: Primarily not available or the variables -- there's a composite of variables that go into the clear definition. In particular, there's an investigator global of zero, a mycological evaluation of clear. If one of the mycology variables was not available and everything else was positive, then that was not considered a success. It had to be all the variables there to make a success.

DR. KILPATRICK: Is this an implicit criticism of the quality of the data set?

MR. THOMSON: No, not particularly. There are timing considerations for these things. No.

DR. KILPATRICK: Okay.

DR. DRAKE: I think you can proceed. I see no more hands raised.

DR. BASHAW: Can I have the first slide, please?

I'm going to be presenting today an overview of the pharmacokinetics of ciclopirox from Loprox 8 percent nail lacquer. This talk very much goes hand in hand with the previous presentation made by Dr. Donaubauer of the sponsor. I'd point out that you have in your package the copy of the PK review written by Dr. Sue-Chih Lee. She could not be here because of a family emergency, and I, as team leader, am here to make her presentation. So please bear with me from time to time. It may be a little rough trying to adapt her talk to me.

Again, we're going to present just an overview today. You have the review. I'm really not going to get into any numbers or any specific details. The sponsor has done a job with that this morning. What we are going to talk about, though, is some of the shortcomings of some of the trials and how some of the data need to be looked at a little bit more critically than I think has been up to this point.

Can we have the first overhead, please?

Basically, this is what the clinical database consists of from a pharmacokinetic standpoint. There were some additional studies that primarily consist of two major features; that is, in vitro work and in vivo work. The in vitro work involved using cadaver nails in two studies, also using onychomycotic toenails that were avulsed and looked at for drug penetration. We have the aforementioned Studies 312 and 313, which have been discussed by a number of speakers already today.

I would point out that you'll find there are some minor differences between the presentations you'll see today and what you have in your package. We realized last night there were some typographical errors. We fixed those, but there may be some minor differences. Just bear with us on those.

Again, we can go to the next overhead.

We can garnish the in vitro studies. We do believe that they do demonstrate that there is diffusion of ciclopirox into the nail plate. We do have some questions and some concerns about the appropriateness of the data from these studies because we think that when you look at the method of application and removal of

ciclopirox in the in vitro studies, they differ from what was going to be used clinically, what the clinical regimen will be. There was much more use in terms of application of alcohol to the nails when they were applying the drug versus what's going on clinically, and the effect of alcohol on enhancing the penetration throughout the nail bed in the in vitro studies could play a factor to make it look a little bit deeper than it really is.

We also think that the method of measuring penetration by dividing the nail into quarters and then looking at the different amounts per quarter is very misleading, because certainly onychomycotic nails differ in thickness from patient to patient, and this was not accounted for. They just divided everything into quarters, and whether or not one nail was thicker than another, 25 percent for one nail might be much larger in another nail. So there are some differences in how they got these numbers. We think it's an inaccurate way of looking at it.

Also, the relevance of the diffusion apparatus itself to the clinical setting, both for

toenails and fingernails, was, in the case of toenails, under occlusion somewhat, wearing shoes and everything; the fingernails are continually getting banged around during the day, flaking off pieces of the nail. Really, the appropriateness of the in vitro methodology to looking at penetration is somewhat questionable, and we think that the results from the in vitro set, which the sponsor did not spend much time on this morning but is part of their application, needs to be looked at with a little bit of skepticism.

It is interesting data, and it does demonstrate diffusion of drug in the nail plate, but there are some caveats to what you can do with that information.

Can we go to the next one, please?

With regard to the in vivo studies, they are somewhat better, and we do think it does show some valuable data. Unfortunately, what we did see from a systemic standpoint -- and there are two issues we're looking at here pharmacokinetically that are really raised up today with regard to the application. One is, is there penetration of drug through the nail plate to

the nail bed? Also, are there systemic levels produced by topical application of the nail lacquer?

What the in vivo studies basically showed is that you can have low but detectable urine and plasma levels of ciclopirox after clinical application. This primarily comes from results one sees in Study 111, Study 312 and 313. However, when you look again at the nail penetration studies that were done, they were measuring penetration of the drug measured from the distal end of the nail, taken from clippings, and this was also a place of application where the patients were instructed to apply it not only to the dorsal side of the nail but also, if possible, to the ventral side of the nail.

So when we're looking at those penetration slides that were shown earlier, those quarter percents, where they show the bottom layer having a large amount of drug in it, how much of that is due to ventral application, applying it to the bottom side of the nail, is unknown.

Also, what we'd really like to know, which one of the panel members asked today, is throughout the

nail itself, there is going to be varying degrees of disease from the distal into the proximal end. There is no assessment of anything beyond the proximal end in terms of nail levels. There were no specific nail bed concentrations taken, and whether or not we have uniform distribution of ciclopirox throughout the nail is really unknown. All of our data regarding the diffusion and penetration of drug into the nail plate comes from the proximal end of the nail itself, not from anything taken further back.

Can we have the last one, please?

In summary, the pharmacokinetic package presented by the sponsor does demonstrate that ciclopirox does penetrate both healthy and diseased nail to some degree, and this is primarily dependent upon the fitness of the nail, and also method of application. Method of application here, if you apply it every day and then remove it every three days with alcohol, the alcohol is probably going to have some effect on penetration of drug, versus applying it every day and then removing it with alcohol once a week. The use of alcohol certainly should have an impact on the

penetration.

Whether or not there is uniform distribution of ciclopirox from the proximal to distal end of the nail plate is unknown. Again, to reemphasize, all the data that we have in vivo in patients was taking nail clippings from the end of the nail -- nothing further back, nothing looking at the entire distribution throughout the nail plate.

There is specifically no information available regarding levels of persistence of ciclopirox in the nail bed itself. There has been, I know, some allusion to the fact that a layer 4 is going to be the lowest layer of the nail. Therefore, it's going to have part of the nail plate in there. It's going to have the nail bed in it also. But again, that's not really been fully demonstrated, and I think there's quite a bit of discussion one could have about the design of the trial, how it was done, as to whether or not it really was a good estimate of what levels were achieved in the keratin in the nail bed itself.

Systemic plasma levels at or near the limit of detection and quantification, most of the individuals

that we saw in Studies 312 and 313 -- actually, if you were to look at only those subjects who had ciclopirox nail lacquer, because there was quite a bit of concomitant use of the lotion and the cream with the lacquer in those studies, the levels that you produce are actually much lower. In fact, most people had undetectable levels. So systemic availability from ciclopirox nail lacquer itself, when you subtract out those who had the cream, those who had the lotion, is very low, to almost undetectable. But occasionally one does find a level or two.

Thank you very much.

DR. DRAKE: While we're changing leaders here, does anybody have clarification? Yes, Dr. Miller.

DR. MILLER: This is a clarification. In the application of the preparation, was it applied just to the nail plate, or was it also 5 millimeters beyond on the adjacent skin?

DR. BASHAW: That's correct. It was applied not just to the nail plate but also to a 5-millimeter strip around it. Also, in most of the studies it was applied not just to those nails who were infected but

also any healthy nails. So all nails were covered. It was a very extreme measure. In the case where you only had toenails involved, the patients also had their fingernails treated. So it was very extreme in some of the situations.

Unless there are any further questions, I will turn over the presentation to Dr. Linda Gosey.

DR. GOSEY: My name is Linda Gosey, and I was to review the microbiology data regarding ciclopirox topical solution 8 percent.

When assessing test results from preclinical activity studies and clinical trials, it is important to understand the characteristics of the disease under study. For distal subungual onychomycosis, the causative agents are the dermatophytic molds. However, T. rubrum causes the vast majority of the infections in the United States.

While we focus on the fungus in the nail plate to diagnose the infection with the KOH preparation or fungal culture, the fungus producing the condition is primarily located in the nail bed. The mold gains entry by invading the distal and lateral ends of the nail.

Distal subungual onychomycosis is a chronic condition in both normal and immunosuppressed patients. However, in the studies conducted using 8 percent ciclopirox, only normal subjects were enrolled.

Next slide.

There are a number of considerations that must be taken into account when interpreting the preclinical activity data. Currently, there are no standardized susceptibility testing methods for the dermatophytes. As with other molds, T. rubrum and T. mentagrophytes MICs can vary due to the methodology employed, such as an agar or broth method. Other conditions such as pH, nutrients in the medium, the growth phase of the fungus, and the isolate selection can also alter the MIC values.

When I reviewed the data, four different investigators had performed in vitro susceptibility studies, and the MICs for the dermatophytes ranged anywhere from 1 to 20 micrograms per mL. Because there are no standardized in vitro susceptibility testing methodologies, a relationship between the in vitro test results and clinical response has not been established.

Ex vivo experiments should be conducted utilizing appropriate test material, where the infection and the treatment mimics that in the proposed clinical trials. The test systems available to evaluate antifungal agents against distal subungual onychomycosis are not optimal due to the nature of the disease and the location of the fungus. One investigator, Yang, did conduct a treatment study in bovine hooves, where treatment was started four days prior to, at the time of, and five days post-infection. In this study, they found that ciclopirox was slightly inhibitory and not cidal against established trichophyton infections.

Next slide.

There are several important issues that were not addressed in the preclinical studies. As we've already heard, it is unclear if relevant concentrations of the drug penetrate into the nail bed. It should be brought up that in these penetration studies, a microassay was used with the organism candida pseudo tropicalis. As a result, we do not know the relationship between the MIC values and the drug concentrations in the nail bed for the dermatophytes.

In addition, the rate of relapse and drug resistance development was not studied in preclinical experiments.

Lastly, studies were not performed to rule out potential interactions between ciclopirox and the systemic antifungal agents used to treat this condition.

Next slide.

Due to the unique characteristics of distal subungual onychomycosis, the optimal model for evaluating the activity of an antifungal agent is a clinical trial. When we assess the data from Studies 312 and 313 at week 48, there were 186 patients in the intent-to-treat population. Ninety-six percent of these patients were infected with T. rubrum, 4 percent with T. mentagrophytes, and none of the patients in the treatment arm had an infection due to E. floccosum. Twelve of the patients at week 48 obtained a treatment cure and also had follow-up data. Nine of these patients were infected with T. rubrum, three were infected with T. mentagrophytes.

Even though these cure rates were low, we wanted to look at the relapse rate at 12 to 24 weeks

post-therapy in these subjects. Four of the nine patients that were initially cured of their T. rubrum infection relapsed. In addition, two of the three patients initially cured of their T. mentagrophytes infection relapsed as well.

Thank you.

DR. DRAKE: Okay. Clarification?

(No response.)

DR. DRAKE: Dr. Wilkin?

DR. WILKIN: I could move to the questions.

DR. DRAKE: Yes, let's go to that.

DR. WILKIN: Okay. The questions for the committee are of the fairly standard variety. Commander Cross is getting that up on the screen.

The first is essentially the efficacy signal. Does the committee believe that efficacy has been found for this product?

The second question is, in essence, has the safety profile been adequately described?

Next slide.

The third question is did the benefits outweigh the risks for this product for this indication?

Then the next question really is fairly close and we would generally expect the same answer. Do you recommend that this product be approved for this indication?

Next slide.

And if the committee's recommendation is for approval, we would like comments from the committee regarding product labeling, any specific recommendations that you may have for the package insert. Also, if you believe additional studies would be helpful to provide information that would be either necessary or important for the package insert, some of these you might think would just simply be helpful and you would encourage the sponsor to conduct these others, you might suggest Phase IV commitments, that they should be a condition of approval that the sponsor would agree to conduct such studies.

Now, regarding the product labeling, remember there were five areas that we asked you to think about as you heard the sponsor and FDA presentations.

Next slide, please.

These were the evidence for nail penetration

of the active; the use of their product with the available systemic treatments for onychomycosis; the different patient groups that were excluded from the studies; labeling regarding concomitant tinea pedis therapy; and then the periodic trimming and debridement of the nail bed.

Next slide.

Now, for nail penetration, in essence, we would like to know how much of this information should be in the labeling and how strong it should be. Has penetration of ciclopirox through the nail in microbiologically relevant concentrations to the nail bed at the proximal edge of the infection been demonstrated? And do you think that occurs under treatment conditions?

Next slide.

Dr. Scher gave one of the possible outcomes when one combined antimicrobial products. He anticipated that if one combines the use of this topical preparation with one of the available systemic drug products for onychomycosis, that there may be a great benefit from that. Of course, that's what would be

hoped for, but we know from combined combinations of antimicrobials for a variety of infections, that three things can happen, and two of them aren't that great. In fact, antagonism is not uncommon.

An example known to all dermatologists, of course, is when there is an infection that needs to be treated with penicillin and the patient is taking tetracycline, the tetracycline for acne needs to be discontinued to give the penicillin a full chance of working, because there can be antagonism.

So the question to the committee is how would we want to portray this in labeling? What are the committee's thoughts on this?

Next slide, please.

One possibility -- and it's just a possibility; the committee should suggest the way they feel about this -- "the product is not indicated when systemic therapy for onychomycosis is required. There's no experience to date using product with systemic onychomycosis treatment."

Next slide.

The exclusions. If you look through the

sponsor's labeling, it was in the briefing package. It was at the very end, and the sponsor has addressed many of the exclusions in there. So basically the question is, has it been satisfactorily presented in labeling in a way that clinicians and those few patients who, from time to time, look at package inserts would find it helpful?

Next slide.

We know in the study protocol that there was concomitant use of Loprox cream 1 percent to treat flares of tinea pedis. That was allowed, and I think we saw in the sponsor's data that actually up to 75 percent in one arm of the trial, the patients may have received at one time or another concomitant therapy for tinea pedis. So how would this be crafted into labeling?

Next slide.

Then Dr. Scher, who has written extensively about onychomycosis -- it was nice that the sponsor invited him here today. We invited him to our last discussion on onychomycosis, the FDA did, and one of the many papers that Dr. Scher has he wrote with Phillip Cohen, and it's in the Journal of the American Academy

of Dermatology. It came out in 1994. It's titled, "Topical and Surgical Treatment of Onychomycosis," and he wrote this with Phillip Cohen.

This is a quote from that paper. "Once the decision has been made to treat a fungal infection of the nail with a topical agent, at each visit the nail plate should be trimmed back and the underlying nail bed vigorously debrided." I think that one can find that written in the literature by the hand of other authors, as well. Of course, that's what we heard the sponsor actually did during these studies. So how could this information be crafted into labeling?

Next slide, please.

We know that each subject was provided with emery boards and alcohol swabs, with instructions for the weekly removal. For the investigator, the target nail should be trimmed as necessary in order to remove the unattached, infected nail, to file off excess horny material from the remaining nail surface prior to treatment applications.

Next slide.

One possibility would be actually to portray

the product as an adjunct, and I give this not as an FDA recommendation but because the sponsor's proposed labeling, which you'll find in the briefing package, is silent on the use of these surgical sorts of things. I would present this as the other extreme. I would encourage the committee actually to think of what they would want.

I just present this as the other extreme to this. "Product should only be used as an adjunct to a comprehensive antifungal program under medical supervision that includes," and the first would be "the use of topical antifungal products to treat flares of tinea pedis." The second would be "both trimming back the nail plate and debriding the underlying nail bed at initial and follow-up visits." And finally, "instructions to the patient to use emery boards and alcohol swabs to remove material from the affected nail weekly."

Next slide.

The final set of questions really is under the circumstance the committee would recommend against approval of this product. We certainly would want to

know why that would be and how the sponsor might address that with information. Are there particular studies that the committee would want the sponsor to bring forward for reconsideration?

Those, Dr. Drake, are the issues that we'd like feedback on.

DR. DRAKE: Dr. Wilkin, may I ask you to do one more thing? Would you repeat your comments again that you gave at the very beginning? Remember at the 1994 meeting, there was somewhat of a shift in philosophy about what was needed to judge a product, and you asked us to keep the proceedings of that 1994 meeting in mind for this meeting. Would you repeat those, please?

DR. WILKIN: Yes. In essence, at the 1994 meeting -- and I look around the room today and I think that you and Dr. Scher and I are maybe the only ones who were both at that meeting and here today. Towards the end of the meeting, the committee came up with the recommendation that complete cure did not always have to be a requirement for a very safe preparation for treating onychomycosis. It's in the transcripts, and

the summary minutes are available if someone would like to see those.

DR. DRAKE: I have the minutes in front of me. It says, "Is there a role for a drug which helps to maintain remission," and the committee thought there might be a role. I have those minutes in front of me if anybody wants to look at them.

DR. WILKIN: That is true. I didn't pick out that part because the sponsor did not develop their product in a way where they were seeking remission as an indication.

DR. DRAKE: Thank you.

For the committee, in case you're a little bit lost, I was a little bit lost on the questions. Some of this information we didn't get until this morning. But under your handout, this handout, if you look about halfway through it, you will see the questions for the committee.

DR. STERN: They're also on page 2 of our agenda.

DR. DRAKE: Page 2 of the agenda. I understand, but there was some additional information

that Dr. Wilkin presented that's in this packet that's not on page 2 of the agenda. So I wanted to make sure that everybody had the total information available to them.

The floor is now open.

Yes, Dr. Stern.

DR. STERN: I think it's sometimes useful for at least some of us to share our perception of the data we've heard today, to make sure we're all coming from the same place as a committee member in terms of what we think we've heard.

What I've heard today is that we have a condition that was used in a subset of patients with mild to moderate nail disease, onychomycosis, not people with severe nail disease in any case. Conditions that would make it more likely for that disease to be accompanied by substantial morbidity, such as diabetes and immunosuppression, were reasons for exclusion from the trial. So these were generally pretty well people.

We have a drug that through nail studies -- in fact, I thought it was interesting to call them exploratory. At least as I read the historical

materials, they were originally thought to be Phase III studies as part of an NDA, but the NDA was withdrawn in the early 1990s because there was no efficacy at 24 weeks. So we have a drug that the data show very well that any prediction of efficacy in any subgroup of patients is highly unlikely from either nail studies previously done or from this data presented today.

In a trial which includes an intervention of monthly trimming back, we have no data to say whether or not that increases efficacy or not, but most of us would believe that this extra care would be more likely than not to substantially increase efficacy of a product. It basically makes about between 6 and 10 percent of people with mild disease better at the end of trial.

The one additional fact that we learned is that if you look at people 12 and 24 weeks later, about half of those small number of patients already have evidence of mycologic reinfection.

So we have something that in a subset of patients who are willing to go without other available therapies, I wonder how bad the disease could have been. About 6 to 10 percent of them who get nail trimming

once a month will get better. I think there is reasonably persuasive evidence to me that if you take people with mild to moderate disease, 1 in 15, maybe 1 in 10 who wouldn't have gotten better if they went to the podiatrist or the dermatologist once a month would get better with this.

I think that's persuasive, and it's always the effect of what is the difference between statistically significant and clinically meaningful. I think that, to me, is the real issue for all our deliberations. To what extent can one approve a product when I would guess that its use would not very often parallel the conditions of the experimental trial, particularly monthly visits to the doctor for nail trimming for people with mild to moderate disease?

If they did, that gets me to my next point of view. To me, thinking about a drug like this is very different now than it would have been 10 years ago, when Minoxidil was approved and another agent that there was a lot of controversy about and that I thought a lot about, because of direct consumer advertising, because now it is no longer really a consumer choice about who

pays for this, but it really has substantial economic implications to a stressed health care system.

While I realize our questions are only supposed to be benefit versus risk, I think we have to look at risk as not only direct medical risk, which I'm quite persuaded for this agent is insubstantial, insignificant, beyond detectability in any reasonable kind of gathering of data, one has to think about what are patients foregoing, what are health systems foregoing in terms of risk? After all, if you ask patients to use this drug, you have something with a 6 to 10 percent efficacy that they have to use for more than six months. They have to defer other therapies shown in well-controlled trials to be more effective for a year to see if this is going to work. So there's also the question of deferring benefit.

That's all I'm going to say.

DR. DRAKE: I just want to point out that it's not this committee's job to consider the cost. That's not our role. Our role is to really focus on safety and efficacy in the questions. So I do want to have the committee understand that that is not part of

our role, although I appreciate your comments. I just want to make sure the committee understands that's not part of our role officially.

DR. KILPATRICK: May I ask, Madam Chair, there is no other alternative topical application with these comparable results? Isn't that correct? There's no other such thing on the market at the moment?

DR. DRAKE: That's my understanding.

DR. STERN: In the United States.

DR. DRAKE: There is a fungoid tincture that's out there.

What is the status of fungoid tincture? Was that through this committee? Does anybody remember? It's OTC, but did it ever come through this committee at any point? It was never prescription that converted to OTC. It was always OTC. Fine.

DR. ABEL: I don't know the answer to that. But may I make a comment that many of these OTC products are being used similarly to how this would be used, and we don't have any comparison studies with fungoid tincture or other topicals that are used to maintain remission following systemic antifungal therapy, or even

prior to consideration of systemic antifungal therapy. So we don't really know, because the patients weren't studied in the same way or treated in the same way, with monthly debridings, et cetera.

DR. DRAKE: So then as far as we know, the answer is -- Dr. Kilpatrick, that's a very good question. In fact, this would be a niche that is a void niche at this point.

DR. KILPATRICK: I share much of the feelings that have been described previously. But again, from a legal point of view, we're required -- and I'm reiterating what you said. Is this drug safe and effective? I believe it's the American public's decision as to whether to buy a product, assuming it is well described in the package as to its experience, even in randomized clinical trials.

DR. DRAKE: Because of the time, I want to make sure that we try to answer the questions, and we're running a little late. I have no problem with that, but we don't want to run inordinately late. I would ask all the members of the committee to please keep your comments focused and aligned to the issue at hand.

I'm going to go right through the questions.

Excuse me, Dr. McGuire.

He can have the floor any time he wants.

DR. McGUIRE: Thanks.

DR. DRAKE: It helps to be a VIP. What can I tell you? He's the previous chair.

DR. McGUIRE: I have two questions related to efficacy. Is the clearing ever disproportionate to the rate of growth of the nail? That is, is an infected nail ever cleared by the treatment, or are we looking at the rate of growth of new nail? Is the product holding the infection static so that it no longer invades?

I thought I would get an answer to that question by looking at the Study 312 Loprox individual profiles, and I thought that the data in the Loprox-treated patients would run from -- or the curves would run from sort of northwest down towards southeast. Instead, most of them appear to be running pretty much west to east, as is the case with the vehicle. In other words, I don't see major changes in the slopes of the curves, but I'm not experienced at looking at this kind of data.

I thought that those data would then be simplified by looking at the LOWESS lines, and again it looks, from those plots, as if the efficacy of the product is small compared to vehicle. But I'd be happy to have someone who is expert at interpreting this kind of data help me with that.

DR. DRAKE: Dr. Kilpatrick, could you address that?

He's our statistician.

DR. KILPATRICK: You asked for short answers. No, I can't.

(Laughter.)

DR. DRAKE: Thank you. You mustn't take me quite so literally.

(Laughter.)

DR. KILPATRICK: One of the defects of the LOWESS line comparison is it does not show confidence limits around those lines, showing whether there was a significant difference towards the end of the treatment period. I agree with previous speakers that one has to consider clinical significance rather than statistical significance. I am persuaded that this drug is shown to

be effective statistically, but I again repeat that if we use the complete cure criterion, only at most 10 percent are cured, and as we've heard, on a very small sample there is a high relapse rate.

I have waffled enough and not answered the question.

DR. DRAKE: Well, that's all right.

While you're thinking about the efficacy, I think there's probably consensus around this table that safety is not an issue with this drug. Is that an appropriate consensus to draw? Is there any dissension from that?

(No response.)

DR. DRAKE: All right. So the answer to Question 2, Dr. Wilkin, is that the committee feels that this drug does not have any problems with the safety profile. It would appear to us that this is a safe product.

Now, while we're still thinking about efficacy, since we're talking about the niche, and this fits very nicely what you just said, into Question 3, do the benefits outweigh the risks, because that's also

kind of tied to safety, and I would like to know if the committee has opinions on that.

DR. STERN: I'm sorry. You lost me. I know that's easy, but can you restate the issue?

DR. DRAKE: I'm moving to Question 3. I want to see if there's any consensus on do the benefits outweigh the risks.

I want to come back to efficacy. We haven't finished that discussion. But I want to talk about, knowing what we know, can I answer some of these questions quickly now, so we know how much time we have for discussion on efficacy.

Dr. Lim.

DR. LIM: I had thought about that. Based on the data presented, yes, I think the benefit outweighs the risk. One may argue is the benefit of a cure between 7 to 9 percent, is it clinically significant enough? I also have the same concerns as Robert, even though we're not supposed to consider the costs. Working in an HMO system, that is still a problem.

DR. DRAKE: I guess I would say that if it's you or your mom that's part of that 7 to 10 percent that

responds, then it's probably more important to you than it would be to those who don't respond. But that's a reasonable proportion of people who might benefit. Is that what you're trying to say in that 7 to 10 percent? In those people, it's important?

DR. LIM: Yes. In those people, based on the data, I think it is definitely -- there is a benefit.

DR. KILPATRICK: We have two very highly qualified representatives of the public on the panel, and maybe they can say whether they think it's representative of cost-effectiveness.

DR. DRAKE: I think that's a good idea.

Please, Ms. Cohen.

MS. COHEN: I don't think you can answer Question 3 until you answer Question 1. You can't separate the two out.

DR. DRAKE: Okay.

MS. COHEN: You just can't do it. I'll give you my answer to Question 3, because I'll give you my answer for Question 1. So if you want to wait, that's fine. But you can't do one without the other.

DR. DRAKE: You're trying to say you can't do

3 without 1?

MS. COHEN: That's right.

MS. GOLDBERG: Because we haven't determined what the benefit is.

DR. DRAKE: I said assuming that there's a benefit to 10 percent, which was what Dr. Lim said.

MS. GOLDBERG: We've got to answer Question 1 first.

DR. DRAKE: All right. Well, so much for trying to get through some of these quickly. Let's go back to Question 1.

Rob, I'm going to call on you, but I'd like some of the other members of the panel to please speak up also. Dr. Stern, and then I'm going to ask some other people to give us their independent opinions.

DR. STERN: I always have an independent opinion.

DR. DRAKE: I know you do. That's why I called on you right away.

DR. STERN: I think when you think about benefit, you have to think about the characteristics of the patients who were treated and the fact that, in

fact, at least there's a trend toward less efficacy as you get towards greater nail involvement. If you remember this cutoff between 40 percent, it was a lower rate of total response by either of the two major efficacy criteria in those who had at least two-fifths of their nail involved than there was among the other.

The other comment I would make that was illustrated by the photograph shown by the FDA is the issue of when I read this manual or these applications and the 10 percent planimetry, I thought that meant 90 percent improvement of the extent; whereas, in fact, as I understand it now, it means 10 percent residual involvement according to planimetry. So someone who went from 20 percent whiteness to 10 percent whiteness, a 50 percent decrease, would have been considered clear by the intermediate criteria if they were also mycologically negative.

So we're talking about, for many patients, perhaps rather small and clinically insubstantial changes. What bothers me about this is you take a drug and you test it in people who are most likely to respond, who don't have much disease to start with, and

you sway it in terms of outcome criteria to even a little bit better get you a statistically significant but not a clinically substantial result, and then you say, well, our hands are tied, it does work better than placebo.

I wouldn't argue that. In this particular condition, in this subset of patients, that is unlikely, without very strong labeling, to be unrepresentative of the people who, when they hear about this drug, are likely to ask their doctors for it, and that's what concerns me. That's not cost. That's the matter of what happens, how drugs are used in subsets of patients, in patients in the general population that are different than the particular subsets who are in a clinical trial.

DR. DRAKE: Ms. Cohen.

MS. COHEN: I have a loud voice. Is that okay?

DR. DRAKE: No. You need to please speak into the mike. Sorry.

MS. COHEN: I have a lot of concerns. Apropos of what you just said, I was in the pharmacy yesterday, and a man came up and asked for something

that he'd heard advertised over television and he wanted to buy it, and it was rather expensive. So this advertising that's directed to the public, we have a great responsibility to see what we do.

In the trials that you have, I have some questions. I don't think there was enough evidence that it got to the nail bed. Secondly, I have no idea -- I would take the worst-case scenario. I don't want to take the best one. I want the worst case, to see what it does with the worst case, because there's such a gradation of who is going to be treated.

The other thing I would like to see is -- well, I guess you drill it or a cross-section of the nail. Maybe you can, from what I understand -- and I'm a consumer now. I would say sure, the top of the nail may look lovely, but what's underneath? I want to know what's happening underneath that nail, and I want to see that it's been drilled or a cross-section and know exactly how efficacious it's been.

I know we can't talk about cost, but it is very important. This direct advertising to the public is a very serious issue, and I'm very concerned about

the effect of it on what people expect.

I see hands raised over there. I'm sorry my German isn't better.

DR. DRAKE: May I ask if it's appropriate to recognize people outside the panel at this point?

You're recognized.

DR. GRIGNOLO: Thank you very much, Dr. Drake. Would it be possible for us to take a few minutes for us to respond on these issues?

DR. DRAKE: Yes.

DR. GRIGNOLO: With some additional perspective?

DR. DRAKE: Yes.

DR. GRIGNOLO: Again, respecting the time of the committee.

DR. DRAKE: Yes.

DR. GRIGNOLO: I'd like to ask Dr. Shuster.

DR. SHUSTER: Can I talk just a little briefly about absorption through the nail? There is perhaps some misunderstanding about this, partly because nail absorption studies are fairly new and not many people do them.

First, the in vitro/in vivo. Most assays going through the skin are done in vitro, because the main barrier is the dead stratum corneum of the nail, and it's perfectly acceptable to use an in vitro system. There is really very little evidence of differences in absorption in vivo and in vitro because it's the dead outer layer.

The second question is the relationship of the inner layer of the nail to the nail bed. Now, strictly speaking, the inner part of the nail, the innermost layer is the nail bed. The nail innermost layer, 20 percent of the innermost layer of the nail is formed by the bed, and the bed is attached to it. So they really are the same thing.

Once you get through the keratin, absorption will be complete because that's no longer the barrier. Now, of course, when there is keratin beneath, as in disease, you have to get through keratin too. But the in vitro studies have shown with this compound that drug penetrates keratin perfectly well. So you'll get perfectly well through any keratin that's there, particularly if it's diseased keratin.

The question of technique of measuring whole nail or clippings, of course you have the option of taking multiple biopsies right through the nail, but that's really not satisfactory. Clippings are fine as long as you wash the material off the top and the underside, and if the findings were due to the material on and under the nail, you wouldn't have gotten the increasing inhibition, once again, with time. That would imply that people aren't washing so well with time.

So I think technically you can say that the drug goes right through, and that takes us to the nail bed, and that the assay methods were quite satisfactory in that respect.

DR. DRAKE: Thank you, Dr. Shuster.

I'm going to call on each member of the committee on this, by the way, so be thinking about your response.

Dr. Mindel.

DR. MINDEL: I know the drug is rapidly metabolized when it's absorbed, but you're using a very high concentration, and you have a persistent low blood

level. Could it be that the effectiveness is due to systemic absorption?

DR. DRAKE: Well, I think they showed data that -- this is just my opinion, but I thought the data was pretty clear that there wasn't very much systemic absorption.

DR. MINDEL: Yes, there isn't much, but there is some, and it's persistent.

DR. DRAKE: Dr. Wilkin?

DR. MINDEL: Nobody answered that question. I just thought this was the time to bring it up, since we're talking about penetration and efficacy of penetration.

DR. DRAKE: Please, yes.

DR. BASHAW: I'd like to address not your question per se, but the last speaker made a couple of points I'd like to readdress.

Regarding use of in vivo and in vitro correlations, in disease states of the skin where the skin is intact, such as hyperpigmentation, yes, one could use in vitro methodology to look at drug penetration. But when one looks at most dermatologic

disorders -- psoriasis, actinic keratosis, other diseases where you have inflammation, where you have disruption of the skin membrane -- in vitro technology, because we're usually looking at cadaver skin, intact skin, is really not a good model. Here, where you have onychomycotic nails, where you have disrupted nail plate, again, its relevance to penetration I think has not been proven, and I want to make that point.

Also, another issue that was brought up regarding looking at the penetration, I think if we look back at the sponsor's own data, they showed a slide where they showed four different levels of nail penetration over 48 days or 45 days, and, in fact, the top three layers had decreasing amount, and yet the bottom plate had a higher amount, which I think does speak to the fact that there was application of drug to the bottom of the nail plate on the ventral side. Yes, it was washed off, but there was some penetration. That would tend to make the data look a little better, and their own data showed that, that you did have decreasing amounts going down within the bottom plate, and also had higher levels, which would be indicative of drug coming

in from the bottom side, which I think goes to some of these issues.

DR. MINDEL: Wait. Could I --

DR. DRAKE: Yes, please.

DR. MINDEL: That also could go along with the systemic absorption coming up from underneath, too.

DR. BASHAW: Yes, it could.

DR. GRIGNOLO: May we respond, Dr. Drake?

DR. DRAKE: Yes.

DR. SHUSTER: Just one quick remark. It's absolutely true that where you're dealing with diseased skin, the barrier is not normal. But in almost every case, absorption is enhanced.

DR. DRAKE: Dr. DiGiovanna?

DR. DiGIOVANNA: I have a question for Jonathan or the FDA with respect to the rationale in legislation involved in approval of medications with respect to the risk/benefit ratio.

If there is a situation where there is a drug that is clearly effective but only in a very small percentage of individuals treated, or only in those individuals who may be treated in a particular way

rather than, let's say, a lackadaisical way that may require a certain rigidity to it, and that drug clearly has a low risk, so it has an effective risk/benefit ratio, then is that a drug that, in general, is recommended for approval?

Or is it, within that paradigm, required that the proportion of patients treated that have that efficacy be very large?

DR. WILKIN: As usual, Dr. DiGiovanna asks these convoluted questions that have multiple pieces to them, and they're always very good. If we only had the exact answer.

What the statutory basis for drug approval requires is that effectiveness be demonstrated. The law really does not speak to what the effectiveness would be, but it says how it must be demonstrated. It must be demonstrated in adequate and well-controlled trials. The statutes also go on to say that a drug must have the effect for which it is labeled. So labeling must accurately be able to portray what is going to happen.

There really is no place in the Code of Federal Regulations or in the Act which says a drug must

have a clinically meaningful benefit. However, it does say that a drug must be safe and effective for its intended use, and because no drug product is ever completely safe, the agency has interpreted that to mean to have sufficient benefit for a possible risk, that there needs to be at least a minimally identifiable clinical benefit. Actually, that's been held up in an important judicial opinion. Warner Lambert v. Heckler has shown that the agency can ask to have a clinically meaningful benefit demonstrated.

DR. DeLAP: If I can just add briefly to what Jon said, because I think this is a fairly important issue that we really want to get the best possible advice on.

DR. DRAKE: Please, yes.

DR. DeLAP: When we're looking at risk/benefit under the law and the regulations, we are really looking at the benefit in the population defined versus the risk in that population. We appreciate that even very safe drugs may have some liabilities for adverse effects. There's no such thing as a totally safe drug. But clearly, we're looking at the balance,

and if it's a very safe drug, then we can contemplate a drug that has a lesser level of benefit than if it's a drug that has a lot of side effects.

There is no threshold of a minimum amount of benefit that you need to demonstrate in the law or the regulations. So I don't think we can point to some rule somewhere that says unless you can demonstrate at least a 5 percent or a 10 percent or a 20 percent, it's not enough. But clearly, there would come a time -- and you could take it to extremes and say, well, what if one person in a million benefitted and you were able to demonstrate that in clinical trials? What would that mean?

So there clearly comes a time when it just lacks plausibility. But the question is, can you ever actually get there? I mean, if it was a one in a million kind of drug, obviously you could never do a study to find that. But one approach is to say that unless you can show the benefit in a reasonably sized study, then it can't be very much. But again, there's nothing in the law or the regulations that says that we have to honor a particular threshold. We just have to

look at it in the context of the risk that the drug has and see if there is a benefit that outweighs the risk.

DR. DRAKE: Okay. So I think we all understand. I'm just going to repeat my understanding so I make sure I understand. There's no minimum level, per se, of percents that have to have a response. Rather, if it's in a subset of patients that it might respond to, if this committee deems it effective perhaps in a small group of patients, and it's safe, then there's nothing to preclude this committee from addressing the areas of concern perhaps through appropriate labeling. Is that a correct assumption?

So we can address our concerns about -- I think everybody on the committee at least feels it's safe. We've gotten that sense of the committee, and my guess is that we're kind of variable on our response to effectiveness. I think everybody understands it's a small subset. But it's also my understanding that those issues could be addressed through proper labeling.

DR. STERN: May I ask a brief question?

DR. DRAKE: Just a minute. I'd like to ask them if this is correct.

DR. DeLAP: I believe that that fairly represents what we're saying. Again, I would emphasize what you just said, that it does depend to some degree on the ability to label -- well, it depends critically, actually, on the ability to label a product appropriately, if that's your determination.

DR. DRAKE: All right. Fine.

DR. STERN: Just a labeling question to clarify this.

DR. DRAKE: If it's just a point of clarification, but I really want to hear from some other members of the panel.

DR. STERN: We're all familiar with black box warnings in terms of safety. Has there been any comparable mechanism for labeling efficacy, sort of a black box warning, this has only been shown to be effective in the following conditions, and having that in a way that it's not buried on page 3 in small type but, in fact, prominent in a way that we have black box warnings in terms of safety for many drugs? Is there any mechanism for that in the agency?

DR. DeLAP: I think the specific issue of

black box warnings, of course, addresses safety.

DR. STERN: But I mean big type, up front.

DR. DeLAP: But the level of prominence that things are given in labeling obviously can be addressed as we feel appropriate.

DR. DRAKE: Fred, in the interest of time, I'd like to have your opinions. I'm going to come around. I've heard from Rob, and I'd like to have Fred, and I'd like to come around the table.

DR. MILLER: What exactly is the question?

DR. DRAKE: I want to talk about efficacy.

DR. MILLER: Efficacy. Well, the efficacy is certainly limited to a very small subgroup in the data that Dr. Bashaw gave us.

DR. DRAKE: Can I back up? I'd like you to address efficacy, risk/benefit, and labeling all in the same issue.

DR. MILLER: Okay. I don't have a problem with the risk/benefit. But the efficacy is limited to a very small subset, and the data that Dr. Bashaw just gave us was 186 patients, 12 who were clinically cure, mycologically and clinically, with relapse in six of

them. So we had six out of 186 patients who were clinically cure at 12 and 24 weeks after the study was completed. That is a very small subset.

I think we need additional data. I think the one question that came up that's really pertinent is if this were to be used in conjunction with a systemic medication, would that be enhanced, and I think that study needs to be done, and only the sponsor would be able to do that.

I'm also concerned about the amount of material in the keratin, because this is the hanging edge which is being looked at, and this is where the medication has been applied. I think we need to see good nail bed studies to really look at the penetration through the nail.

So it's efficacious, but in a very small group.

The labeling issue, I think it has to be black boxed, that indeed this was efficacious in only 3 percent of those patients who were studied, because with advertisements, everybody is going to want to use it if it's advertised that way.

The nail trimming is a real issue. I mean, that is an art, and patients cannot trim their nails. You need podiatric nail clippers to do it, which we have in the clinic, and neophytes don't do it well. I mean, residents, when they're beginning, do not trim nails aggressively enough and properly. So you need the proper equipment, and then you need the technique if you have the proper equipment in hand.

The other aspect to the labeling was that in the studies, they were going onto the adjacent skin 5 millimeters, and then in the sampling labeling here it was just application to the nail. So does that make a difference? If I don't put it on the adjacent skin, and then there's the risk of irritation, am I indeed going to get the same effect? So there can't be a difference in the way it was done in the study and the way the patients apply it.

DR. DRAKE: Dr. DiGiovanna?

DR. DiGIOVANNA: This is one of those typical sorts of issues that the FDA likes to bring in front of the committee, where they give us information that answers some of our questions and just raises a whole

lot of additional questions.

I think there's a great need today that's been demonstrated by a lot of industry and a lot of advertising for addressing onychomycosis and nail dystrophy. Patients want this, and some patients need it because they have other medical conditions either now, or they will develop other medical conditions as time goes on and they get older where having this condition will pose additional risks of secondary bacterial infection and the like.

We do not have any demonstrated effective topical therapy. So I think there will be a great need for this, for one that would be effective in a large percentage of patients.

I believe that the studies here demonstrate efficacy, but again only in a small percentage of patients. It raises the issue of how does one define efficacy. Clearly, there's a difference in the terminology between the FDA and industry, and there certainly may be a difference in what the clinician and the patient would like to consider effective treatment. If a patient has an uncomfortable nail or a nail that

they are unable to cut, and they are then subsequently, after three months of treatment, able to cut the nail or no longer have discomfort wearing their shoes, that to them may be an acceptable response.

I think that the pole here, as I learned from Joe McGuire, may have been set in an area that is a little different than most people would accept. I think it may be a little higher. I think that since we don't have a topical treatment, I think efficacy was demonstrated here. I think the preparation is clearly safe. I think that probably through labeling, one would be able to address the fact that only a very small percentage of patients received a very substantial benefit, but I think we've done that before with drugs like thalidomide, with Accutane, and certainly many other drugs where it's clearly indicated that a very small percentage of patients may accomplish efficacy.

So I think we're in a situation where either we could ask for additional studies to look at other populations, or we could consider this on this basis as an approvable indication if the package insert were to specify all of the issues that the committee would be

concerned about.

DR. DRAKE: Ms. Cohen, I saw you shaking your head a minute ago. Did I not let you address your issue? Do you want to answer these three questions? Because I certainly don't want to overlook anybody.

MS. COHEN: That's very kind of you.

DR. DRAKE: Could you get your mike a little closer to you?

MS. COHEN: Again, this is a real dichotomy of the commercial interests versus the consumer interests. I have a lot of problems with direct advertising to consumers. If someone hears something, or someone else says, "Look, it cured mine, it will probably cure yours," I am not comfortable leaving the discretion of clear packaging to, if you'll forgive me, a commercial interest.

As a consumer member, I'm here to be worried about consumers, and if they would put on the package "only beneficial to a small group of people" on the front, but that's not going to happen. That is not the real world. The real world is very different than what's in this room, and I have to express it as

profoundly as I can. I can't possibly, in good conscience as a consumer member, vote for something when it's going to help a small amount of people, at this time knowing that they will direct advertise to the public. I've said it all.

DR. DRAKE: Okay, fine.

Rob, do you have anything else to add? Then I'm going to go on around the room. I thought you two had addressed it, but I saw Ms. Cohen shaking her head, and I thought maybe I'd made a wrong assumption there, and I didn't want to.

MS. COHEN: Thank you very much.

DR. DRAKE: Oh, you're very welcome. Please raise your hand if you think I haven't given everybody a fair shot at this.

Ms. Goldberg.

MS. GOLDBERG: My perspective at the moment is slightly different than Susan's.

DR. DRAKE: I don't mean to interrupt you, but may I ask the committee members to please keep their comments to themselves at the mike until you're recognized, so that we can all hear Ms. Goldberg?

MS. GOLDBERG: I'm torn between the unmet need for the patients, as some people have already identified today, and then seriously misleading the public. I was hoping that we could do something different in the labeling that would really maybe make a difference and that wouldn't be a naive gesture. So normally I think of package inserts as being directed at physicians, and I was wondering, if we go ahead and approve this thing, if there could be a separate labeling for consumers that identifies the scope of the effectiveness of this drug. That's something I just wanted to throw out as an idea, and I don't know if we have that kind of flexibility.

DR. DRAKE: Let's ask them.

DR. DeLAP: There are products that have patient package inserts specifically for advice and information for people that are using them, in addition to the prescriber information.

MS. GOLDBERG: Have they ever been evaluated as to either their usefulness or effectiveness or if they make any difference? Or is it just tossed in the garbage?

DR. DeLAP: Well, it's hard for me to give an off the top of my head response to that. I think they have been used generally in special circumstances. Again, I don't think I can give you any kind of a blanket answer right now as to how effective they are, which I think is what you're asking.

MS. GOLDBERG: Okay, thanks.

DR. DRAKE: Dr. Lim.

DR. LIM: Just to try to follow the format that Jon has given to us, I think in terms of the efficacy, I think definitely it has been shown that there is efficacy. My reservation has been that the number is small, as I mentioned before, but clearly it is statistically significant, and I think probably clinically significant in that small group of patients.

Question number 2, the safety profile. I would agree with everybody that this is definitely a very safe drug. The benefits definitely outweigh the risks, again keeping in mind the small number of patients.

Assuming that you want us to answer the product labeling question, you're assuming that Question

number 4 is a yes. Is that correct?

DR. DRAKE: I guess I want you at this point to please address -- I think if we move toward approval, it would clearly be, at least from what I'm hearing at this point, with very definitive comments on labeling. But we won't actually address the content of the labeling unless the committee votes to approve. But the committee could vote to disapprove, too. So for now let's say the specific content of labeling, but keep in mind you do have that prerogative if you vote to approve, to have very specific recommendations regarding the labeling.

DR. LIM: Absolutely. Then I do have a reservation about labeling. One is that the study was done, as I think Fred mentioned before, with 5 millimeter of periungual area being painted. Specifically in labeling, it says not to paint on the periungual area. Is that something that would affect the efficacy? I don't think we know. I understand the rationale for doing so, because of the irritation.

I think the method of removing the medication and the trimming should be more explicitly stated in the

labeling. Right now it is in very, very fine print there that I think most individuals would miss. I am concerned whether the consumer would be using it as it was done in the study. So that needs to be put in the labeling very, very clearly.

DR. DRAKE: Joe, Dr. McGuire.

DR. McGUIRE: There are many interesting questions --

DR. DRAKE: Can we get his mike on?

DR. McGUIRE: Maybe it's intentional.

(Laughter.)

DR. LIM: To be seen but not heard. That's what happened.

DR. DRAKE: That's not a bad policy.

(Laughter.)

DR. GRIGNOLO: Dr. Drake, a quick point of clarification.

DR. DRAKE: Yes.

DR. GRIGNOLO: In the European studies, Professor Baran has a quick sentence.

DR. DRAKE: Professor Baran, we've not heard from you all day. Please.

DR. BARAN: Robert Baran, France. I would like to say that in the European studies, the tissue surrounding the nail was not painted. I would like to add also that the nail was not trimmed, and by chance, our results were better than the results from the States.

DR. DRAKE: Somehow that's not unusual.

(Laughter.)

DR. DRAKE: Dr. McGuire.

DR. McGUIRE: Thank you very much. What I was mumbling a few minutes ago was that we have an interesting combination of events here. We have a very good safety profile --

DR. DRAKE: May I have one member at a time, please?

DR. McGUIRE: Me?

DR. DRAKE: Yes, you. You have the floor.

DR. McGUIRE: Okay. We have a very fine safety profile. We have an unmet need. So that's a good combination. Unfortunately, we have very limited efficacy under optimal trial and grooming conditions that are not going to be met in the community. What

Professor Baran just said is very important.

Those three elements are not the most troubling to me. What is most troubling to me is that the clinical photographs that we saw can only represent a very few patients represented on pages 9 and 12, on those linear graphs of clearing. The other thing that bothers me is that the two populations that probably most need a product like this are the diabetics and immunosuppressed patients, who were intentionally excluded from the studies. You can be sure that once this medication is approved, that that population will be treated with the drug, and I don't think we have safety data on those two special populations.

So I find several issues here that are concerning.

DR. DRAKE: Thank you.

Dr. Kilpatrick? I'm going to pronounce it correctly here in a second. I can't pronounce your name or John's name today. We're having a little trouble here. It's the mike's fault, it's not me.

DR. KILPATRICK: Thank you for taking time to enter my report, so I will be brief. I'm in favor of

approval, but I doubt whether if we do so and put all the recommendations for labeling, whether the sponsor will want to market it, because it may be inappropriate.

(Laughter.)

DR. KILPATRICK: Dr. Abel, who has talked about OTC tinctures that are being used, I think this will be preferable to those. I take the point that was being made, that in many patients' minds partial success may be satisfactory, and I'd like to ask, because there's been an implication that this substance works for some but not all, does this imply that there's a subpopulation of individuals for whom there'd be a higher percentage of success, complete success, or is it simply unknown? At the moment, it's simply unknown.

So I'm in support of the sponsor's application with appropriate labeling to be discussed.

DR. DRAKE: Thank you.

Dr. Mindel.

DR. MINDEL: I have nothing to add.

DR. DRAKE: Wow, that's brief.

Dr. Abel.

DR. ABEL: I agree that the sponsor has

demonstrated efficacy, limited efficacy for mild to moderate disease, but there are a lot of qualifications. There is a very long time for demonstration of effect, and possibly this is related to the rate of the nail growth. I'm not sure if I missed the answer to Dr. McGuire's question or not, that it would be interesting to have the data stratified as to the age of the patient or some investigation as to nail growth rate.

DR. DRAKE: Elizabeth, let's ask them to answer that question right now, because it's been asked twice. I think something that's been asked twice, let's get somebody to give us a quick answer to that.

DR. LEVY: In terms of age, it was stratified in patients above I think 50 years, and below 50 years had equivalent efficacy rates of the active relative to the vehicle. So we did not see an age effect.

To a couple of the other comments, it is true that we noted in the protocol that insulin-dependent diabetics were excluded. Non-insulin diabetics were included in the trials, if that's of help to the committee.

Regarding the disease severity, you saw some

data earlier that it was stratified by area of involvement. Dr. Scher made some comments as well that that is not always reflective of the degree of disease in that some patients we saw with relatively modest areas were very difficult to treat with a lot of lateral involvement. There were quite a large number of patients included with that geographically difficult to treat disease.

DR. DRAKE: Dr. Abel, does that help?

DR. ABEL: Thank you.

DR. DRAKE: Okay, go ahead. Please continue.

DR. ABEL: There appears to be a substantial recurrence rate, and I would envision this product to be used perhaps indefinitely to control recurrence rate. If that is being done, then what are the implications as far as systemic absorption?

I think there definitely is an unmet need. Not to reiterate, but this does represent, onychomycosis, a reservoir of infection for the skin. So I think this would be an important adjunct despite its limited efficacy so far.

That's all I have right now. Risk is not a

concern to me, and I think there has to be some -- the labeling will be addressed, and I think post-approval studies may be necessary as part of the approval.

DR. DRAKE: Dr. Jordon, we haven't heard from you at all this morning.

DR. JORDON: I don't know that I have much more to add than what's been said. I do think some of the studies --

DR. DRAKE: A little more into your mike, please.

DR. JORDON: I'm sorry. I think some of the studies are somewhat flawed, and maybe some of these need to be repeated along the comments that Dr. Miller made in terms of the penetration into the nail.

I think in selected patients maybe some nail biopsies and really looking at the levels would be helpful, at least in terms of the penetration of this, because I'm not convinced with what I've seen here.

I think it's a very safe drug. It's got limited efficacy. I would be very aghast if this were advertised as a cure, and I think that's in the labeling part, where I would see we want to concentrate our

efforts.

DR. DRAKE: Okay.

Yes, ma'am.

MS. GOLDBERG: One reason I'm thinking about approving is that everybody is saying it's so safe, and then Joe just made the comment that -- you were suggesting there were certain populations that should be getting it who might not be getting it. I was wondering if you could just elaborate on that a little more.

DR. DRAKE: Please, Dr. McGuire.

DR. McGUIRE: I just made the point that two populations that were excluded from the study, insulin-dependent diabetics and immunocompromised individuals, that's a lot of people in this country, and those are the people who need the drug. We assume that the safety profile for those two populations is the same as it is in the populations who were tested, but we don't know that.

MS. GOLDBERG: We don't in fact know.

DR. DRAKE: Fred, and then we're going to go to vote.

DR. MILLER: Lynn, could I ask one more point

for clarification?

DR. DRAKE: You bet.

DR. MILLER: John had asked earlier again about the experience in other countries, because we go back to '92, and France was approved it says I think here in '94 or '95. Maybe Dr. Baran would comment. Are they using this in an ongoing way, and has it been really efficacious? What have they done with combination medication?

DR. DRAKE: Dr. Baran, the question is what is your opinion from use in European countries? Is it effective? Is it safe? Are you still using it? Et cetera.

DR. BARAN: Yes, we are using this drug for several years. I was the main investigator in France, so I saw all the investigations in Europe. First of all, it's absolutely safe if you don't paint the periungual tissue. Second, we have tried now in some countries, mainly in France, to combine mainly terbinafine plus this drug, and we have much better results than terbinafine alone, and of course this local drug alone.

We have also tried to paint the nail twice a month on patients who have been cured, and we have got a very, very little rate of relapse. I have no data to give you, but this is my experience.

DR. DRAKE: Fine. Thank you.

Now what I want to do at this point -- John?

DR. DiGIOVANNA: Could I just ask one additional question of Dr. Baran?

DR. DRAKE: Yes.

DR. DiGIOVANNA: The one question I tried to ask before about efficacy I still don't have an answer to. That is, in your experience, what is the percentage of individuals that get clear? You said there's a small rate of relapse, but if you treat 1,000 patients for X amount of time -- 6 months, 12 months, 18 months, 2 years -- what percentage can you clear completely?

DR. BARAN: You mean with the drug alone, with the ciclopirox alone?

DR. DiGIOVANNA: Yes.

DR. BARAN: We have gotten roughly 33 percent clinical success, and 7 percent cure.

DR. DRAKE: Okay. Now, here's what I'm going

to charge the committee with. We're going to have a show of hands to give the FDA a sense of the committee. As you know, our votes are not binding, but I want you to realize that if you -- remember, this is three parts. Depending on how we vote on Part 1, you can vote yes or no for Part 1, either way.

Let's take Question 1 on efficacy. I've heard that, yes, I sort of like it, it fills a niche, and I sort of think it ought to be out there, but I have some concerns about labeling. You can vote yes on Question 1 of Part 1, and if you do, if it passes, when we get to number 4, if this actually passes the committee, then we will absolutely take up Part 2, the labeling. All right? If you vote no, then we will go to Part 3 that says here's what else needs to be done.

Also, if you vote yes, not only can you take up the labeling, but you can also, in Question 2 there, you can take up what additional studies in Phase IV would you like to see done.

So is everybody clear about how you can vote and what can be done with the vote? No. Just vote. All right.

I'm going to start and just go one, two, three, four.

What's the show of hands for approval on Question 1? Please raise your hands.

(Show of hands.)

DR. DRAKE: I count one, two, three, four, five, six, seven, eight, nine, ten, and mine would be eleven.

Let's look at number 2, safety. Please raise your hands.

(Show of hands.)

DR. DRAKE: One, two, three, four, five, six, seven, eight, nine, ten, and I'm -- I'm sorry, Ms. Cohen. Did you vote?

MS. COHEN: You didn't have my vote for the first question.

DR. DRAKE: You voted for or against?

MS. COHEN: I voted against.

DR. DRAKE: That's what I thought. I have you down as against.

Let me repeat Question 1, please, so it's very clear for the record. I didn't announce the

opposing vote. So I assume if you didn't raise your hand on yes, you were opposing, but that would not take into account abstentions. So let's start with Question 1 again.

Please, all in favor raise your hands, and hold them so we can count them.

(Show of hands.)

DR. DRAKE: One, two, three, four, five, six, seven, eight, nine, ten, and I'm eleven.

How many vote nay?

(Show of hands.)

DR. DRAKE: One nay, and I guess there are no abstentions.

Now let's go to Question 2, please. How many are in favor of Question 2? Please raise your hand.

(Show of hands.)

DR. DRAKE: Fred, are you voting? Is that your hand? I'm sorry, I couldn't see it.

One, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve.

Any abstentions?

(No response.)

DR. DRAKE: Any nays?

(No response.)

DR. DRAKE: Okay, Question 3. Do the benefits outweigh the risks? Please raise your hand if you say yes.

(Show of hands.)

DR. DRAKE: So we have one, two, three, four, five, six, seven, eight, nine, and I'm ten.

How many are opposed?

(Show of hands.)

DR. DRAKE: One opposed.

How many abstentions?

(Show of hands.)

DR. DRAKE: One abstention.

Number 4, final vote. Does the committee recommend that this be approved for the treatment of distal subungual onychomycosis without lunular involvement due to dermatophytes or a subset of distal subungual onychomycosis due to dermatophytes?

Please raise your hand. All in favor?

(Show of hands.)

DR. DRAKE: One, two, three, four, five, six,

seven, eight, and I'm nine.

Negatives, please?

(Show of hands.)

DR. DRAKE: One, two, three negatives.

Any abstentions?

(No response.)

DR. DRAKE: All right. Okay. This passes.

Now we're going to move to Part 2, which says basically if the answer to Part 1, Number 4 is yes -- by the way, this is simple majority. Is that correct? This isn't even a binding vote. This is a sense. So we'll move on to Part 4, then -- I mean to Part 2.

Does the committee have specific recommendations regarding product labeling? I'm going to give you what I heard, and people then please add to what I heard.

I heard that the labeling must point out that this is not a cure. I heard that loud and clear. I heard that the labeling should point out that this is a small percent of patients, that the labeling must point out it's small. I heard it suggested that you might have a separate patient package insert for the patient

in addition to one to the doctor. I heard that the labeling should point out that it is an adjunct to therapy. I heard that the labeling might need to point out other things that are done, such as trimming, does it need to be trimmed and whatnot.

Now, from here on, it gets fuzzy. These are things that I heard loud and clear. I'm not sure I heard everything. May I have comments on what else I missed?

Ms. Cohen, and then Rob, and then I'll go right around the table.

MS. COHEN: The studies have not been done in conjunction with other medication, and there should be some note to that. Also, Joe's question about people who have diabetes. I think there are so many other things that have to be taken into consideration, because it's not been tested with anything at all, except itself.

DR. DRAKE: Then that would come under one of your recommendations for the second part of this, other studies. Okay, fine.

MS. COHEN: But may I say that patients don't

necessarily read the contents. And, in fact, sometimes they don't get it when they get their drugs from the pharmacy. So I think these have to be put down, like you do food labeling, a label on the box that says --

DR. DRAKE: So I hear a recommendation for some black box labeling. All right.

Dr. Stern.

DR. STERN: I think two points that you've made, but perhaps stated just a little bit more positively. I think the label should be absolutely clear and explicit that the available data about efficacy, in addition to it being limited, are in the face of the technique of monthly trimming, and it's only been used in patients with rather limited disease of the characteristics as described. So I think, as opposed to talking about those, I think that should really be up-front and emphasized.

DR. DRAKE: Okay. Anything else?

Fred.

DR. MILLER: I don't know if you mentioned this, Lynn, but certainly the method of application, and also the way you clean these nails, how periodic is

going to be the cleaning of the nails.

DR. DRAKE: Okay.

John?

DR. DiGIOVANNA: You mentioned that this would be used as an adjunct to therapy. I think somehow we would want to have that worded a little different.

DR. DRAKE: So maybe I misheard that, then. Okay, strike that.

DR. DiGIOVANNA: Well, I think the idea is not that you misheard it. I may have heard the same thing, but I think that implies that there is effective therapy, like systemic therapy, and this is an adjunct to that. I think what I heard was that this was studied in conjunction with a specific program that involved topical debridement or a variety of things, and also involved a procedure of repeatedly removing, but not necessarily every day.

We did get a copy of a proposed package insert that had really very little information with respect to -- for example, it says daily application should go over the previous coat and should be removed, but it doesn't say how it's removed. If it's removed

with soap and water, if you tell them to remove it every day, does that mean they shouldn't wash with soap and water every day?

So I think there are a lot of specifics, and the only data we have really are the data that were accumulated in these studies. So that's probably what would need to be described as to how this information was collected, how the efficacy was demonstrated, in conjunction with the monthly debridings, et cetera. So I think that somehow needs to be constructed in the package insert.

DR. DRAKE: Fred?

DR. MILLER: I'd just like to make one more comment about the insert for the patients. I think it has to be in bold bullets, not in narrative form the way the inserts are generally. I mean, it just has to be bam, bam, bam, and as few as possible, but to cover these things that are really important. Otherwise they just won't get read.

DR. DRAKE: John?

DR. DiGIOVANNA: We hear about things and then we talk in terms, and I think the terms we're

hearing about are patient inserts, package inserts. But what Jonathan said was labeling. So, for example, with respect to another situation in dermatology with Accutane, labeling is really not just the insert, it's actually the way the drug is packaged, and patients really hate the fact that they need pliers to get open the packaging that has this stick figure of a pregnant woman with a big X in front of it.

So the package itself could be conceivably labeled, or something else could be done so that patients wouldn't be misled that everyone who uses this is going to get cured, or that has that information.

DR. DRAKE: And that might help address Ms. Cohen's concern, to make it as obvious and visible as possible.

DR. MILLER: Exactly.

DR. DRAKE: Fine.

DR. McGUIRE: Briefly, one of the before-and-after photographs from Dr. Scher will nullify any packaging insert. All you have to see is a diseased nail and a clear nail, and that's the end of the information.

DR. DRAKE: Ms. Goldberg.

MS. GOLDBERG: I don't have anything to say.

DR. DRAKE: Henry.

DR. LIM: Just to reiterate what I had said before, I think in terms of the package insert it should be more specific in terms of the trimming, in terms of debridement, in terms of the cleaning of the nail.

The other part is that if the company is going to do direct consumer advertising, I think that should be reflected, the obvious limitations should be reflected, including the cure rate.

DR. DRAKE: You know, as chair, I've not asked about this direct advertising. I've heard a lot from the committee, though, about direct consumer advertising. Does this committee have any sway with what you guys do? Are our comments adequate for you? I mean, you're hearing what we're saying, and this is adequate? Okay, fine.

Anything else, Henry?

DR. LIM: No, that's it.

DR. DRAKE: Joe?

DR. McGUIRE: No.

DR. KILPATRICK: I'd like very explicitly for the company to record the complete success rate in the two clinical trials that we heard about today, and to not broadcast the European experience, which is in the current package, which I think, with deference to our European colleagues, may be somewhat misleading.

DR. DRAKE: Joel?

DR. MINDEL: I think the packaging should state that there's approximately a 50 percent relapse rate when the drug is stopped, that there will be no effect visible for approximately the first six months, and that it's not effective or not shown to be effective if there's more than -- in looking at this, the FDA I think used 60 percent, the drug manufacturer 65 percent, but there was some discrepancy. But whichever of those figures is correct, that percent involvement.

DR. DRAKE: Okay.

Dr. Abel?

DR. ABEL: I would also like some statement to be put in there about what to do after they complete the course. In other words, address recurrence.

DR. DRAKE: Okay.

DR. ABEL: Whether that's appropriate, I'm not sure in the context --

DR. DRAKE: Well, I think the FDA wants to hear your opinion, and then they'll do their thing with their labels. Frankly, they know far more about it than I do, or probably any of us on the committee. So I think what's important is that they hear your opinions, and then they can take them into consideration as they design the labels with the company, with the sponsor.

DR. JORDON: Again, on the labeling, I think you need to indicate this is not a cure, and I do think maybe some statement concerning these other groups that Joe is concerned about. I am too, because these are the ones who will want the drug, those with diabetes, those with immunosuppression, that those studies have not been performed thus far, so we don't know about the efficacy in that group.

DR. DRAKE: Okay. Now, I'd like to ask the folks from the FDA, I have not addressed each of A, B, C, D, and E specifically. Rather, I've asked for generic labeling. Are there specific areas on your A, B, C, D, or E that you would like me to ask for specific

comments on that you feel have not been adequately addressed?

DR. WILKIN: I think, actually, we've heard comments on each one of them in the course of the discussion.

DR. DRAKE: So that's okay?

DR. WILKIN: Yes.

DR. DRAKE: Let's move to number 2, then. Does the committee have specific recommendations for Phase IV post-approval studies? I think I'll just, for the sake of being different, start on the opposite end of the table.

Dr. Jordon, I'm going to start with you. Do you have specific recommendations for post-approval studies, and should the commitment to conduct any Phase IV studies be required as a condition of approval?

DR. JORDON: I do think some additional studies on nail penetration need to be performed. I don't know that it needs to be a large group, but certainly a significant group to really assure us that the studies we looked at with that level were true. I think the other thing, too, I would encourage them to

maybe consider some studies on this other group of patients that have very severe onychomycosis, maybe associated with diabetes and immunosuppression, since that group is certainly going to want this medication.

DR. DRAKE: Dr. Abel.

DR. ABEL: I would be interested to know what the minimum requirement is for application to maintain response after the daily use. So, in other words, address recurrence, what do you need to do to prevent recurrence.

To be used with systemic treatment for onychomycosis, I don't think we've seen all that data. So that could be part of the post-approval study.

DR. DRAKE: Joel.

DR. MINDEL: If the labeling and packaging looks like what I think it's going to look like, I don't think we have to make recommendations for what the company would want to do in future studies. I think the company would want to do those studies.

DR. DRAKE: Dr. Kilpatrick.

DR. KILPATRICK: In that same light, although I don't think it mandatory, it would be I think very

informative if somehow we could learn if there are indeed subpopulations who would benefit more than others. In other words, the people who do get a complete cure, are they in some way different from other people? An epidemiological study. But that, of course, is outside the brief of the FDA, as I understand it.

DR. DRAKE: Joe, nothing else?

Henry.

DR. LIM: Nothing to add.

MS. GOLDBERG: I just want to reiterate that additional studies be done in the immunosuppressed population and in diabetics.

DR. DRAKE: John.

DR. DiGIOVANNA: I would think that, particularly with reference to Joe's comment, I think that that is a substantial issue. I think that this drug would be used in those individuals who are not good candidates for systemic treatment and who have substantial long-term problems with onychomycosis. So I would think it should be a requirement that Phase IV studies be done in those sorts of populations where potentially there may be an increased risk, and there

may be a large population that will be using it long term. So the diabetic, immune-suppressed, and also those individuals who have more severe disease, I think that would be an indication.

Certainly studies would need to be done for recurrence, and I think a study would be useful to be done, I think the company would be behooved to use a long-term treatment study to acquire more information for higher percentages of efficacy.

DR. DRAKE: Thank you.

Fred.

DR. MILLER: Nothing to add.

DR. DRAKE: Rob.

DR. STERN: Nothing to add.

DR. DRAKE: Ms. Cohen?

MS. COHEN: Since senior citizens sometimes have problems trimming their nails, I'd like to know what happens if they don't trim their nails, what the effect is. That's the real world, too.

DR. DRAKE: Okay.

MS. COHEN: And I'm a senior citizen, by the way.

DR. DRAKE: Fred?

DR. MILLER: Let me make one more comment. In view of the very limited efficacy, and in view of all the discussion here, I would think that this should not be advertised directly to the consumer, that it should only be among the physicians, and then decisions made, because if it gets in Time Magazine, everybody is going to demand that he or she get it, and physicians are going to have to succumb. If they go far enough or around enough, they'll find someone who will give them the prescription.

DR. DRAKE: I will tell you that I think I've heard that, as the chairman listening, I've heard that loud and clear. I think the summary of what I'm going to provide to you, John, and other members is that I think the committee has recommended approval with this but was very stringent on labeling. My sense is -- and please don't everybody start breaking up just yet, because we're not quite done. I want to make sure that the sense of the committee -- and please correct me if I'm wrong -- is that people are approving this, but with many reservations.

I think they've approved it because there's nothing else available in that niche, and so I think people are trying to make something available that's not otherwise available, and it's safe. So it meets those two criteria, but there's a level of discomfort with the response and efficacy. There's also a level of discomfort with this not being used properly. We don't want patients to think this is going to cure their fungal disease, and so it really must be maintained in the hands of experts to advise them on how best to use it.

So there's this huge discomfort with direct to consumer marketing. I don't know what kind of leverage or notions you have, what agreements you can strike with sponsors, but I sense that this is of a great concern to the committee, that there may be a proper role for it in a small subset of patients, but we do not want people thinking this is a cure in a significant number of patients, but it might be something that can be used in this subset as a kind of a niche drug.

Having said that, does the committee agree

with that kind of summary? All right.

Anything else the FDA needs from this committee on this subject?

DR. WILKIN: I think you've been very helpful. You've addressed the key questions at the beginning. We heard the message of austerity, that you have particular elements that you would like to see crafted into the labeling. I'll not go down the extensive catalog and deprive people of lunch for another 20 minutes. We will take all those into consideration should this actually come to approval. I want to put the contingency there, that we'll go back and review this with the review team, and we'll communicate with the committee members. We'll let you know should there be approval. We'll share the labeling with you.

DR. DRAKE: That's very helpful. Should you decide to approve it, then you will share the labeling for additional comments.

MS. GOLDBERG: Should you decide not to, you'll tell us?

DR. WILKIN: You will know the outcome.

(Laughter.)

DR. DRAKE: I want to thank the folks from the FDA.

First of all, I'd like to thank the sponsor for investing your time and resources and money in trying to develop a product that helps our patients, because that's what our goal is, to help our patients. I don't think most people understand how much money is involved. We talked about money, but there's a lot of money involved in research, and so we're appreciative of the fact that you've made an honest, diligent effort to try to come up with something that might help our patients. So we're appreciative and grateful for that.

We're grateful for your expert witnesses taking their time to come share their experiences with us, from all over the world actually, as well as the U.S.

I'd like to thank the FDA for their very nice presentations and for giving us cautionary endpoints for us to consider, because we don't have time to look at the data to the level that you do. So your expertise is invaluable.

I really want to thank the committee for your very balanced, in my opinion, approach to a very tough issue that we had to address this morning. I thought this was a tough one. It probably would not have come before us had it not been tough. I really do want to thank you for being so balanced.

Rob, I really do want to thank you for helping lead the discussion. You've very valuable, and I want you to know that. I think you contribute a great deal.

Dr. Kilpatrick, I want to thank you, too. Even at the very beginning when I said I wanted to keep the questions focused, you guys were good sports, and I do want to thank you. Your input is invaluable.

Finally, I want to acknowledge Tracy for all of her hard work on this. She's a wonderful executive officer.

(Applause.)

DR. DRAKE: Finally, all you have to do is brag on something, and it blows it. I was bragging this morning about being ahead of time, and now look at us. We're in deep trouble. So what I'm going to do is -- I

checked with Tracy, and we don't have any requests this afternoon under the open public hearing to be heard. Now, that doesn't preclude somebody from still stepping to the mike, but since they've not requested it in advance, then I have a comfort level with delaying the opening or the reconvening of our committee to consider the next issue until 1:30. That's 45 minutes for lunch.

Thank you, committee, for your good help.

(Whereupon, at 12:44 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m.)

AFTERNOON SESSION (1:40 p.m.)

DR. DRAKE: We have some invited guests to this meeting, and I would like to make sure that you know that the three presenters, Dr. Belsito, Dr. Jordan, and Dr. Sherertz, have seats at the table. You're invited to join us at the table. You'll see your name tags.

Dr. Jordan, you have a place up here. You're right here. I see Don Belsito there. I see Elizabeth Sherertz there. Beth, right over there.

You see, this is where a previous chair's experience is so valuable. Joe just points out that I have two Dr. Jordans, but they're spelled differently. I'm going to say Dr. Jordan the left, Dr. Jordon the right.

All right. I would like to call this afternoon session of the Dermatologic and Ophthalmic Drugs Advisory Committee meeting number 51 to order.

This open session this afternoon deals with clinical trials design issues for hand dermatitis. I don't think we need to go around and reintroduce the whole table, except I would like to ask our four guests to please introduce themselves.

We'll start over here with Dr. Jordan.

DR. JORDAN: Bill Jordan, Richmond, Virginia.

DR. DRAKE: And you're a practicing dermatologist?

DR. JORDAN: Most of the time.

DR. DRAKE: And you're an expert in hand dermatitis, right? Or in contact dermatitis, period?

DR. JORDAN: And I dabble a little at the Medical College of Virginia.

DR. DRAKE: Okay, great.

Dr. Belsito?

DR. BELSITO: Don Belsito from Kansas City, Kansas. I'm director of the Division of Dermatology at the University of Kansas Medical Center, president of the North American Contact Dermatitis Group, president-elect of the American Contact Dermatitis Society, and have a specific interest in contact dermatitis,

surprisingly, which includes hand dermatitides.

DR. DRAKE: Thank you.

Beth, Dr. Sherertz.

DR. SHERERTZ: I'm Beth Sherertz. I'm vice chair of Dermatology at Wake Forest University School of Medicine.

DR. DRAKE: Can I get you to speak into the mike? I'm sorry, I forgot to ask you.

DR. SHERERTZ: And my practice focuses on occupational dermatitis.

DR. DRAKE: All right. Again, because this is a different session, I'm going to ask our executive secretary, Tracy Riley -- I'm sorry. Oh, Phil, I'm sorry. I just know you so well, and I'd seen you this morning. Please excuse me. Please introduce yourself.

DR. LAVIN: I'm Philip Lavin. I'm a biostatistician with Boston Biostatistics Research Foundation.

DR. DRAKE: And Denise, I don't know that you've been introduced to the group.

DR. COOK: I'm Denise Cook, a medical officer in the Division of Dermatologic and Dental Drug

Products.

DR. DRAKE: Great.

And Susan, I don't think you've been introduced.

DR. WALKER: Susan Walker, clinical team leader.

DR. DRAKE: You were here this morning. You were at the table. You know, sometimes when you know people, you forget exactly where they were sitting during the morning session. Have I missed anyone? Everybody has been introduced today, then?

I'd like to ask Tracy Riley, our executive secretary -- and I just made a mess. While I clean up my mess, would you please do the conflict of interest stuff? Thank you.

MS. RILEY: This is the conflict of interest statement for the afternoon session. The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting

and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

Since the issues to be discussed by the committee at this meeting will not have a unique impact on any particular firm or product, but rather may have widespread implications with respect to an entire class of products, in accordance with 18 U.S. Code 208(b), each participant has been granted a waiver which permits them to participate in today's discussions. Copies of these 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.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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

Thank you.

DR. DRAKE: Now then, I would like to ask Dr. Jon Wilkin to give us an overview of what we're about today.

DR. WILKIN: By way of introduction, I would point out that this morning's deliberations focused back on a meeting that the committee held in September of 1994, and we went back to that and thought about the deliberations of the committee at that time, and the focus there was on regulatory issues in clinical trial designs for onychomycosis. So that's the kind of utility that we harvest from these kinds of meetings, and what we're proposing for this afternoon is a very similar kind of meeting where we talk about the indication hand dermatitis.

There are products on the market right now for corticosteroid-responsive dermatoses, but there really aren't products that are dedicated for hand

dermatitis. So we would like the committee's viewpoints and those of the invited experts who are truly expert in hand dermatitis and contact dermatitis to consider the issues about clinical trial design to reach the indication hand dermatitis.

I'm not going to go through each question. There is sort of a linearity to that. However, of course, the chair often will take things out of order, in the order that you think is best for the discussion purposes. But we would like comments to these questions, and also comments to questions perhaps we haven't asked that you think may be important for us to know about for studies for hand dermatitis.

DR. DRAKE: Dr. Wilkin, I was one of the participants in one of those 1994 meetings, and what I can tell you is that for many years we heard that none of us know the criteria until we sit down at this table, whether it's a sponsor or the participants, and frequently sometimes the FDA staff themselves. So I think your initiative to try to define some of this prospectively, so that everybody is on a level playing field, is to be commended. I've seen it make a huge

difference in many areas already, so I look forward to this session.

Dr. Wilkin, I'd like to congratulate you and the FDA for this initiative. It's very important to define things prospectively, because then we all know what we're doing. And I want to thank our guests, our consultant experts for coming, because an integral part of this is to have the experts tell us what are the pros and cons, what's good, what's bad about a study, what should we be using as markers and indicators, and what shouldn't we. I mean, there's a whole list of questions, but you're here to help the FDA and our group with what are relevant measures.

We've done this in many areas. We've done it in onychomycosis, for example. We've done it in -- Jon, tell me some of the other areas.

DR. WILKIN: Well, actually, at the last meeting that this committee had under Joe McGuire's chair, we looked at tinea capitis.

DR. DRAKE: And we've looked at psoriasis.

DR. WILKIN: And psoriasis, yes.

DR. DRAKE: We've looked at psoriasis in this

same manner. So it's very important for us to develop what's real and what's not real, thus avoiding some of the questions even that arose this morning. Some of the questions this morning would have been much more difficult to answer had we not had some of that background. So that's the purpose.

Now, having said that, I have no requests in writing for comments at the open public hearing, but I'd like to invite anybody who might have a comment to do so. They must identify themselves and any financial interest they might have.

(No response.)

DR. DRAKE: Seeing and hearing none, then we'll move on to the program.

I think our first presenter is Dr. Donald Belsito.

Do you have slides?

DR. BELSITO: Yes.

DR. DRAKE: And we've got a mike up here for you.

DR. BELSITO: I'd like to thank Dr. Wilkin for inviting me here this afternoon to talk to you about

hand dermatitis, to sort of introduce the subject. I'm going to deal primarily with the prevalence and socioeconomic impacts of the disorder, but also will raise the issue of what is hand dermatitis.

Can I have the first slide?

So again, I'm going to largely be dealing with prevalence and socioeconomic impacts, but I also want to introduce you to the notion of what is hand dermatitis, at least what we know about hand dermatitis.

Part of the problem of talking about prevalence and socioeconomic impact of this disease is that different people define it differently. So I think that's one major problem, exactly what is hand dermatitis.

Is there someone to change to the next slide? Because I don't have the changer here.

In a classic article in 1984, Ernst Epstein said treating hand dermatitis is a challenge because it's not a single entity but an affliction with multiple causes. I'd like to add to that that diagnosing hand dermatitis is a challenge because it's not a single entity but an affliction with multiple, often

simultaneous causes going on.

Next slide.

What is it? Well, if you look at the words "hand dermatitis," it's a dermatitis of the hands, and typically when we talk about dermatitis, we talk about red, scaling, pruritic/burning rashes that, because it's a hand dermatitis, should be localized predominantly to the hands. But how much redness, scaling, and pruritus is needed before you call it a hand dermatitis? Is minor chapping of the hands that we get from winter, is that what you want to classify as a hand dermatitis? Also, how much involvement of other cutaneous sites is allowed before you stop calling it a hand dermatitis and start calling it some other disorder beyond hand dermatitis?

We don't have really good answers to these questions, but I think if you want to look at indications for hand dermatitis, you need to come to some type of operant definition.

Next slide, please.

What is the differential? What I did is I --

DR. DRAKE: Don, I apologize. This is very

awkward. I apologize. We're very sorry to interrupt, but we really have to capture this. Let's try one more time. I think it's on.

DR. BELSITO: There we go. Okay, is that better?

So what I did is I went into Pub Med and I asked them to explode all the different categories of hand dermatitis and see what they came up with, and what you see, in addition to what people who normally deal in contact dermatitis would think about hand dermatitis, we came up with papulosquamous disorders, pustular disorders, infections, malignancies, bullous disorders, and various other classifications that could all be incorporated into what you would call hand dermatitis, although I would caution you against including these.

Next slide.

Among the papulosquamous disorders, the one that comes up most frequently, obviously, is psoriasis, and this is probably the most difficult to get rid of or get out of your classification of hand dermatitis, because quite clearly you can see psoriasis limited predominantly to the hand. I'm not sure that you want

to group psoriasis in with the other hand dermatitides because it can behave differently.

In addition, you can get any of these other papulosquamous disorders, such as pityriasis rubra pilaris, lichen planus, Reiter's syndrome, or secondary syphilis involving the hands, although typically these will involve other body sites as well, which would give you a tip-off that you're dealing with more than just a hand dermatitis. But I think psoriasis is the most difficult to exclude in this category.

Next slide.

In terms of pustular disorders, again psoriasis is probably the most prominent one that you'd want to exclude from this that could come up showing as a hand dermatitis. For those of you who think that acrodermatitis continua is different from psoriasis, that also could appear as primarily a hand dermatitis, as could the pustular bacterid of Andrew, if you believe that that disease in fact exists.

Next slide.

Infectious disorders. I think the big one that you want to be clear to exclude is tinea manuum.

So I think that any protocol that is looking at hand dermatitis probably should have KOH and culture put in to take out those individuals who have tinea manuum. It can look very much like the types of hand dermatitis that you want to be treating.

Other diseases that popped up in Pub Med I think that your average dermatologist would easily be able to differentiate simply on the clinical examination include scabies, herpes simplex, hand and foot and mouth disease, and mosaic warts. But again, these should be easily separable based upon clinical examination. Tinea manuum would require some laboratory investigation.

Next slide.

Among the malignancies, multiple actinic keratoses, Bowenoid keratoses, and radiodermatitis can look very much like a hand dermatitis to the untrained eye. But again, I think that your average practicing dermatologist should easily be able to differentiate these from the types of hand dermatitides that you'd want to look at.

Next slide.

Bullous disorders. Again, I think your

average dermatologist should be able to differentiate these, but it never surprises me that I will get referrals for evaluation and patch testing of what ends up being epidermolysis bullosa or an erythema multiform type of eruption on the hands. You clearly want to separate out these diseases, and perhaps phytophotodermatitis as well.

Next slide.

Lastly, the miscellaneous causes that popped up. Actually, perhaps they should be part of your chronic hand dermatitis because you can get individuals with obsessive/compulsive disorders who are excessively washing their hands, setting it up for an irritant contact type of dermatitis.

Frictional dermatitis. Friction is certainly one of the exogenous factors that can trigger and exacerbate hand dermatitis. And then a variety of other factors. So this component perhaps does belong in what you want to look at as hand dermatitis.

Next slide.

So, needless to say, the disease is multifactorial. It's often both endogenous, things like

atopic dermatitis or a psoriatic tendency, and exogenous, things in the environment that the patient contacts. I think those of us who deal with hand dermatitides all believe -- and I'll be interested in what Beth and Bill have to say -- that the appearance often changes over time, as does the diagnosis rendered. It's not unusual for the patient to present to me for the first time, for me to think that they have an allergy, to diagnose an allergy, remove it, and then for me to change my diagnosis to underlying dyshidrosis or an irritant or psoriasis as I follow the patient over time. That goes along with the fact that the disease is multifactorial in most patients.

Another important thing is that once you've disturbed the epidermal barrier, the skin will be more easily irritated by and/or become allergic to other agents that it would normally tolerate. Mild hand washing may cause irritation when the stratum corneum is broken. I think most dermatologists have heard of what Alex Fisher calls the "parabin paradox," where parabins create little problem on normal skin, but when applied to damaged skin can result in sensitization.

So once you have dermatitis of the skin for any reason, it sets it up to become irritated or allergic to agents that it otherwise would tolerate.

Next slide.

So what are the endogenous factors that most people look at when they're dealing with a chronic hand dermatitis? Well, clearly, the most important is atopic dermatitis, and I'll mention that a little bit, and I'm sure the other speakers will bring that up as well. A tendency toward psoriasis can set the patient up for being bothered by friction, nummular eczema, dyshidrosis or pompholyx, keratolysis exfoliativa, which is an otherwise benign exfoliation of the skin of the hands, other keratodermas, and of course the psychosomatic factors, obsessive/compulsive disorders, things like that, which are all endogenous factors that can set the individual up to become more easily irritated or affected by exogenous factors in the environment.

Next slide.

These exogenous factors are primarily the contactants, particularly irritants which include chemicals like soap, water, solvents, the ambient

environment, how dry or cold it is versus how humid or hot. Occlusion by gloves can itself be an irritant. Then there are the allergens, which can lead to either Type I hypersensitivity, the type that we're familiar with, with latex contact urticaria, or Type IV, the type that you do patch testing with to get the exemitous reactions. Then, of course, friction, and I think friction is something that people oftentimes overlook but is an important factor in bringing out hand dermatitis and then prolonging it.

There can be systemic factors, for those of you who believe in systemic contact dermatitis. It's not such a popular notion in the United States, but amongst some of the Scandinavian countries, they believe that a significant proportion of their cases of dyshidrosis or pompholyx are due to ingested nickel or chromate. Infections, of course, are exogenous factors that can set the skin up to be damaged and then to become more easily irritated by contactants, things like underlying fungal or bacterial infection, and then a variety of other factors that can irritate the stratum corneum or inflame the stratum corneum and result in

contactants more easily penetrating and creating damage.

Next slide.

So, with all this as background, when most people talk about hand dermatitis, what are the types of diseases that we're talking about, and what is their incidence? This comes from an overview article by Landow that was published in 1998. He did a review of the literature just looking at how various authors classified hand dermatitis and what percentage of their classification in each of these factors were.

Basically, he reported that irritant dermatitis accounted for about 21 to 35 percent of the reported cases of hand dermatitis in the literature. Allergic was the next most common, at anywhere from 19 to 33 percent; atopic dermatitis at 18 to 36 percent; pompholyx dyshidrosis at 5 to 20 percent; neurodermatitis or lichen simplex chronica as just chronic scratching and itching at 1 to 5 percent; hyperkeratotic or frictional dermatitis at 2 percent, and a lot of people think of this, or at least I think of this as a form of psoriasis. You tend to see this a lot in individuals who have a background family history

of psoriasis or in occupations where there is a lot of frictional trauma to the hand, so they develop these very hyperkeratotic patches over the fingertips and hypothenar and thenar eminence.

Then there was nummular eczema and id reactions. I would propose, though, if you're looking at hand dermatitis, to exclude the nummular eczema and the id reactions. You can usually pick those up by doing full-body examinations. Nummular eczema is usually on the dorsal hands, but very frequently on other locations on the extremities. But you probably would be hard pressed, just on a physical examination, to separate out these other disorders, and these are perhaps the six groups of disease types that you'd be looking at when you're talking about chronic hand dermatitis, at least on initial physical examination and differential diagnosis.

Next slide.

It's said when you're examining the patient that you can separate exogenous versus endogenous because palmar dermatitis is primarily endogenous. So when you see an individual where the palms are

principally involved, you should be looking at the endogenous diseases, things like dyshidrosis or psoriasis; whereas dorsal involvement is primarily exogenous, irritant or allergic. But I'll show you some data that suggest that this doesn't always work for you, particularly the palmar dermatitis.

It's said that vesicles and pustules implicate an endogenous involvement, and I would agree with that; that nail pitting with normal nail folds is endogenous, and that's largely psoriasis. But again, if the nail folds and periungual areas are damaged, you can see pitting in the exogenous irritant and allergic contact dermatitis. Cutaneous involvement beyond the hands suggests endogenous, and certainly you should look at especially the feet, but really all of the skin, including the gluteal cleft when you're examining these patients to classify them, because there can be subtle clues to endogenous diseases like psoriasis.

Next slide.

This is a study that was done by Duarte. It was published in the American Journal of Contact Dermatitis last year, and what she did is she collected

all the cases of hand dermatitis that she had seen in her clinic population in Sao Paulo, Brazil, from 1993 to 1995, and she had a total of 250 patients. Seventy-six percent of these were women, and that's important, because in literally all the studies that are presented, women outnumber men by anywhere from 2 to 3 to 1. So this is very typical of the type of distribution you see when you're talking about hand dermatitis.

But she found that those individuals who had their volar fingers and fingertips involved were as likely to have irritant as allergic contact dermatitis, and that these exogenous factors were much more likely than the endogenous factors. So that's the issue with the palmar involvement. At least in her study, she was not finding that.

She also found that individuals who had atopic backgrounds with palmar involvement were much more likely to end up being diagnosed as irritant contact or allergic contact. The one thing that she did find that was consistent with the truism is that dorsal involvement largely indicated exogenous, and at least among her patients were primarily allergic contact

dermatitis. So sort of as a screen, if the dorsal hands are involved, it would suggest that you're looking at an exogenous factor, allergic or irritant in my experience.

Next slide.

She also went on to note what her initial diagnosis was, and then what her final diagnosis was after full evaluation of these patients, including patch testing. Out of the 250 patients that she originally saw, she thought that 73 had irritant contact, 79 allergic, 94 atopic dermatitis, and 4 dyshidrosis. I'd just like to point out that this classification as atopic dermatitis and dyshidrosis I think is one that's hard to get to. We've been grappling with it in the North American Contact Dermatitis Group for decades, and I'm still not sure that we have a complete understanding.

But when you talk to people -- for instance, I very rarely will diagnose someone with just limited hand dermatitis as being atopic, because it's usually atopic that has secondary irritant, and it's my opinion that the cause of the hand dermatitis is primarily irritant contact on an atopic background.

So if I was looking at these patients and classifying, probably the bulk of these atopics who had strictly hand dermatitis would be up in the irritant category or in the allergic category and not down here. Obviously, Dr. Duarte has very strict criteria for dyshidrosis. There are individuals who have similar strict criteria, other people who don't. The vesicular dermatitis on the lateral fingers and the palms is dyshidrosis for some people until proven otherwise. Other people have much more strict definitions, and she is one of them. So some of her patients other people may have classified down here as well.

Be that as it may, the biggest point on this slide is that here's an individual who is scaled in the evaluation of allergic contact dermatitis. This is what her specialty is. She thought that 79 of her patients were allergic, but when she patch tested them, she changed her diagnosis to 37 of them. In addition, she thought 73 were irritant and not allergic, and when she patch tested them, she changed her diagnosis in about a third of them.

So without adequate patch testing, it's hard

just on the basis of history and physical examination to classify these people, and I would submit that in the United States this is going to be extraordinarily difficult because we have only 23 allergens that are approved and are out there for widespread use.

Despite what the marketing companies may tell you, there are good studies from the North American Group and other people that these 23 allergens will pick up somewhere between 25 and 30 percent of contact dermatitis, and in particular will perform very poorly in certain occupational settings, and much of the hand dermatitis, as we'll discuss later, occurs in the occupational setting. So in the United States, in any protocol looking at hand dermatitis, it's going to be very difficult to separate out these two classifications until there are more patch test allergens available in this country.

Next slide.

This raises an important point, because in 1998 Wigger-Alberti and Eisner wrote an excellent article which reviewed whether barrier creams and gloves prevent or provoke contact dermatitis, and there are a

number of studies that suggest that they help and a number of studies that suggest that they hurt. I would submit to you that one of the reasons why barrier cream studies are so equivocal is that if there's confusion about whether it's irritant or allergic, it may make a big difference, because if a barrier cream stops the vast majority of penetration but it's allergic, a little bit of penetration can cause a lot of disease.

On the other hand, irritancy depends upon dose, concentration, and exposure, and a barrier cream that significantly reduces those may be very effective. So when you're looking at a barrier cream as an indication for hand dermatitis, I think it's going to be very important to separate out the allergics or the irritants.

On the other hand, if you're looking at a medication that will affect mechanism, such as a steroid or another type of medication, that may be less important, because I think that you can think of irritant contact and allergic contact much like we think about the complement cascade. You can get into the cascade by different mechanisms, one by an allergen and

Langerhans cells, the other by an irritant effect on keratinocytes. But once you get into the cascade, the cascade of chemicals that follows after the first 30 minutes to an hour to two hours is very much the same. If your drugs have the same effect, then lumping those diseases may not matter as much as it does for a barrier cream, where it's a matter of the amount that penetrates through that's important for barrier creams.

Next slide.

What is the prevalence? It's real difficult, as you can gather, to come up with prevalence figures, because different people are lumping different diseases into hand dermatitis. But perhaps the best study is one that was done by Meding and Swanbeck in Gothenburg, Sweden in the late 1980s. What they did is they sent out a random questionnaire to 20,000 people in the City of Gothenburg between 20 and 65 years of age, and as only could happen in a Scandinavian country, they got an 83 percent response rate.

Of those individuals responding, 11.8 percent of them claim to have had a hand dermatitis within the past 12 months. Of the respondents, 1,951, which is

11.8 percent, they went out and interviewed and physically examined 1,385 of these, for a total of 71 percent of their respondents. They found a point prevalence during the course of their examination of 5.4 percent. In other words, 5.4 percent of these 1,385 people had actual hand dermatitis at the time. As Duarte found, their female to male ratio was 2 to 1, and the diagnosis that Meding and his colleagues gave was irritant contact for 35 percent, atopic dermatitis for 22 percent, and allergic contact dermatitis for 19 percent.

So basically, about three-quarters of the hand dermatitis that they were seeing fell into these three categories. Again, with the atopic dermatitis limited to the hands, there are some investigators, including myself, who would be inclined to lump those into the irritant category.

Next slide.

They also looked at various risk factors for the development of hand dermatitis, and in descending order what they found, the most likely risk factor was a history of childhood eczema or atopic dermatitis; being

a woman put you at risk; depending upon your occupation put you at risk; a history of asthma or hayfever; and then occupations in various services, particularly hairdressing and health care. Really, you can collapse this, then, into three risk factors: atopic dermatitis or the childhood eczema and the asthma; being a woman; and your occupation, particularly an occupation that exposes you to wet work or solvents or other types of irritant chemicals.

Next slide.

They concluded that much of their hand dermatitis was occupationally derived, and while they came up with all these statistics about the occupations and the types of hand dermatitis they were seeing, they also recognized that the epidemiology of occupational hand dermatitis, and therefore hand dermatitis itself, will vary in different countries depending upon the socioeconomic make-up of that country.

In addition, various people, including Meding's group in the study, noted that it was interesting that the European studies suggested a much higher rate of allergic contact dermatitis, while the

American studies favored irritant contact dermatitis. Again, a plea for more patch testing. I think in part that's because Americans aren't patch testing, because when you look at the North American Contact Dermatitis Group, in fact the vast amount of our occupational dermatitis is allergic contact dermatitis and not irritant, although I'll readily agree that most of the studies coming out of the United States on hand dermatitis are blaming irritant factors and not allergic factors.

Next slide.

So what are the occupations in which you'll see a large amount of hand dermatitis? The biggest in almost all countries are the hairdressers, who have their hands in soap and water and are exposed to allergens like hair dyes and the hair permanents; food service industry, with the soap and water; medical, surgical, and dental; the construction industry, with cement, with all the friction that's encountered, with the ambient effects of the atmosphere; agricultural and forestry, with chemicals; and again, the chemical industry; the machinists; housekeeping and janitorial;

and electronics.

This is sort of a sick building type syndrome. In the electronic industry, they work under very low humidity temperatures. So you get this ambient effect that sets up a lot of electronic computer workers for irritant contact dermatitis year round.

So these are the principal occupations, and I think they're very important ones in the United States.

Next slide.

What is the prevalence in certain occupations? There is not really good data from the United States. The best data, as usual, is coming out of Europe. This was an incredible study that was done by the German investigational group, where they took 15 cities in northwestern Germany and they attempted to enroll every apprentice hairdresser, for a total of 2,570 students. They actually got 2,352 to enroll.

This is another important part of this study. As many studies give you sort of a gestalt feeling of the examiner as to whether things are improved or not improved, they don't really tell you their grading mechanism. They worked very stringently on operational

definitions for grading the skin into mild, moderate, and severe categories, and I'll just show you their categorization for mild and severe, but I think it's important that you look at criteria for defining the severity.

Next slide.

These groups defined mild dermatitis based upon the morphology as being erythema, scaling, infiltration, papules, vesicles, oozing and/or erosions, any one of these involving less than one-eighth of the area of the skin, with some excoriations but few, less than three small pinpoint. Lichenification less than a 4 sonometer square area for both hands, and extremely flat, less than a half millimeter. If there was hyperkeratosis, it had to be over less than an eighth of both palmar surfaces. If there was fissuring, they had to be small, shallow, and less than three on both hands.

Next slide.

In addition to morphology, they talked about where the dermatitis was localized, and for mild dermatitis basically they wanted erythema and scaling to be present but less than four interdigital spaces, or

you could have one or the other involving more than three. The erythema and scaling had to be less than one-fourth of a dorsum of a hand, and less than one-fourth of the palmar surface of the hand, and had to be around fewer than three nail folds on both hands, and be present on less than three lateral fingers, and there should be less than three fingernails involved with discrete changes.

I don't necessarily present this to you as the model. In fact, I think this is a rather cumbersome model and there are probably better ways of grading it. But I do think it's important that you define some criteria for how to classify these hand dermatitides rather than just some global criteria that the investigator thought this was severe, because what I think is severe other people may think of as mild, and I think it confuses me when I read the literature that severe cases went to mild. Well, what does that mean to me? It means nothing.

Next slide.

The severe were, in fact, severe: erythema, scaling, infiltration, et cetera, over greater than a

quarter of the hands; excoriations greater than three large; lichenification significant, more than 4 sonometers, greater than a half a millimeter in height; hyperkeratoses over more than a quarter of the palmar surface; and more than three shallow or deep but large fissures, although they never really define what is large. Is it a sonometer? Is it 2 sonometers? But at least, again, an attempt to give some type of operational definition.

Next slide.

Again, in terms of localization, obviously more significant involvement over the hand of both erythema, scaling, plus another factor. The other could be like excoriations or papules or one other factor to get into the severe category.

Next slide.

Using this operant definition, what did they find among their hairdressers? They looked at 2,352 people pre-employment. They found a whopping one-third had mild hand dermatitis before they even got into the beauty shop, and almost 13 percent had moderate to severe dermatitis. They didn't say what time of year

they were starting. This was northwest Germany. It can be very cold and dry and bitter during the winter months. That could be a factor. But clearly, a significant number of people come to the workplace already with hand dermatitis, and if you're looking at the prevalence, there's no reason to believe that these people were pre-selected in some way.

A significant proportion, much higher than Meding was reporting in Gothenburg, of people have hand dermatitis. One year later, they reevaluated these people, and 600 of the students had dropped out, some of them because they changed schools to other areas of Germany, but some of them because of their hand dermatitis, and I'll give you that number later. But at this point, a year later, almost half of them had mild hand dermatitis, and a quarter with moderate to severe hand dermatitis after a year of doing hairdressing.

Then three years later, another 600 people dropped out. The numbers stay pretty much the same, but there's probably a lot of selection bias because a significant number of these 600 people dropped out because they were having problems with hand dermatitis.

The period prevalence over this three years was almost three-quarters of the individuals they studied had hand dermatitis at some point, and of the moderate to severe type, almost half of them had it during these three years. Of the 449 individuals who left hairdressing, one-third of them said the primary reason was their skin problem. So this has significant socioeconomic impacts on people and is a significant problem both in this country and in Germany, as this study shows.

Next slide.

Here's another study, again done by the Germans. This is in food service workers. This is bakers. They looked at 91 students pre-employment to one year into their employment. Here they found about 3 percent had hand dermatitis pre-employment -- this is moderate to severe -- with about one-fifth of them developing moderate to severe hand dermatitis anywhere from two to four weeks into their training, with the atopics in this group having a 3.9 times relative risk of developing hand dermatitis. So again, the importance of background of atopic dermatitis in hand dermatitis.

They make this cryptic comment in the paper that there was almost about a third at one month that had the hand dermatitis but don't show the number. At six months, about one-third of the individuals had hand dermatitis, again some dropout. Early on, there's a female-to-male predominance, but after one year the female-to-male predominance disappears, but the atopic risk remains in that condition. Their diagnosis on these individuals, again food handlers, irritant contact was far and away the most likely diagnosis, followed by allergic, followed by atopic, followed by dyshidrosis.

So again, when you're thinking about hand dermatitis, these are the big four, and maybe include frictional dermatitis. But if you believe that's psoriasis, you may want to try to remove that from the rubric of hand dermatitis.

Next slide.

Other occupations. Again, health care workers. These studies are all questionnaire studies, and they suffer the usual problems of questionnaire studies, possible overrepresentation and inflated numbers because only those individuals affected will

respond to your questionnaire. This was in hospital workers in Perugia. They had about 85 percent respondents, and 21 percent of their respondents felt that they had significant hand dermatitis that impacted upon their life.

Most of them were women, again the female preponderance, and most of them were what they considered young. Unfortunately for most of us in the audience, young was less than 31 years of age. The young were disproportionately affected by the hand dermatitis. Again, that may be because older workers self-select themselves out and will quit work when they're bothered, or they become more savvy at how to protect their hands. Overall, the diagnosis they rendered was irritant contact.

In an intensive care unit in Birmingham, again a questionnaire study. Sixty-two percent of the 203 people working in the unit responded. Fifty-five percent of the 126 felt that they had a moderate to severe hand dermatitis at some point within the past year that affected their work or their quality of life. Again it was largely women, and again it was largely

young. This group did not render a diagnosis for the hand dermatitis. But again, a very common problem with significant impact, particularly in professions where there's a lot of wet work.

Next slide.

I think this is the last that I'll bore you with, but just to show you that there are lots of other professions out there that don't pop up. This is florists. You may want to put them in the agricultural category. This was another questionnaire study in Lisbon, Portugal. They had 151 respondents, and about one-third of them had what they called major hand dermatitis. Again, this was an undefined major, so I can't tell you what that meant. Seventy-two percent had minor. Note that these add up to more than 100, because they just asked them, "Did you have a major hand dermatitis that affected your life during the past year? Did you have any episodes of minor hand dermatitis?" So it was possible for an individual to check both answers.

But again, a significant number of individuals with hand dermatitis. One-third of those

had underlying atopic backgrounds. So the big risk for this disease is atopy.

Next slide.

To go back to the Gothenburg study to give you some idea of the socioeconomic impact of this very common problem, I'll just point out that of all the numbers I've shown you, the Gothenburg number is the lowest, at 11.8 percent of the population. But of the 11.8 or 1,951 people that they originally got in their questionnaire, they were able to go back and interview 1,238 of those individuals with confirmed hand dermatitis, and of those 1,238, 69 percent had consulted a doctor at least once during the past year for their hand dermatitis. So there's the cost of the doctor's visit. Twenty-one percent of them had taken sick leave from work because of their hand dermatitis, with a mean of 18.9 weeks and a median of 8 weeks.

So there was some profound outliers out here. Again, I think you could only do this in a socialist country like Sweden. When you look at U.S. values, our workers hardly ever take such long amounts of time away from work because of the way our social system is

structured.

Eight percent of these individuals had left their occupation. Eighty-one percent had been significantly impacted socially or in their activities of daily living as a result of their hand dermatitis. Allergic contact dermatitis or those suffering from allergy were those who suffered the most severe problems in terms of having to leave work and in terms of social impact and activities of daily living.

Next slide.

What's the prevalence in the United States, and what's the impact of that? Bottom line, there are no studies. So what I'm going to give you is my best guesstimate of where we may be in the United States.

In 1989, the North American Contact Dermatitis Group published a paper -- the lead author was Franz Storrs -- detailing our patch test results over a five-year period. In that group, it was found that one-third of all the patients we patch tested had a primary hand dermatitis. Of those individuals with primary hand dermatitis, 28.9 percent of them were allergic, 21.6 were irritant. So again, this belies

what most people say about American studies, that most American hand dermatitis is irritant. In a group that patch tested, we actually found more allergic. 10.3 percent of these patients had what were called atopic dermatitis.

Next slide.

Using another study, the NAMCS study from 1990, it was said that in the United States there were six million visits for contact dermatitis in that year. So if you assume that one-third of the North American Group data will be hand dermatitis -- and these are just guesstimates, and I apologize but the data just isn't there -- then you can say maybe there were 2 million visits for hand dermatitis during that time. If you assume that contact dermatitis represents 50 percent of all hand dermatitis, then you can double this number and say there were 4 million doctor visits for hand dermatitis of all types. But again, just guesstimates.

Next slide.

In terms of cost, no good numbers going back to Mathias' article in 1985. So we're talking about 1980 dollars, not 1999 dollars. In looking at an

occupational setting, because most occupational dermatoses are hand dermatitis, Mathias found that 25 percent of workers with occupational skin problems lose about 11 days from work a year. Contrast that with the Swedes, who lose about eight weeks. Occupational dermatoses are underreported in this country by a factor of 10 to 50 times, and using all these numbers, he guesstimated that there would be about $222 million to $1 billion 1985 dollars lost.

So simply assuming that most occupational dermatoses are going to be hand, and I think that's a fairly safe assumption, these are the types of numbers you're looking at.

Next slide.

But you may want to even increase these numbers, not only because of inflation, but only 25 percent of the dermatitis that was seen by the North American Group was considered occupationally related, suggesting that Mathias' numbers should be quadrupled, or giving you an estimate of about $800 million to $4 billion that was lost in 1980 dollars to hand dermatitis in this country alone.

Next slide.

So, in conclusion, we're dealing with a multifactorial disease. I do not think that there are still good definitions. It can be very difficult to get down to a single etiology because very frequently there is not a single etiology. This is a multifactorial disease that can be difficult to diagnose, and is this allergy? Is this irritant? Is this dyshidrosis? Would you classify this as atopic dermatitis?

Well, this was an atopic carpenter who was allergic to colophony and worked with pine board. So certainly allergy was part of this, but you only know to what extent it was part of it once you see how his hands do when he stops handling pine. I can tell you his hands got better but his problem did not completely clear up.

I think at this point I'll turn it over to Bill to talk about diagnosing this problem. Thank you.

DR. DRAKE: Just one second. Are there any questions or points for clarification?

(No response.)

DR. DRAKE: Okay, then we'll turn it over to

Bill Jordan.

Is this room warm to anybody besides your chair? Could you ask to see if we could get it a little cooler in here? Is that possible? It's a little bit warm in here, I think. Post-prandial narcolepsy is bad enough as it is.

Oh, I have somebody saying it's too cold. Maybe we just need a breeze. Maybe it's just stuffy.

Tracy, are you cold? You didn't eat. Oh, gee, maybe we'll leave it alone. Maybe we won't press the issue.

Could we open a door over there, at least to get a little ventilation in here? That might help. If somebody would be so kind as to open a couple of doors for us, maybe one in the back. I think if we just get some doors open, that might help a lot. Maybe ventilation.

Dr. Jordan.

While he's getting rigged up, tell me, Don, why do you think women have this disproportionate amount?

DR. BELSITO: Because I think, despite

women's liberation, women still do the vast amount of work around the home, they're still involved in more occupations where they're exposed to soap and water, and they do most of the food preparation and are involved in those irritants.

DR. DRAKE: This is an issue for clarification. When you gave your slide showing the different occupations, I just quickly counted of the ones it would seem to be predominantly perhaps in men versus predominantly in women, and some were clearly an overlap. But out of the 10 categories you had, it looked like 50 percent of those would be done more by men than women. Did you have numbers on those categories, percentages?

DR. BELSITO: Right. They were pretty much put up there by descending order of involvement. So cosmetologists and hairdressers, which are dominated by women, were a big group. Also, when you look at the medical and dental group, although it's sort of collapsed, the biggest problems tend to occur among the nurses and the aides and not among the physicians. So again, another group that's predominantly women.

DR. DRAKE: Okay, thank you.

DR. JORDAN: We did not discuss our talks before we got here, so I want you to know you're going to get some variations, but not significant variations in my opinion.

This is my 30th year of hand eczema, and things change over the years, and sometimes you change your mind. But everything he says is quite interesting because it's difficult.

I've got to go backwards one. I don't know what I stepped on. No, back to the beginning, one more. I want to go to the first slide. That's the one.

This is what dermatologists dream about at night, hand eczema. Nothing else. The reason is that you got this in the other slide, and I'm not even presenting this as true, because I don't think it is true. But there's so much of an element of truth to it that I wanted to bring out one of my little quirks in life, which is right here, the term "dyshidrosis," which I do not believe in, but it doesn't make any difference whether you believe in it. It fits categories good enough for instruction here.

That is, when you first start patch testing before you get reasonably well known, you're going to discover more allergic contact dermatitis. But the more well known you get in your area, the more recalcitrant patients they start sending, and the harder they are. The harder they are, the rate of relevancy starts going downhill precipitously. And because you've got tertiary type people coming rather than right off the street, it depends where on the firing line you are. I'm sure that private practicing dermatologists see more acute allergic contact dermatitis than I do. I typically see what nobody else wants to see anymore. They've actually seen three specialists before they even get to me.

So you've got to pay attention to who is giving the talk and how deep they are into their arena. As Don said, there's a group in here that I'm strongly biased, and I will tell you what my biases are, that this group is a lot larger than people think it is. To me, there's some evidence that dyshidrosis is just a vesicular wet form of atopy. But it doesn't take away from anything.

There really is an irritant contact

dermatitis. That is, if you're not a closet atopic, and I'll explain what that is, if you put your hand in brine all day long and bring it out, you can develop the most chronic scaling, inflammatory dermatitis that never does anything but do exactly what you did from putting it in, and it will look that way, and it will clear up in two weeks if you get it out of that pan.

But there's a large segment of the population who, if they put their --

DR. DRAKE: I never thought I'd have to dress you here today, but you lost your mike.

DR. JORDAN: They tied that one down to my leg.

DR. DRAKE: I'm putting things in his pocket, and I'm putting things on his tie.

(Laughter.)

DR. JORDAN: But there really is a pure version of every one of these. There's a pure allergic contact dermatitis, cause and effect, the disease lasts two to three weeks and it goes away. There's a pure irritant contact dermatitis, the same way. The disorder lasts a period of time and then it goes away.

There are people who bring in a tendency to have a self-sustained hand eczema, and these are, like the slide shows, they come with a strong atopic background. I have full text hand charts dating back to 1988, and I can tell you that people will be hands for two or three years, and then two or three years later they're feet, and then they rock back to hands again. They're still doing the same job.

In fact, these people are the ones you have to follow for 10 and 15 years, and they evolve like a soap opera story. They're into this for four years, and then you meet them on the street and they no longer have hand eczema, it's now on their feet. Then when they're 70 years old, they come down with explosive exfoliative dermatitis all over. So hand eczema is part of an intrinsic eczema, and it's typically what I usually refer to as a closet atopic. The difference is this portion right here, which is a pure version of it. This frequently kicks off that mild, subliminal irritation to blatant irritation, and then they are now sustained in this sort of pattern.

What do these people do? They anoint or

ameliorate their problem constantly. So they can get allergic contact dermatitis because they're the users of the world. They're the ones who bring in bags with eight or nine or ten items in it, and this is where you can get most of, I found, the relevant contactants. You will definitely get some from the workplace itself, but it's often traceable to things like formaldehyde, the biocides, and even the fragrances.

If I can have the next slide?

Of all the papers I ever did, the only one that I thought I might redo that I thought wasn't the world's most perfect, accurate paper was this one that I published in about, I think, the late 1970s. I actually looked at about 220 cases of hand eczema, hand dermatitis, and I came to the conclusion that the standard screening tray picked up 16 percent of people that had what I thought was allergic contact dermatitis, and if you took that material away, they actually did well in follow-up. That was 16 percent.

Beyond the standard screening tray, you go in the closet and you just take the stuff they bring, and we can find another 8 percent. So it came up in about

22 to 24 percent, and then the rest of it was this group in here. Well, I think over time our rates have fallen because of the more complicated the cases become to be, and then the rest of them are hand eczema alone, no positive patch test. But there's this very interesting group right in here called Group B. These are people with hand eczema who have both contact dermatitis and intrinsic eczema. They have been putting stuff on it and they do this and they do that, and it's very hard to tell that patch testing makes a huge difference, except to point out some things they're doing that they could stop. In that sense, they may get better.

I was very interested in the discussion on fungal nails, talking about what's a complete cure, because I said, boy, that sounds like us in the patch test clinic. How much is a complete cure, or are they better off having been tested? That is the Group B. I didn't invent the term, but Klaus Malten, in Nijmegen University in the Netherlands, coined the term "hybrid hand eczema," and it is quite true. What Don said was multifactorial, Malten called the hybrid hand eczema, and that is typically an atopic personality, atopic

trouble, in and out of varying atopic states, also subjected to irritants, and in dealing with the problem or at the workplace ends up with allergic contact dermatitis.

So they're all of the above, and that makes it very hard to deal with, but that's quite a common scenario in my opinion.

Next slide.

These are sort of the major preservatives in the United States. The parabins rank least. This one and this one are some of the highest, and these are formaldehyde. These are hand eczema patients who are either closet atopics or dealing with their workplace. They're then going back and getting GoJo in the back of the men's restroom, which may have a formaldehyde-releasing preservative, or they're in a number of other areas in dealing with their problem. So the allergic contact dermatitis is actually an epi phenomena on top of a combination irritant-atopic background.

I think that's one of the real problems that we have, and it's one of the real problems we have with work-related injuries. The workplace and the laws are

written like Solomon. They want you to divide this child right down the middle, this one's atopic and this one's pure allergic contact dermatitis, and they don't recognize any combination, because the way the laws are written is that if an item in the workplace did it, then it did it. Then they want to know why this patient is still going to his mailbox six months later, out of work, picking up his check, and his hands don't look any better than they did the day he left from work. They're still going on just as bad.

So this is a problem of the hybrid hand eczema. It's also the problem we would have in trying to design studies in limiting certain types of diagnoses. This is pretty rare. We only have headache -- that's a pretty generic term -- and backache. Dermatologists have hand and foot dermatitis, which means a number of disorders.

Next slide.

This is an Italian chef in Richmond, a very good chef, and those three fingers hold garlic, and he really is allergic not just to garlic but to the true extract out of garlic. But if he stops work for six

months, you find out that his hands are somewhat better but he still looks like that, and the garlic is long gone out of this man's environment. That is sort of a typical example of what happens, that even if you start off with allergic contact dermatitis, you can even provoke an eczema. You will drive one out, so you can get it both ways. It's a two-way street.

You can have hand dermatitis that's an atopic type that you now get allergic, or you can have some bad allergic episodes, and now if you're a closet eczema, you will sustain the problem for a while.

Next slide.

This is a typical version of splitting and cracking and hyperkeratosis. This is an atopic lady who did have a true relevant allergy. Her husband had a stroke, she kept him in the livingroom, actually, and she fed him thorazine. This was way back when thorazine was in a liquid, and it was on the bottle, and so she got thorazine on her fingers. So she got allergic to thorazine. She was really helped by patch testing getting rid of the thorazine, but she never did totally clear up. She had sustained eczema for a very long

period of time after an adequate demonstration of even catching her doing it in the right hand and doing everything else with a positive patch test.

Next slide.

This is a vesicular version. Just so you would know, we even bothered to get the extract. This is allyl isothiocyanate, which is the allergen in radish. This is a radish extract with that particular chemical, bought from a rare chemical warehouse. But you see it's vesicular. She's a salad maker, and she quit salad bar work after that and still had a hand dermatitis for some many, many months to years, because I heard about her from her friends, who said she's still having problems. I said she couldn't. After I wrote her up in the British Journal of Dermatology? She couldn't continue to do that. Well, she did.

(Laughter.)

DR. JORDAN: Next slide.

This is a typical pattern, and it also fits psoriasis, because psoriasis will do the same thing. Sometimes they're exceedingly difficult to tell apart. In fact, there will be times when they look like eczema

and other times they look like classic psoriasis. They are the thenar eminence of eczemas. They are very patchy, and there are some clues as to what contactant would hit in that way. I mean, she's not a golfer or anything.

There are some patterns in the intrinsic eczemas that are quite consistent at times. There's the stigmata version, where you just have it right dead in the palms, or you have the thenar eminence version, and then the patchy discordant areas on fingers. It's very common to jump a finger that's actually more used than the finger that it's on. So the fourth finger can get totally wiped out, with the third finger and the fifth finger looking fine. They look just wonderful. So the atopic type has some odd patterns that are not explainable any other way.

Next slide, please.

This is an entire palm. Often it will have a line right across before the wrist. It abruptly looks like it's palm skin that has a problem. You can't even smear a contactant that cleverly. It'll go in a number of other places, but this is a typical one of the palm,

and I agree, the back of the hand a little more. I tend to favor them, although there are some palmar allergic contact dermatitis. You tend to favor the endogenous or intrinsic dermatitises of the palm.

Next slide, please.

That's a palm. I just wanted to show you some non-steroidal treatments. This is just PUVA as a non-steroidal, because that's basically -- as we speak today, it's either prednisone, topically or orally, and photochemotherapy will also bring about resolution, and that's one of my hobbies, the home photochemotherapy of hand eczema.

Next slide.

This is another typical version, splits and cracks, and then there will be three or four decent fingertips, and then this thing takes off back here very severely. A lot of times it's a hand eczema that doesn't make sense from the pure topical standpoint. Then later you'll find that if you meet this woman two years later, it's down on her feet or she had it on her feet as a child. That's not an uncommon story, particularly in the atopic, that they had it on their

feet. The rest of the family is riddled with asthma and hayfever, but this is the only one of the siblings that has eczema.

Next slide.

There's another PUVA-treated set of hands, just to show you a non-steroidal way of dealing with it that's exceedingly hard to do, and do the training and everything.

Next slide.

You see how spotty? This is an atopic that happens to urticate with poultry. If you drag white meat of chicken across her, she'll whelp up, but she's an atopic with a Type I allergy, which is very common in the latex glove scenario. These are typically nurses that are atopic with hand dermatitis that get the latex allergy. It exists in other areas. It's fish in some countries, and this is chicken. You can get it to meat. These will urticate, and they have patches of chronic eczema.

Next slide.

These are what I wanted to show you. This is a typical fourth finger, but look at the pads of these

two as compared to the others. Then they take off again here. So it's got an irrational pattern to it, particularly the intrinsic eczema types, which I call basically atopic. I could go all day long on why I believe most of them are, but I do believe that these people start out being mildly irritated and then thrown over, and now they have their own self-sustaining intrinsic eczema.

Next slide.

This is the thenar pattern again that we get in the intrinsic eczemas that are non-contactant, in my opinion. You can see how clear that hand will stay, and they'll tell you that it stayed this way for two or three years before it moved somewhere else. Well, where was the rest of the hand in the two or three years if it was doing that? That's typical of a pattern. Sometimes you'll get just a wrist pattern with this pattern right here.

I'm one of the believers that nummular eczema is atopic dermatitis in the coin-like position. You can cut out a lot of these people if you do like you skin a deer. Take their skin off and pin it to the side of the

barn door. That rash that has this crazy pattern is actually nothing but round rings draped over fingers, or the palm side of the hand. So there's a strong nummular-looking component, but you have to imagine skin spread out and not just look at it straight down. It has a strong nummular component.

Then if you see them a year or two later, then they may have nummular dermatitis. You have to sort of remember that any time you're looking at a hand eczema for a month, it's sort of like one section of the CT scan. That's just one short visit for a chronological problem that lasts for years, and the people who see them a year later will wonder what in the world you were writing about when they read your description of the problem.

Next slide.

There are my wrist people. See the thenar, then the wrist, then the wrist, then the thenar eminences again. Now, you try to come up with a contactant other than maybe a formaldehyde, but what in the world is happening to the rest of that hand if this problem has been going on for two years? How does the

rest of the hand stay so clear? So the ones that I call the atopic background or these intrinsic eczemas had these kind of odd, crazy patterns that nothing else will duplicate.

Next slide.

The splitting drives people crazy. That's what really brings most of them in. These things right here really hurt, with the inflammatory component and the hyperkeratosis. Then when they dry out for weather or other reasons, they'll put a rent or a tear in here, and these are quite hard to deal with. In fact, some of these people do as well on the psoriasis medicine, Soriatane, or one of the retinoids, because the retinoids have a preferential dehyperkeratinizing factor on the hands and feet. So for a little dose, you get a lot of slimming on the hands and feet, and that actually will make some of them do very well.

But this is typical of what you might get in a mechanic. He rebuilds carburetors and he's got this problem, but the injury just never lets them do better because the atopic eczema is an isomorphic disease. It comes where injury and friction are very dominant.

Next slide.

This was just a florist. I second the motion on the floral people. They and the hairdressers are nightmares. The Peruvian Lily walks away as the single big allergen in the floral ostromaria or whatever. But if you see one of those come in, you know right away that they're into Peruvian lilies. Then the thing is that they move them, and two months later or three months later they're still doing as bad as they ever did. They'll do bad for a year, and that's probably because many of them are atopics who get allergic, so they're hybrids.

Next slide. I think that's it. That does end it. But I think you can see that we don't vary that much. We have a different take on hand eczemas a little bit, but it's basically quite a difficult area, and it's also fraught with frustration in trying to make them do well. If you see them within six weeks of a problem, you'll probably be the hero. If you're the third man on the line three years later, forget it. You will not be the hero of this disorder.

Any questions?

DR. DRAKE: Thank you, Bill.

Do you have any questions for Bill?

(No response.)

DR. DRAKE: All right, Beth, let's do you. Then we'll do break, and then we'll come back for full discussion. The consultants, we want you to all stay, of course, for the discussion, because I'm sure there will be questions for you then.

DR. DiGIOVANNA: Lynn, can I ask a question while Beth is setting up?

DR. DRAKE: Sure.

DR. DiGIOVANNA: I think it's a short one, I don't know. Just with respect to terminology, in my career there are people I've interacted with who have found my use of the term "eczema" as offensive. There's one very famous dermatologist who I work with specifically who would kind of get riled up. I have for my training a gestalt or a concept of the term "dermatitis" and the term "eczema," and you've used both of those terms, and I wonder what they mean to you.

DR. JORDAN: There was an old journal, Transactions of St. John's Dermal Society. I think

Calnan said eczema is like jazz, it means different things to different people. I usually reserve it for the more weeping ones. Then we have an oxymoron, chronic eczema, which you cannot have. The problem is in the hierarchy. Dermatitis is too non-specific, where you could visualize that they went through an acute phase, even though the disease is many times chronic. They go through usually at the onset or at some part, it does get rather inflammatory and juicy or sticky.

But I agree. It's kind of like mycoses fungoides. We cannot seem to get rid of it. It's entrenched. But dermatitis is even more non-specific. I say hand dermatitis a lot, but I'm also very guilty of saying the eczemas. I try to tell residents that that's just the way we are. But it technically means "weeping."

DR. DRAKE: Thanks, Bill.

DR. SHERERTZ: I will use the term "eczema" and "dermatitis" to mean the same thing, and that is one of the problems, that some people use eczema for atopic disease of the skin, and some people use it more generically. So, to me, eczema and dermatitis just

means the action is in the epidermis and it's red and, depending on the stage, if it's acute there may be blisters, if it's chronic it may be thickened and red and lichenified and scaly.

I think it is a description, not a diagnosis. So I'll be fascinated to see what kind of criteria can be developed.

If you didn't before you sat down this afternoon, you probably have a love/hate relationship with the whole idea of hand dermatitis at this point. This is a person who fixes furniture, working for a moving company. If you think about it, you probably don't want to use that moving company if that's what he does.

(Laughter.)

DR. SHERERTZ: You can't tell what the problem is here, but he was allergic to the glue. This I think everyone would say, yes, that's hand dermatitis, and this is a chronic stage, with a lot of lichenification, a lot of scale. You don't see a lot of erythema at this stage.

How do I treat hand dermatitis? Well, I like

to know what I'm treating first. So I came up with this "Old McDonald" ripoff -- you know, EIEIO? I use AIAIOU when I'm teaching residents. I put up the fingers and say, "A-I-A-I-O, and then U." All of these have been talked about already today, so I'll try to blitz through.

Atopic is the personal family history of eczema, hayfever, asthma, starting as a child. So, yes, you can have hand dermatitis in children. When atopics get older, they're still atopic, and as we've heard, atopics end up with hand dermatitis because this is where irritation occurs. So I want to know if the patient is atopic as I start to treat because that has implications for what I'm going to tell the patient to expect in terms of palm course and whether we're talking about control or cure. If they're atopic, we're looking for control of the disease.

We've already heard today that eczema begets eczema. Once the skin is damaged, other things can damage it more when they didn't ever bother the skin before, and that includes what they're doing at work, what they're putting on it, and what we're telling them

to put on it.

All of us have had some degree of irritant contact dermatitis, most typically starting this time of year, the coldness, the dryness, the chapping that we all get. Certainly, all of us in health care, if we add the hand washing into that, by the end of a busy week in a practice, we all have irritant hand dermatitis. That usually can be repaired by getting away from what's irritating the skin and putting moisture back in the skin. So on a Friday night, after I've been in clinic all week, I soak my hands in water to rehydrate the skin, and then I put plain petroleum jelly over the hands that have just been soaked to seal moisture in the skin, and by Monday my hands look great. Actually, by the next morning they look great.

I imagine in the government this is a problem a little bit. This is frictional irritant dermatitis from handling paper.

(Laughter.)

DR. SHERERTZ: Actually, if you think about occupational injury, the most common occupational injury these days is repetitive motion injury involving the

joint. Now, if it involves the joint, what's happening to the skin to get it there? So I think mechanical irritation of the skin is a big problem occupationally, and that's part of the irritant in the AIAIOU. So I want to know what the person does for a living, and I want details of how much they do in certain jobs before they're rotated to something else, because that makes a difference in managing the patient and telling them what to expect.

Is there allergy? Well, I think Don said if there's vesicles, he considers it endogenous. I guess I would disagree with that because I think you can see vesicles in the hands and it be allergic. Particularly if I see vesicles on the fingertips and there's a lot of itching, I would suspect allergy is a component. So I'll look for that in the history.

Oops, wrong button.

When a dermatitis goes on longer, again it gets red and lichenified. Here somebody has done a biopsy. I will tell you it wasn't me, because I know a biopsy is not very specific for this and won't help me. What will help diagnostically is the patch testing

that's already been talked about. The location on the dorsum of the hand doesn't really tell me that it's going to be an allergy or not. In this case, it was, as part of it. This is a mechanic who has irritant factors, but he also was allergic to the lanolin in the hand cleaner.

That's A, that's I, and that's A for allergy. Then I want to know if there's secondary infection, because that is something that needs to be treated too, and we know that infection causes inflammation of the skin. So secondary infection, when the barrier is disrupted, is going to make dermatitis worse. So I will look, and if it looks infected, with fissuring, with golden honey-colored crusting, I will suspect that there is infection with bacteria, mostly staph and strep, and treat that systemically with antibiotics.

Why systemically? Because I want to be very careful about what is put on this skin topically, and I don't want to use topical antibiotics.

So that's A, I, A, I. Now O. Don talked about the other things in the differential diagnosis. This is a man who is known to have psoriasis, and here's

another example of the fact that things aren't clean. He has psoriasis, but he also had vesicles. He worked fixing airplanes by gluing them back together, you'll be happy to know, and he had allergy to epoxy, which made his psoriasis worse. So sorting that out is going to affect his treatment.

Other things, sometimes dermatophyte damages the skin, and then the skin is more prone to irritation. That's documented in the literature. Here is somebody starting with irritation and then gets fungus. So it can go either way. But sorting out these factors is key to treatment.

Finally, we're not going to talk about latex urticaria. Bill talked about somebody who had urticaria to chicken. Urticaria, in its clean sense, will show wheals. But remember, these are health care workers who also have irritation, so they may have a history of immediate itching, but they may not have wheals. They may have what looks like dermatitis because there is a factor of irritant contact dermatitis as well. Here's one of the nurses in our clinic who wore the latex glove, got the wheal, and, of course, I ran and grabbed

the camera, along with the Benadryl.

So the key to treatment I think is sorting out what are we talking about when we're talking about this patient's hand dermatitis. AIAIOU. We can't change this. We can, to some extent, avoid irritants. We can definitely, if we find allergy, make a big difference here. We can definitely treat infection, and these other things need entirely different treatments. This one is modifiable. This one is a little tougher if it's a chronic intrinsic dermatosis.

Treating when it's acute, when there's a lot of vesicles, there's maybe some superficial erosion, treat with antibiotics. And what about topical steroids? Well, topical steroids, I would use an ointment. The reason I use ointments is because I don't want to put ingredients on inflamed skin that could further irritate or set up an allergy. What strength of steroid? Well, when it's acute dermatitis, I'll use a very potent topical steroid. But I also taper the corticosteroid to try to minimize it over time.

I am very specific about what to stop. If I tell a patient, "Use this," and they leave the clinic, I

haven't told them what to stop using in terms of the bath lotion that they're rubbing on their legs with their hands or whatever, and I think that's important too.

We talked about treating infection. In the acute sense, if you're going to use corticosteroids, it has to be enough. It has to be doses up at 40/60 milligrams of prednisone or equivalent for several weeks in the acute stage, and I don't like to use steroids for chronic hand dermatitis, because it's a cover-up.

Removing from work? Well, what was the work? And is there something they can do at work that won't involve their hands? There are also, obviously, socioeconomic factors as well.

In terms of corticosteroids, I mentioned ointment. I will start with mid to high potency. I do think tapering is very important, because just as with other inflammatory skin disease, you can get rebound. Patients use the sample tubes they're given or the tube they have and don't refill it, and all of a sudden stop it, and they'll rebound their dermatitis, and then they'll seek another doctor. So I think it's important

to tell the patient what to do.

It also is important to taper because we've seen, and in Epstein's article he talked about ending up with atrophy of the fingertips from using potent topical steroids to subdue chronic dermatitis.

In general, I don't think over-the-counter hydrocortisone is adequate for acute dermatitis. As dermatitis gets more chronic, I think the vehicle is more important than the strength of the steroid.

Here is chronic hand dermatitis. Who knows? It may be contact with irritation. There is secondary infection to treat. But this needs moisture as much as it needs anything else that we could prescribe.

So for chronic, it's thickened. We heard about using retinoids to combat the thickening. Emollients can be very helpful, and that can save money too.

What about occlusive and other things to do? I'm not a big glove fan. I think if you put medicine on and put gloves on, the medicine soaks into the gloves as easily as it soaks into the skin. So I am not a big cotton glove user. Others feel differently.

There are some concerns about constantly occluding inflamed skin because it seems that you'll sort of make the barrier repair lazy, and so I don't like occlusion constantly for that reason. I want the skin to have a chance to remember what it's supposed to do to repair itself.

In terms of barriers, just like you have to have different gloves for different types of chemicals, you need to recognize that barrier creams, there's not a one-size-fits-all to protect the skin. In fact, barrier creams can make dermatitis worse, particularly in the workplace. They're usually given to someone who has dermatitis, so they're putting something on already-damaged skin.

On the other hand, if you teach people how to protect their skin and use barriers up front before there's dermatitis -- this is another German study in the auto industry. They had a 10 percent prevalence of hand dermatitis before they instituted a hand protection program, and it really made a difference. So protection up front can be helpful.

We've heard about PUVA. Ultraviolet B can

also be used for hand dermatitis. I would never do this without patch testing first and seeing what allergy I could change in the patient. When dermatitis gets chronic and severe and is life-impacting to a great degree and nothing else is working, rather than going to chronic systemic steroids, sometimes I will use low-dose weekly methotrexate, and others have used other types of cytotoxic drugs.

This is another example where it's going to be very life-impacting, even if it's "just a little bit of hand dermatitis," because of the tremendous pain associated with this location.

So I think you get the picture on how to treat hand dermatitis in my version, and let me just show you a very dramatic version of why it's important to sort out hand dermatitis.

Here's a patient who was about to have her finger amputated because of dermatitis, primarily involving that finger but also involving other parts of the hand. She'd had antibiotics, she'd been to doctors quite a bit, she had had studies to see if there was still blood flow to the finger. Fortunately, she had a

dermatology consult who diagnosed allergy to neomycin as at least part of the problem. That was confirmed with patch testing. By identifying the factor in this person's hand dermatitis, treating it with topical steroids and antibiotics for the infection -- that's an A and an I -- she was much better.

So sorting out hand dermatitis can save a lot of money, not to mention function.

But more often we're dealing with this kind of patient, a 57-year-old anesthesiologist who had been told by one of my colleagues, "You have hand eczema, live with it," and that's not very satisfactory to someone who is an anesthesiologist.

These are the patients that we're up against. So think AIAIOU and treat those factors. That's my approach. Thank you.

DR. DRAKE: Wow, that was good. Beth, that finger you showed that looked gangrenous that was subject to amputation, we just had a case like that at Oklahoma, and it just happens one of my faculty happened to be in the hallway, he was scheduled for surgery the next morning, and the ID guy grabbed him and said, "Is

this really what it looks like?" Because they brought him in for an amputation of his thumb. Steve walked in and said, "Gee, are you putting a lot of Neosporin on this?"

No, he said, "Are you putting anything else on this?" And the guy was a farmer from down south Oklahoma, and he said, "Yes, I've been using Neosporin by the tube, and it hasn't helped it a bit." So they treated him, and he went home with his thumb still on his hand. I mean, it was really very dramatic. It just happened to us, too.

Thank you for an excellent presentation.

Questions for Beth?

DR. MILLER: Lynn?

DR. DRAKE: Yes.

DR. MILLER: Beth, what was the anesthesiologist's etiology?

DR. SHERERTZ: Well, this was one of my colleagues who said, "Hand eczema, live with it." Of course, I patch tested him and he was allergic to thiuram, an additive in the rubber. So changing gloves made a big difference for him.

DR. DRAKE: Other questions specifically before we take a break? Yes.

DR. DiGIOVANNA: Did you ever use cyclosporin systemically or topically?

DR. SHERERTZ: I have not.

DR. DRAKE: Have you?

DR. DiGIOVANNA: No, but I've heard of other people doing it.

DR. JORDAN: Oh, it works.

DR. DRAKE: It does?

DR. JORDAN: Yes, because it works in atopy.

DR. DRAKE: All right. What we're going to do now is, since we're almost caught up on time, thanks to the efficiency of our presenters -- I want to compliment you. Thank you. You got us caught up even though we had a late start. Let's take a break and let's reconvene at 3:30. Then we'll have the questions and the discussion. Thank you.

(Recess.)

DR. DRAKE: Can I ask the committee to reconvene? We're running a little late because I've been running around looking for Tylenol. Thank goodness

for one of my fellow physicians who had some Tylenol in her purse. I can't imagine why I have a headache.

Okay. Now, as soon as I get everybody seated here, Joe suggested I could dump a glass of water again and get everybody's attention. That works.

(Laughter.)

DR. DRAKE: All right. We've had some very nice presentations.

Dr. Wilkin, would you talk to us about the questions and what kind of information the FDA would like from this committee?

DR. WILKIN: Well, essentially, we would like the committee and the experts to think about the clinical trials and the endpoints that will be used in those clinical trials for sponsors to develop products for the indication of hand dermatitis. So the first set of questions is really what is hand dermatitis? What kind of indication would that be? What needs to be excluded? I think Dr. Belsito mentioned that these patients should have a KOH, and if it's positive, that person would not be a candidate for this kind of a trial. So the first is to get an idea of who belongs in

the group "hand dermatitis" that should be studied.

Are there special subsets of hand dermatitis that either should be excluded or definitely included in that group?

Then we would like to know what kind of endpoints are clinically relevant. It's obvious if someone has hand dermatitis and they get complete clearing, we can all pick that patient out as having success. But because this is generally not an infectious process or just an infectious process but multifactorial, many of the patients will be benefitted by something less than complete clearing. I mean, I don't think we can hope the vast majority are going to get to that 100 percent state. So what we'd like to know is we'd like to know what are other levels of control that would be useful to achieve.

Then finally, how long should patients be followed before actually looking -- at what kind of time window should they be assessed for these endpoints? And if they do achieve complete control, how long should they be followed post-treatment to look for relapse?

I think there were probably other questions

that came to mind. The members of the committee may want to add other questions to this list.

DR. DRAKE: All right. Thank you.

Rob?

DR. STERN: In thinking about hand dermatitis, to me one of the big differentiations and one of the things that's specific about hand dermatitis is really the plantar surface of the hand. I just wondered, when I think about how I'm going to treat acute inflammatory dermatosis of the dorsum of the hands in terms of therapy as opposed to ruling out causality, it's a very different problem. I think if you look at the majority of the slides we saw, we're really talking about plantar hand dermatitis.

I just wonder, if I were going for a product for "hand dermatitis," to think of it specifically as a hand product, I would really be thinking about the plantar ventral surface, not the dorsal surface of the hand. So I just wonder if we should sort of concentrate on what we mean by the hand, because, after all, everything below the wrist is the hand, and to me therapeutically, differential diagnosis-wise, difficulty

of treating it and clearing it is quite different on the dorsum and on the plantar surface.

I don't know if other people feel the same, but as an outsider, that's a bit my feeling.

DR. DRAKE: Dr. Wilkin?

DR. WILKIN: If I could just clarify one point. Are you suggesting that there should be evidence provided in the NDA that the product would work for both the dorsum and the plantar, or really just the plantar?

DR. STERN: I guess what I'm suggesting is the plantar surface is the tough one. To me, getting an indication for hand dermatitis of the back of the hand is no different than getting an indication for hand dermatitis of the upper arm of the same etiology, or of the left leg. Whereas the criteria and evaluation of the more plantar 55 percent, because it really goes back a little bit beyond the midline, but basically everything forward of that half is different, and you might have different criteria and different ways of looking at it.

DR. DRAKE: Dr. Abel, and then Henry.

DR. ABEL: I think it would be very helpful

to look at the stage and to classify it as acute vesicular, which could be secondarily infected, as Dr. Sherertz pointed out, and needs to be treated with antibiotics, versus this chronic lichenified dermatitis that predominantly affects the hands, as you mentioned, because I think it's treating two different kinds of -- it's two completely different types of treatment when you have the weeping, vesicular, probably secondarily impetiginized dermatitis.

So I'm sorry I might have missed the questions that we're supposed to hone in on here, but I think if a product is to be developed, we need to talk about what stage, what type of hand eczema. I happen to prefer -- I use the terminology "eczema" and just think of it more as an acute, subacute, or chronic, and "dermatitis" to me is a more general inflammation. I think your point is well taken. If it's on the backs of the hands, perhaps that's something that would respond well to treatment. It could be contact type of dermatitis, allergic dermatitis, and maybe we have the answer there, whereas the other tends to be more chronic.

DR. DRAKE: Henry, I know you had your hand up, but are you responding to her?

DR. JORDAN: Both.

DR. DRAKE: Okay, I'll let you respond, and then Dr. Lim. Please respond.

DR. JORDAN: I like that concept of at least keeping it in the same territory in the design. I think it could be plus or minus patch test if you put more of the criteria after you have the duration. In other words, simple allergic people that solve it themselves wouldn't be in it, and I'm not picking a date. I'm just saying they had this thing in the area that he's talking about X amount of time, and that would put us into the -- you'd have the umbrella of these chronic people.

The problem with the vesicular is that often the hand actually is exhibiting both. There are parts of it that are vesicular and other parts that are chronic. That's why I could see staying in the palm that has been explained or unexplained greater than, say, 90 days, 120 days, regardless of the patch test, and it didn't get well. So it sort of would pick up a hybrid type person, because I think that's the most

common kind of hand there is. There's the relevant positive patch test, along with a very confusing picture of why they still keep on doing what they do.

Most hands are one or the other, but frequently you'll see that they'll come in because this finger is acting up, but they're not pointing out the whole rest of the other hand, which is chronic with splits. So you have splitters and crackers and vesiculars sometimes all in the same area. But I'd like to see something moved into the -- if I had to pick out a criteria for who to test a drug on, a certain amount of duration and a certain reach, and I'm not picking the time. It would just get rid of the simplistic problems. That would be unfair, because the real true people out there are these chronic recurring, the same ones that drive the workplace crazy and everybody else crazy, and you can usually say they've had it at least 90 days and haven't shown a twit of doing any better.

DR. DRAKE: I agree that those are the problem cases, but with respect to our mission here, and the FDA's mission, if a company comes up with a new product, even though it's for the garden variety, run of

the mill hand dermatitis that any dermatologist could probably have a shot at clearing up, I don't want to have our discussion limited to the kinds of very difficult cases that our experts end up seeing because you're the last line of defense.

I mean, I think as we look at the protocols, you're going to have some very good new products that are coming forward that are designed to treat the run of the mill hand dermatitis and not these extraordinarily complicated cases. So as you think through your criteria and how you might want to set up a protocol, please keep in mind that we can't just set it up for the toughies. It's got to be for any new product that might come along, and then we can certainly have some extra suggestions for the toughies.

DR. JORDAN: My fear would be you would write it and say we want atopics or we don't want atopics, but we want allergic contact dermatitis. In other words, the message was that even though they all exist, you can't define it by a diagnosis. So you're going to have to come up with some other characteristic that describes the group other than using a technical name for it.

DR. DRAKE: Dr. Lim.

DR. LIM: I'd like to ask the experts if, in view of what Bill presented, that the eruption could move from hand to foot and from foot to hand, whether we should include also the dermatitis on the soles as one of the criteria, or are we going to be adding another layer of complexity and we should just focus in on only eruption as it occurs on the palmar surface of the hands?

DR. JORDAN: Well, I like to treat both. But I think you could, for purposes of a study, you would just pick -- I have no objection to staying with one area. It would have to be noted. I think you could get all the history you need if these are hand and/or feet.

DR. DRAKE: Dr. Belsito I think had a comment on that too, Henry.

DR. BELSITO: Right. I think the problem with that, if you include that in the rubric of the diseases that you want to study and perhaps exclude other diseases, one of the problems is you're going to largely get the endogenous and you're going to exclude all of the exogenous, the irritant allergic causes. So

I think you have to be careful there.

I would say the same thing for palmar involvement. If you restrict your definition of a hand dermatitis to one that principally involves the palms, if that's where you're going, you're going to rule out a lot of the exogenous causes of hand dermatitis. By the same token, you're going to bring in more psoriasis into that. If that's what you want to do, that's fine, but the mechanism for psoriasis may be very different than the mechanism for the types of diseases that we've been talking about, the allergic and the irritant, and even the atopic dermatitis, which is maybe more of a TH2 response than a TH1.

But certainly with the allergic and the irritant, you're looking at sort of the same repertoire of inflammatory cytokines, and even though atopic dermatitis is thought to be TH2, you're also again dealing with a lot of that same type of repertoire that can get affected by a steroid in very similar areas. So I'd just be very cautious about saying you want to look principally at palmar involvement, because a good amount of the hand dermatitis we see is both dorsal and palmar.

But I agree with Rob, certainly it's the palmar that's the more difficult to treat. But I would just be cautious using that as a defining characteristic.

DR. DRAKE: Dr. Abel. Beth, are you responding to the same thing? What I'm trying to do is let the panel members ask questions of the experts, have the experts respond, and then we'll go to the next panel member.

So, Beth, would you respond?

DR. SHERERTZ: I would limit it to the hands for the same reason that Don said about endogenous problems. In terms of palmar surface, when I saw the questions, that's what I wrote down as the part to evaluate, because it's the most symptomatic and it's the one that affects activities of daily living and so forth.

It also, though, when it's on the palms, it's also very much impacted by the occupation, and that can be a confounding factor. So if somebody has an irritant occupation and hand dermatitis involving the palms, their endpoint, it may take longer for them to get there than for someone who is in retail. So considering the

occupation is something that's going to be important as well, I think.

DR. DRAKE: Dr. Abel?

DR. ABEL: I just wanted to make a comment about the feet. In anyone with hand dermatitis, when I was in residency I was always told that we must look at the feet, and I think it's also important to exclude an id reaction, someone with severe tinea getting an id reaction on the hands. So I think it will help us narrow our diagnosis or home in on the diagnosis to examine the feet but concentrate on treating hand dermatitis.

DR. DRAKE: Dr. Stern?

DR. STERN: I have two related comments. One is a question or a clarification. I assume we're asking mainly for guidance in clinical trials, what we think might be useful schemas for evaluating therapeutic agents that are proposed for hand dermatitis.

With that in mind, I went and looked in the literature to see how other people have done it, and there are a number of schemas. They basically have in common looking at desquamation, erythema, vesiculation,

and what they call infiltration in fissures, and having a variety of scales very much like opacity, and some do and some don't consider percentage of area involved.

I would also say unlike psoriasis, where at least with current technology getting good photographs, both for technical and privacy reasons, of all areas is very difficult to go beyond signal patches, the nice thing about hand dermatitis is we saw so well today that in fact this is a very nice disease for global evaluation because you can get good photographs of the hands in any clinical trial situation, and both measure abnormality in planimetric or quasi-planimetric methods that you can't do accurately, at least in most clinical settings, with psoriasis or any other whole body disease, like atopic eczema involving whole sites.

So I would think about here's a place where percentage involvement to me is, in fact, often more correlated -- not that a little finger can't drive you crazy, but in general, often is fairly highly associated with difficulty of treating end morbidity as it applies to these areas, an area you can measure, an area you can have independent panels judge other than the

investigators for additional blinding and independent verification.

So I think I could think about, A, photographs; B, the kind of schemas that have been used in terms of what's going on; and C, both as part of the photographs and clinical assessment, percentage of these areas. I think you can think about a lot of different scales, but to me, in going back to the literature, I certainly didn't have any favorite, but those seemed to be the essential elements for things that might be useful for judging how well a product for this area worked.

DR. DRAKE: Yes, Ms. Cohen?

MS. COHEN: Can I ask a question? If you treat psoriasis on another part of the body, is it treated differently on the hands, or would you use the same thing?

DR. STERN: Hands are tougher and often we'll have to use either more intensive therapy, or, if it's disabling, move to, for example, a systemic therapy, that if that person had that same percentage body area coverage in other areas, A, we probably would have made

it better in another way, and B, we wouldn't have considered it in terms of risk/benefit. But when they're disabled because of their hands, you're willing to take greater risks. So the answer is yes. It's tougher.

MS. COHEN: And I noticed, and I suppose this is an extension of whatever is on the hand, I noticed that some of it went up into the arm. Now, does that, when you clear the hand, automatically take care of the arm?

DR. STERN: No, but it's usually easier to clear the -- assuming you've taken away whatever the precipitant is, especially in allergic cases, it's a lot easier to clear the arm than it is to make the palm better, and that's what I was sort of emphasizing, that to me, what's unique about hand dermatitis is getting this side better, not getting that side better. It's the same as eczema or dermatitis in other areas.

DR. DRAKE: I want to go down this list here. I want to look at the list. Should all the subgroups be studied as one entity, or should they be evaluated separately? Let's look at this question very

specifically.

One of the problems that I see from the experts' presentations is the fact that you are exactly that, experts. If you start thinking about a new product out there, as somebody who has run a couple of clinical investigation units, it's very hard, I think, for non-experts to be as good as you are, because I think the subtleties here are remarkable. I was impressed with the subtleties of the differences, and I am a dermatologist. But to me it was very interesting, there's a lot of subtleties.

The second thing is that not only is it a subtle disease, but I think it would be hard to get people in a matched study unless you used the patients as their own controls.

Let me ask you a question. How many people have the same presentation or a similar enough presentation on both hands that you could use the subject as their own control, treat one hand with product and one with vehicle?

DR. SHERERTZ: Usually, the dominant hand is more severe.

DR. DRAKE: Irrespective whether it's irritant or allergic?

DR. SHERERTZ: Well, it depends. In allergic, like in the garlic finger allergy, it's in the non-dominant hand because that's where the allergen is. So it's variable, and I'm not sure it would work very well certainly in surface area to use themselves as a control.

DR. DRAKE: Dr. Wilkin?

DR. WILKIN: Well, not only are we looking for efficacy in the clinical trials, but we're also looking for safety, and sometimes we're looking at fairly potent topical agents that can become systemically absorbed and have a safety signal systemically. If, in the artificial setting of a clinical trial, you only treat one hand, you're looking at less than what the safety might be under the usual exposure once the drug would be marketed. So we have been pretty much against going down designs of that natural pairing. I mean, it's a very sensitive way of looking for efficacy, but it doesn't give us much in the way of safety.

DR. DRAKE: Okay, very good point.

Dr. Belsito?

DR. BELSITO: Beyond that, it would be very difficult for application. You would essentially have to have someone else apply a topical medicine, because you'd be contaminating the hands in the course of the application.

But I'd like to get back to your first point, and that is separating out the diseases versus grouping the diseases. I think the one thing I tried to stress and I think you saw with the other speakers is that this is usually a multifactorial disease, and so it's going to be very difficult to get a pure irritant group versus a pure atopic group.

So I would argue for looking at a diagnosis of hand dermatitis, but then deciding what you want to exclude. I think clearly you want to make sure you exclude the bacterial and the fungal infections with appropriate cultures before you allow people in. I think clearly you want to exclude the urticarial group, and of course the big one in today's society, particularly among health care workers, is going to be

the latex allergy people. So you want to look at that. Food handlers you'd want to be careful about, the protein contact dermatitis with the fish and the chicken, as Bill showed. So you want to get rid of those groups.

You may want to look at ways of defining out psoriasis by making sure that these people have had all of their skin looked at for other signs that might point you to psoriasis, including having the fingernails looked at very closely for pitting in the absence of any periungual involvement. I think if you've eliminated the infections and you've eliminated the urticaria and you've eliminated psoriasis and other diseases that might involve the hand by looking at all the skin, I think lumping these people is a fair approach to it, because beyond that, even the experts are going to disagree on what these people have.

I may say they have irritant; Bill is going to say it's all atopic that's just been unleashed by an irritant. So you're going to get different diagnoses from different people and it's going to be very hard to come up with any type of matched and controlled group in

that situation.

DR. DRAKE: The order in which I saw the hands were Dr. DiGiovanna, Dr. Lim, and Dr. Kilpatrick.

DR. DiGIOVANNA: My question was addressed.

DR. DRAKE: Okay.

Dr. Lim?

DR. LIM: Actually, Don gave my speech. We were trained in the same place, so I guess we think alike.

The only other thing I would add is that PRP, that it's going to be very, very difficult to treat. But I would fully agree with Don, that those should be pulled out. But beyond that, then we could just treat them all as hand dermatitis and enroll them as a group.

DR. DRAKE: Dr. Kilpatrick?

DR. KILPATRICK: I'm wondering whether we can square the circle by doing both at the same time. So I'd like to ask what the FDA's attitude is to subgroup analysis. It would have to be a very large study in which you'd demonstrate overall efficacy, safety and efficacy, but then permit in the protocol subgroup analysis into the various subgroups as agreed by the

experts.

DR. WILKIN: Yes.

(Laughter.)

DR. WILKIN: We certainly would love to know the stratification. Perhaps one stratification would be palmar involvement and the other would be dorsal, and the question is would one need to reach statistical significance for the two, and I think that's difficult to say at this time. But I have to say, it's very appealing, the paradigm that is being presented.

I mean, to be sure, this is an artificial assemblage of patients who are all presenting with dermatitis of the hands. As was pointed out, the dermatophytids, the tinea manuum, bacterial infections, the urticarial presentations, the food handlers, the psoriasis, those who have pitting or psoriasis elsewhere on their body, that seems to be this group that it's difficult at best to make a diagnosis in anyway. I didn't get that when I was reading the literature before this meeting, but I certainly got that message today. It's sort of a reductive epiphany.

DR. DRAKE: Jon, I have a question, and this

relates to Don. This is to both of you from me. If we're eliminating food handlers, I understand the rationale behind these others, but food handlers, it seems to me the products that might treat hand dermatitis would help food handlers as well as somebody that's touching something else.

DR. BELSITO: I wouldn't eliminate the food handlers. I would just be very cautious when you're dealing with individuals in the food handling occupation to make sure that you're not dealing with what Niels Jorth described as protein contact dermatitis, which typically occurs from poultry, fish, and potatoes have been reported. But it's a particular dermatitis that's IgE mediated. So it's really not the same group that we're looking at.

I certainly would include food handlers. Again, I would just be very cautious when you're dealing with them to make sure that you're dealing with "exeminous dermatitis" and not an IgE-driven process that looks exeminous.

DR. DRAKE: So one wouldn't necessarily want to eliminate food handlers from studies.

DR. BELSITO: No.

DR. DRAKE: But you might want to be sure you document it so that you could pull that out as a subset -- i.e., Jim's comment to look at them to see if there's a difference. All right.

Yes, Dr. Miller?

DR. MILLER: I certainly see what you're saying, Don, and I agree that we have to eliminate the endogenous diseases that we can identify, and we have to be sure there's no infection and no fungal disease, and then you try to get it down to a group, a subgroup, and let's say irritant dermatitis or allergic contact dermatitis, which are the two big ones, and then you throw in the atopic dermatitis.

You might say, well, I want to get a group of patients with irritant dermatitis, but how can we be certain that we don't have an allergic contact? Because, depending upon which center you're in, the number of contact that's available to you in the evaluation for allergic contact dermatitis could be very different than another place where there's a limited number. And then how do we define atopy?

I think one of the big problems we have is the imprecise way we use language. We had talked about this before, and I think in this realm it's especially pertinent with dyshidrosis, pompholyx, eczema, and even atopic dermatitis, atopy. What we've done -- and there are 15 of us in the department, eight faculty and seven in training -- we've gone around the room and said define eczema, define pompholyx, and it's amazing when you finish, you really don't have a standard. Even atopic dermatitis is difficult to identify.

So you do need a subgroup, and I think the important thing is to really describe what you're treating, describe it very specifically, because if you have acute components and chronic components, it's important to say there are vesicles, there is induration, there is lichenification, and then at least you'll know have these factors been eliminated. It can't just be a general term like "dermatitis."

DR. DRAKE: Dr. Lavin?

DR. LAVIN: One of the problems that we're immediately getting into when we're talking about subgroup analyses is that we're going to be getting into

large sample sizes, and large sample sizes mean many different institutions participating, each of which would have to be following some type of standardized patch testing or some type of standardized ruling-out protocol, as we've talked about already.

So one of the key things to be able to even think about such a trial is to have standardization across the leading centers where these patients are coming from. That represents to me a real major challenge in trying to get off the ground, and it's not unlikely to see a trial that might have as many as 1,000 patients in it, because you really won't know up front whether it's just the atopics that you're getting or the irritated patients or combinations of both, and the last thing you want to get is a panel meeting where there are six different claims made, and let's give significance for two of these six, and you wonder if you've just been at a statistics merry-go-round and you've won the three or four just by chance alone.

So you don't want to get into that kind of situation. So the more carefully we standardize up front, the better return we'll have on the quality of

the trials at the end.

DR. DRAKE: Rob?

DR. STERN: Well, again, if the purpose of this is to look at the effective agents in clinical trials, I think we've heard how difficult precise stratification and classification is, and our best hope of mankind is randomization. I agree with Dr. Lavin that the primary endpoint before subgroup analysis should really be, in the patients eligible for the trial as a whole, was there significant effect? And then if it meets that overall test for all people who were eligible after appropriate exclusions, as Don has talked about, then the question is do there seem to be subsets?

But with all we've heard from three different experts and the people around the table, I think it would be impractical, if not impossible, to get cross-center, accurate and reproducible categorization beyond certain fairly evident "look at the picture, and yes, this is hand dermatitis, and we've ruled out A, B, and C." I think it might be useful both to the sponsor and to clinicians if all of those hands, after randomization the treatment works better, to allow them to have

categorized them, and then to do subgroup analyses to see if there are some hints there, but not as a primary reason for approval.

So I think that's one way. It's helpful. I think the clinicians, as long as it's not fudging the numbers and cutting it 18 different ways until you get a P value, if you have a primary grouping that makes it, I think subgroup analyses can sometimes be useful in terms of design of studies and application of the agent.

DR. DRAKE: Don?

DR. BELSITO: Also, in terms of the primary grouping, you've seen that one of the major groups is allergic contact dermatitis, and I think it would be highly unethical to have a patient continue to use a product that you thought they might be allergic to to see what kind of effect you would have on the allergy. I mean, most of these patients are presumably going to have -- and you heard also from Bill that a lot of the allergy we see is an attempt on the part of the patient to treat the dermatitis.

As part of any study, the patient is going to be withdrawn from all the things that they were putting

on. So that component of chronic hand dermatitis is almost, by definition, going to go away during the course of a topical study. So I think it's very hard to isolate and to study all these components because they're usually all involved to some extent.

DR. DRAKE: I have a follow-up question. What would you consider an adequate wash-out period given what Bill had to say about the length of time for response, even if you remove the offending agents?

DR. BELSITO: Well, I think you need to be careful with these people in terms of a wash-out period, because I think it would be cruel and unusual punishment to ask them to stop applying all emollients to their hands. These people desperately need emollients. But I think if you take them away from a product, say for a week, and look at a blank emollient for their use, something like petrolatum, you could have them continue to use that during the course of a study. But you would severely restrict the number of participants you would get if you said, "You can't use anything on your hands for a week." It would be very difficult.

The other issue becomes that there are

certain occupations where they do require their workers to use barrier creams. It's very common in some of the automobile industry, people I deal with, some of the rubber industry. It's part of their occupational safety. So I think that's another issue. If they've had chronic use of a barrier cream, do you want to stop that? That could potentially put them off work during the course of a study. You could lose another group of important patients that you want to evaluate.

DR. DRAKE: John?

DR. DiGIOVANNA: It's very difficult to think prospectively about how to design a study when you know it's going to be used in many different ways for many different products and for many different indications, and then to try to predict how it's going to affect how an ultimate product will be used.

That gets to the issue as to whether you're a lumper or a splitter. What was suggested here I think is eliminating a number of the factors that add very difficult confounders, such as the presence of infection, possibly the presence of an urticarial type of disease.

In other situations when we design trials, there's an interest in including a diverse proportion of the population which reflects how that drug might eventually be used. For example, what is unique about hand dermatitis? In some ways, like psoriasis, we have products that are particularly studied for scalp psoriasis. I've seen that. Would a product that was particularly studied, let's say, for psoriasis of the palms and soles have any different usefulness or utility than for hand dermatitis?

So a lot of the same factors might go into that, and I wonder about the wisdom of separating out psoriasis from the hand eczemas, since that's clinically not necessarily such an easy thing to do in some situations, I think I got from Dr. Jordan, and that very well may be an indication that someone might want if they had a product that was tailored to be used on volar skin. Would that not be also useful for psoriasis, which is probably one of the more common entities that would be involved?

So I just wonder what those criteria would be for inclusion, and inclusion that not only would allow a

uniform study population that several different centers could identify, but that also would be potentially reflective of the population where that drug might eventually be used.

DR. DRAKE: Comments from our experts?

DR. BELSITO: I think one of the things that I alluded to in my talk, as well as one of the issues you're going to need to look at, is what is the product? You may want to treat a barrier cream in the requirements for that very different than you would treat a medication such as a steroid that has a specific pharmacologic activity. So with a barrier cream, you're obviously going to be more interested in selecting out the irritants and the atopics from the allergics and looking at them differently, because the little bit that gets through can still drive the allergy but may be very helpful in minimizing penetration for the irritants, the atopics.

So I think that's one issue: What is the drug or the medicament you're evaluating, and what is its proposed mechanism of action for this group of diseases called hand dermatitis? So that's an issue.

I do think that it's important to try and separate out certainly the infections. I'm less concerned about the psoriasis. You are still going to get some psoriasis in your study, even if you've gone through and looked at all the skin and it's all negative. I think it's embarrassing to physicians who have bounced patients around and they finally get to me, and by the time they get to me, they have the classic elbow and knee sign, and I walk in and I say "It's psoriasis," and they say, "Well, why didn't my doctor tell me this before?" And I say, "Well, how long have you had these placques on your elbows and knees?" "Well, they just developed in the last couple of weeks."

So they were hand dermatitis for a year or two, and suddenly they start declaring themselves. So even eliminating the obvious psoriasis population, you will still get that component into your study. It will just be smaller.

Now, maybe you don't want to eliminate it. Again, I think it's going to depend upon the drug that you're evaluating. It may not be as important for a steroid, but if you're evaluating a barrier cream,

psoriasis can be provoked by an irritant. But my experience with the disease is it's much more provoked on the hand by friction, which a barrier cream isn't going to prevent anyway.

So again, I think you need to look at the disease, the drug that you're looking at as well, how it's supposed to help this beast called hand dermatitis.

DR. DRAKE: Joe?

DR. McGUIRE: One of the commonalities of patients who come to me after being referred from Physician A, B, C, D, nearly all of them are infected. As I looked at the clinical presentations today -- looked at your slides, Don, and looked at your slides -- I would have treated nearly every one of the hands that I saw with those systemic antibiotics. So what I'm suggesting is that, whether I'm right or wrong, we need to take into consideration some early diagnosis and consideration of infection before we get into the treatment period, because most of these, certainly the chronic long-term hand dermatitis are going to be infected, whether they're dyshidrotic or contact dermatitis or irritant dermatitis.

DR. DRAKE: Jim?

DR. KILPATRICK: The other element I heard being brought up but not discussed explicitly was how long should the study continue, and how long should subjects be followed afterwards? This was number 7, actually. But Dr. Jordan and I were talking about a natural history study. I'm not attempting to pour cold water on the feasibility type of study, but there's another element, which is the continued follow-up of these patients if they do develop different symptoms and presentations after various treatments.

DR. DRAKE: Yes, Don?

DR. BELSITO: Well, again, I think that's going to in part depend upon the specific drug and the mechanism in terms of how long you might expect it to act. So I don't think that there's any boilerplate that you can say, okay, you want your study to go on for four weeks, two months.

I think certainly what you'd want to do is to define criteria for degree of severity. The types of things that I look at are erythema, scaling, presence of fissures. I think you can also try and do some Likert

scale for pruritis and burning. You can incorporate that and use those tallies, I think, for global.

But again, I'm always confused by when people say the dermatitis was severe and they got significant improvement, what does that mean? That doesn't mean anything to me when I read it unless I see some criteria for defining what severe disease is. So defining criteria for degrees of severity.

I would let the companies who are coming to you with drugs -- they should have some market analysis, they should have some indication of how quickly they think they can see an effect, and then you probably want to ask them for some type of long-term follow-up -- that may be over a period of a month, six months, whatever -- to see what kind of relapse rates they get, does the disease get reclassified, and what's going on.

But it's very difficult, because you're going to get a number of different types of products coming in for the indication of hand dermatitis, to come up with one boilerplate as to how best to design a study.

DR. DRAKE: Yes, Ms. Cohen?

MS. COHEN: Are there drugs that you're using

now that are effective or not effective, and what can you learn or what do you need to have that is not happening now? Because it seems as though if you've had some experience and there are things on the market, then it should give you an idea of perhaps how you can improve on what you need to do.

DR. BELSITO: Well, there are drugs on the market. Obviously, the steroids.

One of the problems is that a significant proportion of these patients are going to be chronic, and so one of the problems with the steroids, as Beth alluded to Ernst Epstein remarking in the paper, is that a lot of these patients end up with a chronic atrophy from the steroids.

There are things on the market. The response rate in part depends also upon the patient's occupation. You know, the individual that is an ICU nurse that can't take time away from work because of the way work comp is structured is going to clear a lot more slowly than the individual who can take time away from work. The individual who presents with a severe hand dermatitis that doesn't have a lot of exogenous factors

that you can influence will probably clear a lot less slowly, because you can't tell someone who washes their hands twice a day and that's all they're doing to further cut back on hand washing. It's very difficult to do that, whereas if you have someone who's washing them 30 times a day and you can get them to cut it down to 10 times a day, that can have a dramatic improvement on their clearing.

It's such a multifactorial disease, there is no one size fits all here. It's a very difficult disease to deal with and it's a very difficult disease I think to design a generic boilerplate type of study. You almost have to go with the flow depending upon what's the product and looking at that.

DR. DRAKE: I noticed Dr. Abel, and then Phil. Dr. Abel had her hand up.

DR. ABEL: I think one of the most frustrating things about our present treatment of chronic hand eczema is the fact that it improves temporarily with treatment, one can even get clearing, but then with tapering the steroids and discontinuation and just continuing emollients only, they recur again.

So it's only in those people in whom you can take away these trigger factors, these exacerbating situations, and one certainly can't do that with, say, a young woman who's taking care of young children at home and babies at home. I mean, she's washing her hands 10 times a day and involved in child care. That's not listed as an occupation, but it could be -- should be -- and I think you might have to categorize patients as far as what their conditions of exposure to irritants are, whether they can be removed or not, or whether we have to work around these environmental trigger factors.

DR. DRAKE: Phil?

DR. LAVIN: I want to follow up on the point that Susan made regarding the control group, and that's what her question is really alluding to. When these studies are put out and there is a new compound out there, one can't really have placebo controls here. One can't really have emollient controls, either, in patients whose diseases are particularly severe.

So one has a real issue here of what is the choice of a control group? That's a common problem in studies of osteo and rheumatoid arthritis, and it's the

same kind of problem you might face in a psoriasis study or an oncology trial.

So one has to think very seriously about having an active control, and then what would that active control be, and that's not one of the questions that are on the table here, but that's going to be something that everyone's going to have to wrestle with in trying to come up with that first design.

DR. DRAKE: Jon?

DR. WILKIN: Yes. Well, actually, there are choices other than placebo control and active control. There are some variations. One would be where patients who are randomized, and so they could go to the active or to the placebo, have an early escape clause that's built in for safety and ethical reasons, so that if they are getting worse, they're qualified as a failure, and they can rapidly go to something that's active. So I think there are some ways around a pure placebo arm that goes on for many weeks.

DR. DRAKE: Phil?

DR. LAVIN: I guess the problem with designs like that is that if you have a disease like this, where

the response rate or the success rate is 20 or 30 percent and you run a study that might be half a year, 26 weeks, and then you have 60 percent dropout rates in your active group and 80 percent dropout rates in your other group, you run the risk of a trial that really is busted just because of the high number of dropouts on both sides. Then you have noise on both ends of the equation, and it becomes very difficult to interpret. So I worry about having escape clause trials just yet, until the response rates are sufficiently high.

DR. DRAKE: Don, are you responding to that?

DR. BELSITO: Yes.

DR. DRAKE: And then John.

DR. BELSITO: Well, I mean, you certainly could always have an active control, and I guess that would include a mid to high potency steroid, but as Beth pointed out, you'd want to limit the length of time and try and taper off, which, if your study is going to be going on longer than several weeks, is difficult.

However, I would argue that emollients are effective treatment for a lot of hand dermatitis, and having the vehicle to the drug is not unethical, as long

as that vehicle doesn't contain a relatively frequent sensitizer. So I don't necessarily see that, for at least certain drugs, you would need an active control, and the vehicle control could easily be argued to be ethical treatment.

DR. DRAKE: Dr. DiGiovanna?

DR. DiGIOVANNA: I just wanted to address again or bring up one of the issues that Dr. Abel brought up with respect to exposure. This is very like a final common pathway with many different etiologies, and if one was going to look for patients with hand eczema or hand dermatitis, certainly there would be some that would have, for example, an occupational exposure that they may be able to alter, and there would be some that would have an exposure that they most likely would not be able to alter.

I would think that that would be one of the factors one would want to consider in designing a study if you were going to be looking at the effect of a preparation. You probably wouldn't want to lump those patients who could not be removed from their work exposure, for example, with those patients who you might

be able to, because I think there would probably be a standard regimen of attempting to eliminate the most common things in the general population, but there would be those people with exposures that you clearly could not that somehow need to be addressed.

DR. DRAKE: Jim?

DR. KILPATRICK: You may have implied this, but one way to do this is to exclude those nurses, mothers looking after babies, et cetera, for the trial, and simply focus on people who can follow the protocol, whatever the protocol is.

DR. DiGIOVANNA: But that's like such a large percentage of these patients, and it's really saying there are those individuals where we are relatively sure that there is an exposure -- we may not be able to identify exactly what it is -- versus those individuals where we really can't find an exposure and there may be, but we haven't been able to identify it. So I think that's a very large percentage, the florists, the hairdressers, the metal workers, the nurses, the health care professionals. I think a very, very large percentage.

DR. DRAKE: Don, just go ahead and answer, and then I'm going to try to get us zeroed in onto some of these questions here again. We've been wandering afar.

DR. BELSITO: Or alternatively, rather than trying to separate this out into a pure allergy or a pure irritant or a pure atopic, which I don't think you can do, to accept that there's hand dermatitis that is a hybrid and look at a group where you can alter other behaviors, like workplace exposures. That group is going to actually be very small, in my experience, versus another group where you know they're washing their hands 30 times and there's nothing you're going to be able to do to influence that. You know, you can't have a person working in the ICU washing their hands only twice a day. It just doesn't happen.

And see how your drug performs under both of those conditions, and then maybe it will be effective for all types, maybe it will be effective only when you can maximally modify the environment to remove as many possible exogenous causes, but if you're looking to stratify, I would argue to stratify that way, rather

than to try and stratify by disease, because I just don't think it can be done for hand dermatitis.

DR. DRAKE: Jim?

DR. KILPATRICK: There's another way possibly for a sponsor, a potential sponsor, to go if FDA traditionally requires two, or at most three, well-conducted randomized clinical trials, but maybe this is a situation when we have to depart from that type of expectation and have a series of trials. First of all, a trial which will demonstrate efficacy in a very small, but nonrepresentative, group of patients, and then attempt to go on into these other types and do a series of very focused studies before the drug is marketed.

DR. DRAKE: I want to ask a few very focused questions that are on our list, and we've not specifically addressed it. In the presentations -- and I'm sorry Beth just walked out. I was trying to get to her before she left, but you specifically ask about dyshidrotic hand eczema, if it should be included in these studies.

Now, I kind of heard from Dr. Bill Jordan that he doesn't really sort of lump this into that

group. You do?

DR. JORDAN: I just think it belongs to another group.

DR. DRAKE: But would you include them in a study set if you're studying hand dermatitis?

DR. JORDAN: Oh, absolutely. Absolutely.

DR. DRAKE: Okay, and so would you, Don?

DR. BELSITO: Yes, I would.

DR. DRAKE: Okay. Good.

The second question I want to ask you, I'm going back to Question Number 6, and Rob already alluded to that, is it important to separate dorsal surface from ventral surface when you're studying hand dermatitis? Should that be defined in the protocol? I mean, it's easy enough to do it.

All right. So that should be. Okay, so we can say that.

DR. BELSITO: You may want to separate them out into the palmar involvement with or without dorsal involvement and the primarily dorsal involvement, but I wouldn't exclude the primarily dorsal involvement, because a good number of those will be your moderate

irritant contact hand washing population without the atopic background, and you want to help those people. You know, people like myself that Beth alluded to that, now that it's November, after seeing 50 patients in clinic in a day, my hands are red and raw, and unless I do something for them, if I do the same thing the next day, they're going to be redder and rawer. So I wouldn't completely exclude the primarily dorsal only, but you may want to look at primarily dorsal only versus a palmar plus or minus dorsum.

DR. DRAKE: Ms. Cohen?

MS. COHEN: Since, from what I gather you're talking about people who chronic problems, then it seems to me the study has to be designed for a much longer period of time than like we saw today, 48 weeks, particularly because it's chronic. I can't see that you could do it in a shorter period of time.

I see you shaking your head.

DR. STERN: I think of this as a chronic disease that exacerbates and ameliorates over a period of months to seasons, but not years, and that also, at least if you live up north, is a disease that is very

much harder to treat when the heat's on than when the heat's off.

So I think the complexities of keeping patients on a study, plus who's likely to come to the study, I think if you're talking about a 12- or 24-week study, I don't have any fixed notions, but that's sort of the time frame that I think gives you a pretty good idea of whether something's going to work one or two seasons, and I'm not expert enough to --

MS. COHEN: But the very nature of what you said proves the point, that if it does change and it's affected by other things, then you have to know what those other things are.

DR. STERN: But as I understand this, we're looking for new products, and perhaps I read something extra into this, new products that might even because of potentially higher risk, and I'm maybe reading things in, that the sponsor would hope would be particularly appropriate and effective for small area applications where other things don't work, and that's why the targeting. I may have been reading much too much into what Dr. Wilkin said when he talked about the toxicity

and absorption, but we may be talking about things that are not just one more steroid cream, but perhaps something that you wouldn't consider to just approve for eczema anywhere because of its systemic absorption or because of its local effects, which may be greater. I may be reading too much into this.

DR. DRAKE: Bill Jordan?

DR. JORDAN: I understand what she's referring to, but it's almost the same thing as women with recurrent cystitis. You're not going to cure them forever by putting them on an antibiotic. You'll cure that case, that entity, and that doesn't mean they're not going to get it again, and hand eczema works the same way. You couldn't take the long view, how long they did. You have to do it episodically. You have to clear the episode.

The thing that I would object to that I'd love to read in a protocol one time, besides the exclusion criteria, which I agree, and a certain element of chronicity, is that the weakness of every study I've ever read which had morphologic responses is that they sit there and they give you grade the erythema, grade

the papules, grade the vesicles, grade this, and it's all one conglomerate picture.

There's easy technology which I use all the time. It isn't very fancy, but a 1x Polaroid of the targeted area that you're treating. It takes gorgeous color pictures in focus. It's 1x. You can measure anything off the film you want to.

That should be used along with the control area, of 1x them, 1x them, and get a very documented chronic study, rather than having people say, "I think it's a 2 plus. Well, let's see what I said last week. Well, this looks like a 2, but it's got 3 for this and 1 for that."

That's what I think is where the garbage is. Give me a 1x Polaroid any day, and I will believe you have a product worth going on the market, even though you're not going to stay well forever.

DR. DRAKE: I think we saw an example of that this morning.

Jon, I want to do something right now. I want to summarize a little bit of what we've heard, and then let you tell me what else you need from us.

All right. One thing I've heard today is that it's probably okay to lump these as "hand dermatitis," providing you do some exclusions on the front end, such as infections for KOHs or bacterial urticaria or psoriasis.

And by the way, any of the panel correct me as we go along, but I'm just trying to at least get a focus.

DR. JORDAN: I think you should explain what is lumped, but saying that different people might weight them differently, but these are the disorders that are within the chronic category. In other words, I'm an atopic man, he's an irritant man, but there's going to be irritant dermatitis or atopic, and state right out there that some people might weight it one way or the other, but this is what's going under the term of intrinsic hand dermatitis. Irritant alerts questionable. Not blatant allergy, because I don't know that if you had a blatant somebody to put neomycin on, they shouldn't go in the study. That's where you're defended by a certain element of chronicity. After you have that, then you can put everybody under there and

say you yourself can figure that even if the investigators were totally off the wall, it's just a weighting from one area to another.

DR. DRAKE: Let me get through my whole list, because some of the things you mentioned refer to my list. Conserving time, let me get through my list, and then we'll add to it.

So lumping was Bill's comment. The second thing I heard fairly strongly, and saw a lot of nodding of heads -- by the way, this summary comes a lot from catching people nodding in agreement or disagreement, so you have to understand, some of this is the chairman's personal observations of the panel.

But one thing I noticed was everybody was nodding yes when we talked about having criteria for degree of severity, including things like erythema, scale, fissures, and maybe even some less objective findings, but more subjective, such as maybe a scale for burning and pruritis. All right? So that was something I saw a lot of nods on.

I think everybody agreed that in any protocol it doesn't matter what you define, but you really must

define it as whether your opinion is chronic or acute, because they respond differently in all likelihood.

The notion of documentation about the time away from what may be an offending allergen versus time of relapse are closely intertwined, and so somehow the protocol, if somebody's clearly noting the occupation and noting what somebody thinks might be a precipitating factor, such as "I work as an ICU nurse and I wash my hands 25 times a day," is very important information to capture, so that at the end of the study you can make some stratified decisions based upon stratification of the data.

That also is directly related to relapse, because it's going to be hard to keep anybody in relapse a long time if the offense is they've got to wash their hands seven times a day. So then you're more after control. So just documentation of that.

And I put down as Number 6 documentation of confounding factors, and being a child caregiver is a compounding factor.

Just let me finish and then guys can comment on this.

The other thing I heard was, like creative financing, we've got to have some creative study design. In other words, if you're studying a barrier cream, that's certainly going to be a different protocol than if you're studying something with an antiinflammatory, for example. Plus, what's your target? Is your target active disease, inflammatory disease? Is it more of a chronic thing? What's the occupation? So the creative study design really must be utilized.

Jon, you mentioned crossover studies, and I have to tell you, I agree with, because when you've got hand dermatitis, I think what I heard is that it's very difficult, and there were lots of nods of heads, to remove people from everything and expect them to be just totally in a vehicle, albeit emollients can be wonderful vehicles, but I don't think there's anything wrong with the suggestion, and I saw lots of nods, Jon, when you made that comment that there's some room for this. Again, this is part of the creative study design.

I think you have to document whether it's ventral or dorsal and clearly define what you study.

I maybe used the word "crossover" wrong, Jon,

but you talked about setting up protocols differently. Early opt out I think is what you used.

DR. WILKIN: Yes.

DR. DRAKE: That's what I'm trying to address.

DR. WILKIN: Okay, because I don't think I used the word "crossover."

DR. DRAKE: You didn't. I did.

DR. WILKIN: That actually means something else.

DR. DRAKE: Two different things, I know, but I was thinking about using a crossover here, too. So back to creative design.

I think you have to document, and what I've heard is whether it's ventral or dorsal, because that does make a difference in response.

Finally, what we heard is that photos might be a very useful part of any hand dermatitis study, because then when you go back and really try to evaluate it, you actually have a documentation of exactly what you were treating. That might help minimize some of the intersite and intrasite variability.

Now, that's kind of what I have on my list. Is that a representative list? What did I leave out?

Don, and then Elizabeth.

DR. BELSITO: I think it's very all-encompassing, certainly, of what I was getting at.

The one thing that I would add that's very helpful that can improve reliability among centers is when you're looking at things like erythema, scaling, fissuring, is you give a photographic documentation to the evaluators and say this is what we're defining as minimal erythema, this is the color that we're defining as mild erythema, this is severe or moderate erythema, here's mild scaling, here's severe scaling, here's mild fissuring. You know, it really lends itself to defining criteria photographically, so that you may not need to photograph everyone, but the investigators, at least, have burned into their mind and have visual cues, when they're seeing patients, these are the ranges. You'll still get some variability, but at least I think you've made it a little more clear in the investigator's mind.

DR. DRAKE: Dr. Abel?

DR. ABEL: A question for clarification

regarding exclusions. Are we excluding people with positive patch test reactions where we know that they can eliminate that?

DR. DRAKE: That's a very good question. That's an excellent question.

DR. ABEL: I mean, we're going to obviously include irritant. I mean, what we are studying now, I think we are left with chronic irritant hand dermatitis, dyshidrotic eczema, and atopic, but it seems that if we know the offending allergen and they can eliminate that, then maybe we ought not to include that group of patients.

DR. DRAKE: That's a very good point and it's a very good question, but you might want to include some of these subjects in studies if -- of course, a lot of our experts said sometimes once this process sets up, then it goes on and on and on, and so if you can get them some relief early on, then that might be helpful.

Is that what I understood from you guys?

DR. ABEL: Or look at it separately.

DR. DRAKE: Or look at it separately? What do you think? If somebody's patch test-positive, should

they be enrolled in a hand dermatitis study?

DR. JORDAN: A blatant --

DR. DRAKE: Bill, you go first, and then Don, and then John.

DR. JORDAN: Well, if you go back to Elizabeth's, we've all had like the neomycin on the finger. Well, you know if you stop that and give them steroids, that's it. So as far as I'm concerned, they're not part of what we're really asking. We're asking a harder question than that, and that's why I said there should be this element of chronicity -- time to be determined by other people than myself -- and that it should be kind of an ongoing problem gently, rather than a hot poison ivy. I've got a beautiful example of pulling poison ivy. Well, I know that's going to do well. I don't throw that into my hand dermatitis group.

DR. DRAKE: Don, and then John.

DR. BELSITO: Well, I would agree with Bill. You know, if you set up an operational definition -- okay, we're looking at more the chronic hand dermatitis that's been going on six weeks, eight weeks, whatever number you want to pull out of the air to define as

chronic -- then hopefully you've gotten rid of the blatant allergies. You don't want to study those. Those have already been taken care of.

But there's going to be a significant number of hand dermatitis that was triggered by the allergy. You know, you take that atopic -- or I happen to believe that there is a disease, dyshidrosis, but I don't think it matters -- who pulls the poison ivy, you get them over the acute event, and now they're stuck with erythema, scaling, fissuring that goes on and on and on and on, those people you certainly want to include because those are the people we're talking about here.

DR. DRAKE: So I've added to my list. I have one more add on, then, that there's probably some minimal level of chronicity that should be incorporated into these studies.

Okay, John?

DR. DiGIOVANNA: Yes, I think that the issue that Dr. Jordan mentioned with respect to chronicity eliminates those individuals where you have a positive patch test result and it can be removed. I think that what we've heard today is that there are many

individuals who have positive patch test results and they still have this entity that goes on and on and on, and you either can't remove them or you have removed them and something else is going on.

So I think a lot of individuals in this group are going to have that, and I don't think that's going to be something that's so easy to remove, and I think that etiologically probably a lot of the people who may not have positive patch test results don't have them because we don't have those allergens to test and we don't have their workplace allergens and we have very few agents to test. So I think that the chronicity issue really deals with that, having someone who has a problem that has a certain duration.

DR. DRAKE: I'd like to ask our FDA folks, right now, what's missing? Where are the holes? Where are the gaps? What can we help you with?

DR. WILKIN: Actually, I think you've responded to questions that we hadn't even thought of and we got very good answers. It's been very helpful.

One of the features that some of the experts and committee members have already alluded to is that

some of the specific aspects of the clinical trial will be driven by the pharmacology of the agent, and I think we recognize that, and then there is a linear aspect to drug development. There are Phase II studies where one will find out which subset the response is going to be best in and exactly how long one should treat. So a good Phase II program, armed with the kind of advice that the committee has given today, I think would prepare us for good end of Phase II meetings and excellent designs for Phase III.

DR. DRAKE: Ms. Cohen?

MS. COHEN: I still want to go back to chronicity. All right. If you say you can't design a study for a long period of time, wouldn't it be helpful, then, to know the periods of quiescence between it appearing again? I think just to say it cures it for that period of time, I think it's the length of time in between that it reappears again that's important also.

DR. JORDAN: That shouldn't be hard. I mean, that would be reasonable.

DR. DRAKE: And Phil, you had a question, too.

DR. LAVIN: Not so much a question as just another comment on endpoints. I think in a study like this there's an opportunity to have 100 endpoints, if one wants. I like the idea of working off a picture, a Polaroid, because it really points at the key idea of having one defined outcome, which might be a blinded evaluator looking to see whether or not the patient had a response or a degree of a response.

So in a setting like this, when you have multiple endpoints, it leads to all sorts of issues of statistical multiple testing. We have to avoid that type of multiple testing. It's the thing that will undo any credibility here. So that's something that also has to be added to the fray.

DR. DRAKE: John, and then Don.

DR. DiGIOVANNA: I just wanted to make one point. I'm not sure whether it did come out or it didn't come out, but Lynn, when you ran through your list, one of the things you had reiterated from the earlier discussion was one disease that might be excluded might be psoriasis, but we did talk about creative clinical trial design. I could conceive of a

product that might be targeted towards volar skin, like we have products targeted towards the scalp, for example, for psoriasis, where one might want to have, for example, a topical antiinflammatory that would be efficacious potentially both in psoriasis and be able to be used on volar skin, but also efficacious for other sorts of dermatitides confined to that area. So I think that as long as it's a creative trial design idea that goes through, that's what we're looking for.

DR. DRAKE: And Don?

DR. BELSITO: I would agree with Susan Cohen that you want to look at how long before relapse rate. My experience, for instance, with systemic steroids is that you can certainly clear these hand dermatitides, but within several weeks many of them will flare with even more severe disease. So you want to guard against that, but there's going to be a severe confounding factor there, and that's going to be what does the patient do and how easily are they able to remove themselves from the exogenous factors that drive this hand dermatitis.

So yes, you do want to do the follow-ups, you

want to look at how long they've remained clear after a treatment, primarily to see do you get these rebound flares where the patients actually get worse, but you're going to have to be very careful to also document what kind of exposures the patients are getting, because you may end up with two or three or four different groups of patients: those who have self-selected themselves out by quitting their job, and you see in my presentation that a significant number of apprentice hairdressers did just that. They got tired of their dermatitis and they removed the exogenous causes that were driving it.

So you're going to need to look at that. You know, did they stay in the same line of work? If they were in the same line of work, did they continue to get the same types of exposures they had before their dermatitis cleared? I think that's very important types of information you'll want to glean in a follow-up study.

DR. DRAKE: Dr. Abel?

DR. ABEL: Another issue regarding documentation would be to document all the adjunctive therapy. I don't know if this type of thing could be

standardized, but in any study we have to know what they're using for cleansing, how often, what they're using for emolliation, are they using gloves, are they not using gloves, with cotton liners, without cotton liners -- all of those things have to be documented.

DR. DRAKE: Dr. Wilkin?

DR. WILKIN: I agree it's helpful to know that. Were you suggesting that they do standardize? Because then, if they do standardize, it's sometimes difficult to tease out the contribution of the drug in the absence of the other factors.

DR. ABEL: But so often it's a combination -- I don't know the answer to that question. So often it's combination therapy.

DR. WILKIN: Yes.

DR. ABEL: And so it's difficult, because if you only use the active agent and you don't use emollients in addition, you might not get to the endpoint.

DR. WILKIN: Okay. I heard emollients, but I didn't hear a specific --

DR. ABEL: And other things.

DR. WILKIN: -- emollient, and I think that's the key thing.

DR. ABEL: No.

DR. WILKIN: Because what we like in Phase III is all comers, and actually, a list of emollients would be much preferable to just simply naming one that everyone would need to use.

DR. DRAKE: Okay. That's good.

All right. Other comments, questions?

(No response.)

DR. DRAKE: Do you have what you need?

DR. WILKIN: It was very useful for us. I think personally I should have gotten CME units for this afternoon.

(Laughter.)

DR. WILKIN: We had excellent expert speaker presentations and the comments from the committee have been very helpful for the understanding of trial designs for hand dermatitis. Thank you.

DR. DRAKE: Good. Now, before everybody leaves, I want to thank our experts for coming today and for all their valuable input and their presentations.

It was extraordinarily helpful.

Tracy has some housekeeping things. Before I finish everything, Tracy wants to know have you filled out your little blue piece of paper as to whether you're coming to dinner tonight and if you're bringing somebody with you. Please make sure she has that.

Also, is this restaurant within walking distance?

MS. RILEY: No.

DR. DRAKE: We've got to take a cab? Is there going to be a bus or how do we get there?

MS. RILEY: We'll sort of put together a caravan.

DR. DRAKE: A caravan. So do you want us to meet in the lobby like at 6:15?

MS. RILEY: Yes.

DR. DRAKE: All right. The dinner's at 6:30, so meet at 6:15 in the lobby so we can all caravan to this little restaurant.

Now, the other thing is, I think in the morning Tracy advises me that the agenda for the closed session in the morning is less extensive than originally

thought, and so we can start later. She suggested starting at 9:30, but would you prefer to start a half hour earlier, so you can have a little longer time at lunch to visit with each other and not have to hurry for lunch in case we run over? Because tomorrow afternoon will be packed and I want to start right at 1:00, because I'm going to lose my committee. What will happen is, we'll see one going out the door after another to catch airplanes, so I want to make sure we don't start late tomorrow afternoon. I want to start right at 1:00.

Jim?

DR. KILPATRICK: For those of us who have to fight the Beltway, I would prefer starting at an early time and working through to an early close.

DR. DRAKE: So everybody can get out of here early? Well, we're a little bit hindered in that we can't start the afternoon session -- Tracy, help me with this. Can we start the afternoon session early? We can't start it any earlier than 1:00 because that's when it's posted, is that correct?

MS. RILEY: That's when it was noticed.

DR. DRAKE: That was noticed, so we have to abide by the notice, but as we schedule in the future, maybe we can keep that in mind that the more difficult sessions could be scheduled in the morning, and that way we spill over into the afternoon, so that people don't run out to catch planes, because I've seen it happen too much.

Tracy, how long do you think our meeting will actually take in the morning?

MS. RILEY: About two hours.

DR. DRAKE: About two hours. So if we start at 9:30, then we could have lunch at 11:30. Is that all right with everybody, 9:30?

Now, I certainly again want to thank everybody for your participation. I know afternoons get long, and I do thank all of you, and I particularly want to thank Ms. Cohen and Ms. Goldberg, and Joel, I have to tell you thank you, and Jim. You have a lot interest in this because you're a statistician and epidemiologist, et cetera, et cetera, but you know, Joel, you sat there very patient through this this afternoon. It's just remarkable.

DR. KILPATRICK: Madam Chair, Joel feeds me the comments.

(Laughter.)

DR. DRAKE: Is that it? Joel feeds you the comments?

Anyway, I sure do want to thank all of you, because we dermatologists, this is sort of our life and we like it and we live it, but for those of you who've come and given your time, this isn't part of your everyday life, and so we're particularly appreciative.

And so the meeting is adjourned and we'll see you at 6:15 at dinner and at 9:30 here in the morning.

(Whereupon, at 5:00 p.m., the meeting was recessed, to reconvene in closed session at 9:30 a.m. on Friday, November 5, 1999.)