seeing a lot of the office, strong topical steroids are being routinely. They are used because we have a lot of samples of them, for one thing, and for another, a lot of the people who are handing them out don't have any understanding as to what is strong, what is mid-level, what is a weaker topical steroid

Second of all, KOHs are not being done. Sometimes, they are not being done because the CLIA regulations get in the way and people don't want to have a lab. Sometimes they are not done because people don't know, or don't want to know, how to do them.

If the patient is put on steroids and doesn't respond, then they are put on antifungals. But, by that time, the fungus may have grown down the follicle and produced the folliculitis which the topical antifungal cannot reach and, therefore, you created a significant problem by the way a lot of people take care of the these kinds of lesions.

[Slide.]

I didn't put up this slide to make fun of nondermatologists. I put up this slide because when I was a nondermatologist, back 40 years ago, I was a general medical officer in the service. At that time, I didn't know anything about dermatology except I didn't want to look too stupid. So I had a cream that I would put onto something.

If it worked, then I was a hero. If I wasn't, it got referred to a dermatologist.

In those days, the cream of choice was Mycolog. It had in it something that was a steroid and it was antibacterial and it was antiyeast. I didn't know the difference between a yeast and a fungus at that point, anyway. So that was the way I used the product.

Indeed, that is the way a lot of people are using the products that we have today. The nondermatologist often does not understand the difference between the potency of different steroids. They rarely understand the difference between the clinical presentations of yeast or fungus infections and often, even though there are specific differences that one can see clinically, they are not taught and they do not remember these differences when they see patients. The nondermatologist may not recognize the difference between eczematous conditions and tinea.

So a lot of this is being done by the seat of their pants. So they are using a medication which they think will take care of everything. That is one of the ways that this drug gets used.

I am amused at how careful we are in our labeling, but I think a lot of people who are using this drug are not reading the label. They are using the drug because they perceive it as cure all and, therefore, are using it in a

lot of situations where we might otherwise not wish them to use it.

[Slide.]

Steroid antifungal combinations are perceived as a single treatment that will work for everything. Of course, this is not true.

[Slide.]

In my day, Mycolog, the original Mycolog, contained the things I talked about. Mycolog 2 got rid of the neomycin and the other antibiotics. And Lotrisone today is what gets used a great deal.

[Slide.]

The other thing to remember is, as was said before, patients don't throw things away. If you want to really frighten yourself, open your medicine cabinet and look in it because there things there from twenty years ago that you are saving just in case you have a really bad pain and you need that codeine, or whatever.

It is amazing what is in my medicine cabinet, and I try to be careful. So patients save this stuff and then, when they get the groin inflammation again, they go back and they use it over again. Although prescribed for a limited amount of time, sometimes nondermatologists refill prescriptions that they should not refill and the drugs get used for longer periods and patients often continue to use

it.

There is an old theory that if a little is good, then a lot must be better and so they continue to do it.

[Slide.]

I also want to point out that a lot of people don't do KOHs. I always go back to Dick Dobson who gave a wonderful talk that I heard. He said, "There are only two times when you do a KOH. One is when you suspect a fungus and one is when you don't suspect a fungus."

I think that is something I have been teaching for a long time. I think it really does make diagnoses, and most of the time it has been extraordinarily helpful to me in thinking about what I am dealing with.

[Slide.]

So the steroid antifungal combinations; usually the steroid isn't need for the dermatophyte to work. The steroid helps the symptoms of Candidiasis and, indeed, of some of the dermatophyte infections in the early stages. But, after a few days, the steroid is no longer needed and may be harmful.

There are other products and, as Ted said, a product such as cycloproxoleamine, and others, have other inflammatory effects which may be as strong as many of the steroids that we use.

I think that we make a mistake, often, in medicine

where we put things in boxes. "This is an antifungal." That doesn't mean that it can't also be inflammatory or antibacterial or anti-something else. But we think of it as an antifungal and, therefore, we don't think of it as doing anything else. It will do what it darn pleases and we have got to find out what that is. For cycloprox, it is also inflammatory.

[Slide.]

When you have Majocchi's granuloma, topical measures do not work. You need systemic medications, griseofulvin and terbinafine or, if you are dealing with yeast organisms, itraconazole, fluconazole, would be the drugs of choice.

Thank you.

DR. DRAKE: Dr. Elgart, thank you for a very precise and informative presentation.

Dr. Feldman? If any of you prefer, there is a podium and a mike there, if you prefer to stand at the podium. It is clearly your preference.

**Use of Lotrisone in the United States**

DR. FELDMAN: Thank you for letting me speak today.

[Slide.]

I am going to speak on the use of the combination of clotrimazole-betamethasone diproprionate in the United

States.

[Slide.]

Most of what I am going to present today are data that the federal government has collected through the National Ambulatory Medical Care Survey. I am going to talk about the use of the clotrimazole-betamethasone product to treat fungal disease, its use in general and, in particular, use by pediatricians and then, perhaps, a little bit about diaper rash.

[Slide.]

The National Ambulatory Medical Care Survey is a terrific resource for understanding outpatient practice of medicine in the United States. It is performed by the National Center for Health Statistics. They survey 35,000, give or take, office visits across the United States per year.

These are not hospital inpatients or government-employed physicians. So it is a real terrific survey for looking at skin care which is practiced predominantly in the outpatient setting. The survey has information on patient demographics, diagnoses and what medications are used, among other things.

[Slide.]

Some details about the study are in the handout. I don't think we need to go into them now.

[Slide.]

Regarding the treatment of common fungal infections, one can use monotherapy or combination therapy. I think there are three real common reasons why combination therapy is used. One is if there is inflammation that needs treatment. That is the one that we have spent a lot of time discussing.

But, as Dr. Rosenberg mentioned early, probably a much more important reason is if you are unsure of the diagnosis. Then a third reason that I don't think has been touched on quite so much is if you have no clue what is in the combination and just happen to be using it because someone told you to.

[Slide.]

There are problems with combination therapy. There is increased cost to the medication. We just heard about reduced efficacy and we have also heard about reduced safety, adding the risk profile of the corticosteroid agent when, perhaps, there is no good reason to.

[Slide.]

This is just an example from my practice of someone who developed a tinea incognito.

[Slide.]

The picture on the left is steroid atrophy. The picture on the right is an example of cutaneous atrophy in

the groin area. This patient was not treated with the Lotrisone product. This was a patient treated with Elecon, another high-potency topical steroid agent that is probably misperceived by many people.

[Slide.]

We worry when these products are used in sensitive skin areas like the face or the groin area because the penetration of steroid, as you can see, is much greater in those areas than it would be on the foot.

[Slide.]

So the combination treatment I am going to talk most about, of course, is the clotrimazole-betamethasone product.

[Slide.]

This box of samples was in my clinic. One of the things I noticed about it is, on the cover, it says that it is appropriate for use in jock itch without any statement about the length of time for which it could be used safely or the age range, at least not here on the cover of the box, for which it could be used safely.

I think having a combination steroid antiinfective product is a great idea for things like seborrheic dermatitis on the face where we know there is inflammation and an infective component for intertriginous eruptions where we think of inflammation and an infective component.

But the steroid that was chosen here is really not appropriate, at least for any kind of prolonged use on the face or groin area and, perhaps, there is not enough effort to make people aware of what the potency of that steroid is.

[Slide.]

We looked at visits in the United States in this National Ambulatory Medical Care Survey for common superficial fungal infections. What we found is that dermatologists rarely prescribe betamethasone-clotrimazole when they make a diagnosis of a fungal infection. So 4 percent of visits where a dermatologist has made the diagnosis of a superficial fungal infection, something like Lotrisone is prescribed.

In contrast, the internists, over half the time they make the diagnosis of a common fungal infection, they are prescribing the combination of clotrimazole and betamethasone diproprionate. I suspect that rarely, if ever, it is because they are treating the inflammation. I suspect that it is one of the two other reasons that we mentioned earlier, either that they are not sure of the diagnostic ability in making fungal infections or they just don't know what is in the product.

Family doctors, of course, less than internists. I think they have a better understanding of skin disease. And pediatricians use the combination even less than the

family doctors although, in a pediatric setting, there is probably much less reason to ever use the product.

[Slide.]

Given those data, we wanted to explore in more detail how the combination clotrimazole-betamethasone diproprionate is used by the different specialties. So we looked, first, here at visits to family physicians. We looked at those visits that were for superficial fungal infections based on ICD-9 coding.

We also looked at when they made diagnoses of inflammatory disorders.

[Slide.]

What we found is that the combination product is used for superficial infections but even more commonly when the family physician is making a diagnosis--I'm sorry; it is used when the infectious conditions are diagnosed as well when inflammatory conditions are diagnosed, much less frequently so by dermatologists.

[Slide.]

As was mentioned earlier, looking at the diagnoses that are treated, inflammatory dermatosis, or the diagnosis of an inflammatory disorder, is the most common time that this product is used but it is also commonly used for groin infections and for diaper dermatitis.

[Slide.]

There was frequent use in patients age 0 to 4. 40 percent of all the topical steroids used by family physicians, in the 0 to 4 age group, was the clotrimazole-betamethasone diproprionate product. For all ages, you can see that genital, anal area and diaper-dermatitis eruptions were common reasons for Lotrisone to be used.

Interestingly, 23 percent of the visits at which a family physician made a diagnosis of seborrheic dermatitis, clotrimazole-betamethasone diproprionate was prescribed.

[Slide.]

Internists showed similar findings. They don't see that many pediatric patients, but three of their top five diagnoses were genital area eruptions that they were treating with the product.

[Slide.]

The data on pediatricians, in this National Ambulatory Medical Care Survey, was analyzed for the years 1990 through 1994. These data are published.

[Slide.]

Pediatricians are very unlikely, in general, to use high-potency topical steroids. I think there is a real tendency, among pediatricians, to be very conservative in their use of topical steroids and to say away from the high and super-high potency class 1 and class 2 agents.

[Slide.]

You can see here, for corticosteroid monotherapy, what pediatricians are using. You can see they really tend to stay away from the high-potency topical steroids. It turns out they use far more Lotrisone than the combination of those two class 1 and class 2 steroid monotherapies.

I think that suggests, at least in part, that they don't realize what is in this drug.

[Slide.]

Of the diagnoses that they were treating, tinea corporis was the most common but dermatitis, I was very surprised to see how frequently well-baby visits were associated with the use of Lotrisone.

Let me just go back. You can see the total use of Lotrisone over this time period is 700,000 prescriptions. Going back, the combination of high and super-high is about 300,000, so there is much more Lotrisone than they are using highs and super-highs.

[Slide.]

56 percent of the pediatric use of Lotrisone was in the 0 to 4 age group. In that age group, well-baby visit was the most common diagnosis. Dermatologists, at least in this study period, did not prescribe Lotrisone to any child in the 0 to 4 age group.

[Slide.]

Of particular concern to me is the use of the

product in diaper rash in children. I think there are plenty of other good treatments that are more effective, less expensive and certainly less risky than to use this product in kids.

[Slide.]

This just summarizes that pediatricians tend to be conservative. Their use of Lotrisone seems excessive compared to the use of other potent topical steroids. I think our take-home message from this was that they may be unaware of the steroid potency of Lotrisone and there could be strong efforts made to make pediatricians aware of the potency.

[Slide.]

To further analyze this, we left the National Ambulatory Medical Care Survey for a minute. A survey was done at the 1999 American Academy of Pediatrics meeting where 106 pediatricians completed the survey. These were all pediatricians who currently prescribed the product for at least some of their patients.

[Slide.]

This is the proportion of patients who are treated with Lotrisone in various conditions. You can see diaper dermatitis is treated--23 percent of patients with diaper dermatitis are treated with Lotrisone by these pediatricians.

[Slide.]

This is interesting. This is the proportion who never prescribe Lotrisone for various conditions. So about 40 percent of these pediatricians never prescribe Lotrisone for diaper dermatitis meaning that 60 percent of the pediatricians who prescribe Lotrisone prescribe it at least some of the time for diaper dermatitis.

[Slide.]

We thought that the primary reason pediatricians use Lotrisone despite the warnings would be that they did not realize what topical steroid was in it. We asked them; "What topical steroid do you think is in Lotrisone?" Only 18 percent recognized it to be a high-potency topical steroid.

Unfortunately, there was no relationship to whether they knew it was a high-potency topical steroid and how often they prescribed it to their patients for diaper rash.

[Slide.]

We also asked how often they used it in excess of the recommendations in the PDR. 25 percent of the time, they were using in excess of the two weeks recommended for tinea cruris. We didn't address diaper dermatitis here since Lotrisone is never appropriate for use in diaper dermatitis.

[Slide.]

We addressed how diaper dermatitis, in general, is treated looking at the National Ambulatory Medical Care Survey data, looking at those visits that had an ICD-9 code of 691.0 which is diaper dermatitis. But we also included balanitis, vulva vaginitis, intertrigo and candidiasis in patients under the age of 4.

[Slide.]

There were 8 million visits. They were primarily to pediatricians and family physicians, very few to dermatologists.

[Slide.]

The most common treatments were nystatin and clotrimazole No. 1 and 2, but then the combination products including triamcinolone and betamethasone diproprionate both which, I think, are probably too strong for any kind of prolonged use in the diaper area.

[Slide.]

So, in summary, the clotrimazole-betamethasone diproprionate product is not the best treatment choice for either inflammation or for tinea infection if you know that that is what you are dealing with. It is most frequently used by non-dermatologists. It is generally not being used to treat highly inflammatory tinea infections. In fact, the use of it appears to be inconsistent with good medical

practice.

DR. DRAKE: Thank you very much.

They say the mark of a good speaker is being able to present the information they want to present in a finite period of time and have it understandable. I want to say that has been true of every single speaker we have had today. I am really very impressed.

Right before we go to the sponsor presentation, I would like to ask the panel; we have heard some--

DR. SPRAKER: I was just raising my hand. At some point, I would like to make some comments to follow up his discussion but wherever it is appropriate.

DR. DRAKE: Please, Mary. I just have a question but please let's hear your comments because you may answer it. I am going to ask the panel if they have any questions for our group of experts before we go to the sponsor for a few minutes.

Dr. Spraker, please.

DR. SPRAKER: I would just like to give the panel a bit of historical perspective about the Lotrisone problem from the vantage point of the pediatric dermatologist. About ten years ago, at our Pediatric Society board meetings, there were discussions regarding the Lotrisone problem because we were hearing about striae that were induced in the diaper area and we were hearing from

pediatricians in our communities when we were asked, "Why are you using Lotrisone for treatment of diaper dermatitis?" that the drug reps were going to the offices and telling them about Lotrisone and implying, or the pediatricians were getting the message, that Lotrisone was appropriate therapy.

So we were very concerned about this problem and a number of pediatric dermatologists actually went to Schering to talk about the Lotrisone problem. From those discussions, a number of things were accomplished.

The company agreed that it would no longer send the reps to the pediatricians' offices. I don't recall the details, but at least they weren't going to be talking about the use of Lotrisone in pediatric patients.

The second thing that came out of these discussions was the company developed an education program for pediatricians regarding potency ranking of topical steroids because all of us recognized that most pediatricians, and I think probably primary-care physicians, as you have said, Steve, really do not know that there is such a thing as a potency-ranking chart.

They are aware that there are weak steroids, medium ones and strong ones, but they really don't know anything about the different groups. So there were, actually, I think, quite good educational materials that were prepared and distributed.

Many of us are educators for pediatricians and were often speaking at meetings to large groups of pediatricians. So, in that era, many of us, that was one of the things that we would talk about, "What's New," or a whole lecture on potency ranking of topical steroids, pros and cons of topical steroids, when to use what, that type of thing.

So we had hoped that the Lotrisone problem had been addressed and maybe solved. So it was quite disturbing, then, to see these papers and this data presented which clearly show that we still have problems out there.

I guess I have several recommendations. Some of them have been in your materials already. I strongly feel that the box and the tube should state that the drug is not to be used in the diaper area because I think the mothers, or the parents, will read that. Even if we change the material, what is written in the package insert that is going to be in the PDR, you can't assume that the physician is necessarily going to see that.

But parents read those things and they will come back to the pediatrician and ask, "Why did you prescribe this when it clearly says this is not to be used?" So I think that that might be a very effective vehicle for changing habits.

I also think that there should be a big black-box warning in the PDR that emphasizes, not just a statement but a big black box, that, "This drug is not to be used for the treatment of diaper dermatitis."

The side effects should be enumerated, not just a one word, "Because of cutaneous atrophy," but we should list how many patients have been reported with cutaneous atrophy, how many patients in these young age groups have had problems with striae so physicians are given more information to work with.

It is interesting to me that the PDR never states what the potency ranking of a topical steroid is, as far as I know. It hasn't been the custom, I guess. You have to have your little chart. Maybe that is something that, not at this meeting but at another level, but that that could be addressed so that routinely potency rankings are included in topical steroid PDR information.

I do agree that it would be a very good idea to send a letter to pediatricians and primary-care physicians just addressing the problem and the things that have been done to address the problem.

DR. DRAKE: Thank you, Dr. Spraker.

Dr. Epps?

DR. EPPS: I just have a few comments. I agree with much of what has been presented today. Certainly as a

board-certified pediatrician and dermatologist, I kind of get to see both sides of the coin. As a pediatric dermatologist at a referral center, I tend to see a rather distinct population and those are the ones that are not successful.

I would say that, certainly, the number of cases in which the drugs are ineffective or the drug--the response was not good to therapy is vastly underreported. The majority of patients that I do see have had at least a little bit of Lotrisone applied.

The reasons for that may numerous. One, the diagnosis was not made or it was incorrectly made. Or it wasn't prescribed properly or it wasn't used properly. There are a lot of factors into why a particular medication didn't work.

But, clearly, if patients are being treated for 16 weeks or 150 weeks or whatever, it wasn't appropriate and may not be working. Also, as far as making the diagnosis, there are a lot of red, scaly spots, not only the tinea and eczema, but there is pityriasis and psoriasis, whatever, but there are a considerable number of other conditions that were not seen and, certainly, Dr. Elgart elucidated nicely a problem with the class 2 steroid.

In fact, yesterday, I had a patient who was using--the child was two, had a spot on the face. There was an

area of vasoconstriction on the cheek and the mother was told that it would "bring out the fungus" so that it could be treated. So there is a lot of misinformation out there.

In addition to the vasoconstriction, another side effect--I am not sure the population that was tested on in children, but another side effect that I do see sometimes is hypopigmentation. I don't know whether people of color or what types of skin were included in the study, but I do see hypopigmentation not only on dark but also fair-skinned children, in patients. That can persist long after and it takes a while to resolve.

So that may be another side effect which should be considered. Although it is listed in the insert, it wasn't specifically addressed in the side effects. It may have been in the "not otherwise specified," but it wasn't addressed more specifically, and maybe that needs some attention.

Additionally, as to the large number of prescriptions which seem to be increasing despite efforts of education and letters, which doesn't really necessarily relate to what our function is, but some of the HMO insurance plan formularies will have two or three antifungal, nystatin, Lotrisone and maybe that is it.

Anything else you prescribe is not covered. Sometimes, a pharmacist will also substitute what you

prescribe. It is not even appropriate in all instances for what is being treated. So that is a problem, also. Clearly it is probably beyond the panel, but that may be another reason why things are going up, especially with some of the formularies.

So I would strongly--if approved, certainly I would support some of the comments about avoiding the diaper area. Some patients are also being treated with Lotrisone for tinea capitis, which is not working. So it is not just the diaper area. People are using it on the face. People are using it on the scalp. Clearly other modalities and medications would be more appropriate.

I guess I am from the school of "know what you are treating," and not applying something because, clearly, mom is going to call you every single day until it goes away. But if you apply the proper treatment, it will go away and everyone will be much happier.

DR. DRAKE: Thank you. Eduardo, and then Joe.

DR. TSCHEN: Since, I guess, we are discussing the proposal for labeling, I will propose that, just like the label has, "not for opthalmologic use," I would like to see it say something about "not for use under occlusion," or "not for use in the diaper area."

I think occlusion also is important because the axillas under the breast, the groin area, I guess just

because of the nature of how they are, is an area of occlusion. So I think it should be clear, just like, "not for ophthalmic use," "not for diaper-area use," and, "not for use under occlusion," should be very clearly specified in that.

Most of the cases I see of rosacea are due to this product. Again, I don't think this product should be used in the face. So then we keep on adding different things in there, but I think it should be very clear that I don't think this product should be used on the face, either.

DR. DRAKE: Joe, please?

DR. McGUIRE: Mary, is there and indication in children to use Lotrisone? Is there a pediatric indication?

DR. SPRAKER: In my opinion, the only time to use Lotrisone for anybody is in inflammatory tinea pedis and toe web infections. It is very unusual for children to have extremely inflammatory tinea pedis. I don't think I have ever prescribed Lotrisone so I haven't found a need to use it for anything.

DR. McGUIRE: I have never used Lotrisone in a child. I wonder if I am too old to learn or I am missing something. I wasn't asking you, Lynn.

DR. DRAKE: First I got called somebody's mom and then--John?

DR. JORDAN: I have a question for Dr. Epps. You

raised a point that I found interesting with respect to hypopigmentation. I wonder if you have, in your experience, seen, in very inflammatory dermatophytes, if there is post-inflammatory hypopigmentation and, in those situations, if you do, do you ever use a steroid to minimize that?

DR. EPPS: Generally speaking, I don't. Even in inflammatory tinea, I don't usually--sometimes, you see hyperpigmentation if it is truly inflammatory. I don't see the hypopigmentation. That is usually when they keep using it after the medicine, but I don't really use Lotrisone either for the similar reasons. I don't see much tinea pedis in kids, mainly above there.

Sometimes in some of the teenagers or they are a little bit older, but, even still, it is not that inflammatory. As far as the pigmentation is concerned, no; I don't see that hypopigmentation. Usually it is "hyper."

DR. DRAKE: Lloyd, we haven't heard from you. Dr. King; I don't know if you have much to say, but you have been awfully quiet down there.

DR. KILPATRICK: You oftentimes can't be beat upon if you don't open your mouth and prove that you don't have a great thing to say. My comments; we don't use it in children. To the best of my knowledge, we have a pediatric dermatologist and the only time I can remember seeing it prescribed was inflammatory tinea pedis.

We do have a great experience of it inducing steroid acne, and so that would be my only comment. I don't know why, if you are going to ban it in one site which is the groin in children, you would allow it on the face either. So I think that what I would propose is that you increase the black-box labeling and make it very clear what the indications are.

If it is not on the tube, mama's won't read it. If mama ain't happy, ain't nobody happy. So they have come back to tell you.

DR. DRAKE: Other comments? I have a question in a minute, but anybody else from this expert panel? Do you have other things to add? I would like to ask a question. I was at Emory for a number of years with Earl Jones who is quite a famous mycologist and expert in this arena.

Pursuant to the comments that were down here, how difficult it is to identify, sometimes, fungal elements in inflammatory areas, and I hate to quote him because I may be quoting him wrong, but I wanted to give you a gestalt of what he taught us as young faculty. Dr. Spraker, you were there, too, so maybe you can help me out on this.

I seem to recall, and I practice this way, that Earl always used to say, "You cannot find hyphal elements in the middle of an inflammatory mess. You have to scrape at the edge." But he would go ahead and say, "You must scrape

at the edge because the edge is where the living organisms are where they haven't been gobbled up by the inflammatory process and you will find them at the edge."

I tend to use that all the time and I tend to teach my residents that. I usually find them. Mary, I would like you to comment first and then I would like some of our fungal experts here to comment on that particular theory. I don't know that we ever proved it by a study, but--Dr. Spraker?

DR. SPRAKER: I learned that somewhere, and I am not sure where. It could very well have been from Earl. Tomorrow, we are going to talking about diaper dermatitis and how difficult it is to diagnose Candida diaper dermatitis because KOHs are often negative. Clinically, you know that the patient has to have Candida diaper dermatitis, and the KOH is only positive 30 percent of the time, approximately, unless you go for a satellite pustule, and then I think it can be more likely to be positive.

Again, I think it is because the host mounts such a wonderful inflammatory response by shedding off the stratum corneum. By shedding off the stratum corneum, you get rid of the organisms.

Merve?

DR. ELGART: My recollection of what Earl did, and he had some beautiful things that he did while he was still

in the service, he took people who had not been exposed to fungus infections before, he called them "fungal virgins." A wonderful comment.

But he would put a culture of material on in a central spot and watch it. The fungus would grow, but there would be no inflammation for about week until cellular immunity appeared. When cellular immunity appeared, then there was a large inflammatory response, but the scale, by that time, was a little beyond where the inflammation was and so the inflammation sort of had to catch up with it.

Eventually, the inflammation would catch up with it and everything would disappear, but there was still live fungus at the edge and that was work that he did, oh, probably in the mid-60's, I suspect.

DR. DRAKE: Yes; the work was done. And he did teach you; you scrape at the advancing edge where there is still normal, healthy tissue.

Ted?

DR. ROSEN: There are several ways to find fungi, too, don't forget. First of all, if it is inflammatory--we are all talking about inflammatory like we have the same things in our mind which may not be true. There is red. There is intense maceration without scale, interdigital. There may be huge blisters, centimeters of blisters on the bottom of the foot.

If you have bolus tinea, that is very inflammatory, very uncomfortable, but very easy to find organisms by taking the blister roof and turning it upside down and looking at the edge of the blister.

If you have intense maceration between the toes, it is extremely difficult to have a positive KOH in those circumstances even at the edge but you will often have a positive culture. I understand that, in the current milieu, cultures are expensive and many people are loathe to do them or the plan won't reimburse for them, et cetera.

But it is not just the bedside, which would be the ideal because it is cheap and it is quick, but culture also can determine when there is a fungus there even if KOH is negative. So there are at least a couple of steps that could be taken.

DR. JORDAN: I don't know. We seem to be tippy-toeing around some issues here. I want to ask the panel, and Mary you brought this up, the indication for this product being inflammatory tinea pedis. I will ask this of the panel just to get an impression.

If you have a patient and you have got a positive KOH, you have got a positive culture, would you use this product over antifungals we have available to us now or some form of systemic therapy?

DR. SPRAKER: I wouldn't use the product because I

think the inflammatory response the host mounts might be good and beneficial, getting rid of more of that fungus. That is my personal philosophy on it. It is very difficult to prove any of those things, however.

As a mother, I only had one child who had Candida diaper dermatitis. This is different but, in some ways, I think it is the same kind of issue. When my son got a florid case of Candida diaper dermatitis, I said, "Okay; I am not going to add any topical steroids to this and I am just going to use the antifungal."

A day later, I just couldn't stand it and I smeared on some kind of topical steroid. So I understand from a personal level the temptation and the need. I think Kligman has shown with Candida that you can take dead Candida organisms and put them on skin and get an inflammatory reaction that induces cytokines, or something.

DR. ELGART: It is an irritant contact dermatitis.

DR. SPRAKER: Merve is saying an irritant contact dermatitis. So the inflammatory response to these fungal organisms is really quite interesting

DR. ROSEN: I am going to answer Bob's question directly because, as you all know, or many of you know, I work in the VA. Everybody has tinea pedis there, virtually, if you look. Many of them are inflammatory, whether you want to talk about interdigital or bolus tinea on the bottom

of the foot.

I wouldn't use this product, period. If I were going to use a topical antifungal, I would use one of the newer ones, as I mentioned. They have inflammatory effects. They can be used at a much shorter time period and much less frequently. And then I would look at the nails because, in some cases of tinea pedis, if not many of them, the source is really the nail and they require systemic therapy as well.

That is an additional point, but I, personally, would not.

DR. FELDMAN: I would not, in this situation or in any other situation. I think there is always a more potent antifungal, if I know it is an antifungal. If I know it is inflammatory, I know there is a cheaper antifungal that is of the appropriate potency. Even, as Bill was saying, if it is the situation where it is not sure, then I would pick, as Dr. Stern said, an antifungal of the appropriate type along with an appropriate topical steroid.

DR. ELGART: I have to agree with the other members of the antifungal experts, but I think, also, what we are dancing around a little bit is the fact that the indications on the label is not the way the product is used by the people who actually use it. I think that is really where the problem lies is that the use is perceived to be

different by those who use it than by those who write regulations.

DR. DRAKE: I don't feel a compelling need to use up all of our time, but I do want to make sure that everybody is heard from for this panel with questions. So I am going to poll my panel as well as the FDA. I am just going to go around and ask if there are any further questions you have for our panel of experts.

Eduardo?

DR. TSCHEN: No.

DR. DRAKE: John?

DR. DiGIOVANNA: No.

DR. DRAKE: Fred?

DR. MILLER: No.

DR. DRAKE: Bob?

DR. JORDAN: No.

DR. DRAKE: Wilma?

DR. BERGFELD: No.

DR. DRAKE: Dr. Chesney? Welcome back.

DR. CHESNEY: Thank you. How well has Lotrisone been studied in children? Do we have a lot of data on its use in children? Is it being used without any data?

DR. DRAKE: Actually, one of the things we might do--I'm sorry, during the presentation from the FDA--they gave a good one. There is a little bit in there that might

efficacy response over its individual components in controlled clinical trials. The Lotrisone Lotion has shown inflammatory, antifungal activity and similar inflammatory potency as the cream in clinical trials. The lotion, therefore, should be labeled the same as a cream.

[Slide.]

I would like to shift gears a little bit now. I have covered the efficacy. I would like to dwell on the safety of Lotrisone Cream in clinical practice and give you an historical perspective for what the safety has been with this particular product.

I think some advantages of coming from the sponsor's point of view, this is obviously a product that we are very interested in and we track it very closely. We follow adverse events. I am notified every time there is an adverse event. I get that report on my desk.

[Slide.]

This product has been in clinical use for sixteen years. Each year, there are 3.25 million patients treated with Lotrisone, a tremendous number when we talk about dermatology practice.

DR. KILPATRICK: Excuse me; where was that number from, for example? How do you know that 3.25 million patients are treated each year?

DR. PLOTT: We know from the sales of product that

we sell. We know how many tubes go out the door and we know, on an average, how many patients it takes to use a tube. For example, 1.6 prescriptions will be given to one particular patient.

DR. KILPATRICK: That is what I was getting at. You don't actually have the--

DR. PLOTT: That is the ratio of prescriptions to cases.

DR. KILPATRICK: That is an assumption.

DR. PLOTT: No, sir. We know how many tubes walk out the door.

DR. KILPATRICK: I know you know how many tubes walk out the door, but you don't know--I am a statistician and I am quibbling. I appreciate that, but patients are different from tubes is the point that I am making.

DR. PLOTT: I am saying that conversion is 1.6.

DR. KILPATRICK: I am saying there is some variation in that.

DR. PLOTT: That is an average.

DR. KILPATRICK: Exactly. That average may be inaccurate. I am just questioning the apparent specificity of your figures.

DR. PLOTT: That is across the sample of 62 million prescriptions. So I would say the confidence intervals are narrowing so that would could make a

won't call the FDA. In our VA hospital, we can't even get them to pick up the phone and call the pharmacy service.

I don't have a number and you don't have a number. Nobody has a number but, just in general, could you make a generic comment about the possibility that there are adverse events including atrophy, failure, worsening, that are not reported at all, and do you have any handle on that or any way to estimate that at all?

DR. PLOTT: I think the presentation that was made previously by the postmarketing group mentioned the variation and the weaknesses of this particular type of data. I can't tell you about adverse events that are not reported. I prefer to stand on data, what I know.

DR. DRAKE: I am going to take the Chairman's prerogative and say please, let's let Dr. Plott finish his presentation and please save your questions for the end because he deserves an uninterrupted time. I don't want him to feel under attack. I want him to be responsive and have an opportunity to present his case, and then we will ask questions that are pertinent once you are done.

Dr. Plott, please continue.

DR. PLOTT: Thank you. Let's go to the next slide. I think I have covered what I wish to here.

[Slide.]

I would like to point out the current trends in

clinical practice today as of 1999 for is the last full year that we have data for, which is 82 percent of all Lotrisone Cream prescriptions went to patients that were over 12 year old which is the appropriate age population.

For the patients where there were prescriptions written under 12 years of age, which is not labeled, the number of prescriptions is declining. In fact, in 1999, 17.9 percent of all Lotrisone prescriptions were for children under the age of 12 years old and 1.4 percent, again, of all Lotrisone prescriptions were for diaper rash.

In 1999, the tracking data suggests that there were just over 600,000 cases of diaper rash treated. Of all the diaper rash, 2.9 percent, or 18,000 cases, were treated with Lotrisone.

[Slide.]

So that you have an idea for the diaper rash picture which I think is the most important disease process that we are really talking about here today, non-antifungal treatments were used in 34 percent of cases. A topical steroid was given in 8 percent of these cases. Mycolog, a product that Dr. Elgart mentioned, a combination product that is only generally available generically, was used in 15 percent of cases. Lotrisone was used in 3 percent of cases.

I would propose to the committee that the general guidelines that were discussed early this morning are very

important not only for this product but for other products as well. In diaper dermatitis, that is important. The use in diaper dermatitis has declined. It has declined between 50 and 60 percent over the last ten years or so.

[Slide.]

Much of this decline has been in the under-1-year-old age group where there has been about a 75 percent decline from 1992.

[Slide.]

Adverse events in the under-12-year-old age group are certainly a concern for us. Any use in underage patients is inappropriate. It appears that these patients would be more frequently at risk if this product is used in an inappropriate condition like diaper rash, or if it is used for an extended period of time, 16 weeks.

The mean treatment period for the patients that were in the briefing book was 16 weeks. That is four months. That is much too long for any patient to be on a product like this and not to be reevaluated by their physician.

Physicians recognize the benefit and manage the risk of Lotrisone. That is probably why there is such use in this population. Physicians understand, because they have been educated. They know that they can't use this product for a long duration of time. They know they should

not be using it in the underage populations.

[Slide.]

In fact, I would like to point out some very important information that was not in your briefing packet that probably should have been, and that is the current label for Lotrisone. The package insert and the information that you have is the older label.

In May of this year, the label was changed. It is a more prominent label for Lotrisone Cream and we have been proposing the same labeling for the lotion. Let me point out what that label says because, like most physicians, I typically don't read labels.

In two places, the Indication and Use Section, and in the Pediatric Use Section, it is bolded and in all capitals, "Not to be used under the age of 12 and not to be used in diaper dermatitis." I don't know how more clear it could be; two places, bolded and all capitals on the label.

In fact, if you look at the label, in the Dosage and Administration Section, it says, "The use of Lotrisone Cream for longer than four weeks is not recommended." That should be a clue; right? "The Lotrisone Cream should be discontinued of the condition persists after two weeks in corporis and cruris and after four weeks in tinea pedis. Lotrisone Cream should not be used with occlusive dressings." It says that in the label today.

In the Information to Patients, we are trying to communicate to people. "Notify physician if there is no improvement in one week in tinea cruris and tinea corporis and in two weeks for tinea pedis." There is a clue; see your physician if you are not getting any better in short period of time.

"In the groin area, use the medicine for two weeks only." No matter what you have got; two weeks only. Schering has an ongoing effort to try to educate all physicians, especially about the appropriate ages where this product should be used and the duration of treatment and what the appropriate conditions should be.

We agree with the agency and we support augmenting our educational efforts to the pediatrician where we believe that it is going to do the most good in eliminating diaper dermatitis usage.

[Slide.]

Schering supports expediting reports of adverse events in patients that are under the age of 12-years-old. That is something we agree with. That is easy enough to do.

[Slide.]

Lotrisone Lotion should be labeled consistent with the current cream labeling. The product is safe and effective when it is used as it is currently being labeled today. We believe that that current label needs time to

take effect and see an impact that was just implemented in May 2000.

But Schering will continue to reinforce the appropriate use of this product as it is labeled.

Thank you for your listening. I would be glad to answer any questions.

DR. DRAKE: I am going to recognize Dr. Wilkin first since "he da boss."

Todd, while I am waiting on Jonathan, I just want to thank you for a presentation that, I think, answered some questions before they got fired at you.

DR. PLOTT: Good. Thank you.

DR. DRAKE: I also want to compliment you because Dr. Spraker, who doesn't use your product on kids, said that you guys were responsive to their initiative to you when they went to see you. So I think that is also very positive. I think this is an example where, if we work together, we can accomplish the goals that we want and that is the benefit of our patients.

So I want to thank you for the company's efforts and being responsive to the concerns of the dermatologic and pediatric communities.

DR. PLOTT: Thank you.

DR. DRAKE: I think that is positive and I think your presentation shows it. One slide you did not have I

wanted to make sure the panel--I was impressed with this--maybe I was looking down or something, but the linear decrease in the use of Lotrisone in those under one year old declined 75 percent from 1992. That is pretty impressive. And that was before your new label this May; right?

DR. PLOTT: That's right. I don't think that we have seen the impact on the decline in prescriptions in this age group yet because it has only been implemented since May.

DR. DRAKE: What I want to do now--Dr. Wilkin?

DR. WILKIN: I would just mention that we prepared the document before the time that Dr. Plott indicates that they submitted this material about the cream labeling. So it is true that was not in here.

DR. DRAKE: Okay; so that is positive. Now, let's have some questions. Dr. Stern?

DR. STERN: I have a number of questions. Let me start with the one that I think is most important. Would the company be amenable, rather than to changing the label, to, in fact, as has been suggested, to put on every box and every tube the same warning about, "Do not use in persons under 12?"

If we are trying to effect change, that is the way to effect change and not in the label since we are talking about 600,000 to a million people or tubes a year, depending

on whose estimates you use of inappropriate utilization. To me, a lot of it has to do with risk and benefit. I think we have firmly established that this is an agent that does not have huge therapeutic advantages over other agents.

It is not treating a life-threatening condition and, therefore, we have to look at less-than-optimal use, perhaps, more critically than we would in an agent that, in fact, has some unique therapeutic properties. So when there are 600,000 to a million inappropriate uses a year and it seems everyone agrees that that inappropriate use is pretty easy to stamp out without much loss of benefit by direct labeling of the product and its container, how does the company feel about being really proactive and not just doing labeling but, in fact, labeling the product, per se, the thing in the mother's or the father's hands?

DR. PLOTT: My response to that is that just in May have we revised this labeling, as I have indicated, that we have not see an impact on what that labeling change can do. Second is that, while there is inappropriate usage, as physicians, these physicians feel that they understand the risk and the benefit of this particular product and they are willing to take that risk because they know of the benefit.

The jeopardy that we put ourselves into in aggressively labeling this product is that we can get between the patient and the physician in that relationship.

DR. STERN: I think that there were data presented earlier that, in fact, the learned intermediaries who are principally prescribing this in the under-12 have a very low prevalence of knowledge about the potency of the steroid which is actually the issue here.

So there is an information gap. I guess, again, to me, it is risk and benefit. When you have a product that so far I have not heard anything that this is something with a unique therapeutic advantage, as opposed to being effective and safe when used as labeled, and you have a problem that involves hundreds of thousands to a million persons a year, it seems to me that you want to take direct steps and not wait and see what the trends will be in two or three years.

The only loss in doing that is really a loss of sales. The gains in doing that is that is how you can substantially--most individuals would believe that that would be the action most likely to change the use of this drug because--for all the reasons we have heard all day today.

So if you can really do something, why not do it? I understand it is going to cost you 20 percent of your market. But it is the 20 percent you are committed to getting rid of, according to what your label is. So why not do it?

DR. PLOTT: We have really gone further than simply putting a label or something on the box which is to go further to educate the physician. Writing something on the tube may not change the prescribing habits. It is going to be the education of the physician and, in this case, specifically, the pediatrician that is going to be different.

DR. STERN: I just had one other comment.

DR. DRAKE: Go ahead. Then I am going to go the rest of the panel.

DR. STERN: As you know, or as you may know, I have had some interest in spontaneous adverse-drug-reaction reporting over the last 25 years or so, or 20 years or so--

DR. ROSENBERG: 30.

DR. STERN: No; that's him. I will say 25 for me. But, in all seriousness, the whole focus on spontaneous reporting is basically unusual and serious, usually together. In looking at the numerators you have, I think you can only look at them in context.

I guess the context I would ask, because for not very serious reactions, it is product dependent, usage dependent, age-group dependent and company dependent. So I guess I would ask what are the rates per million tubes of reactions of this degree that are reported for the comparable two parts of this agent? How many ADRs did you

have for Lotrimin compared to the number of sales you have had? How many have you had for Diprosone over a comparable period--not Diproline but Diprosone--so we can get some idea about what the signal is in your system for agents that are at least both topical and, in fact, are the components?

Do you have those data?

DR. PLOTT: I do not have that data here. I can point to what we experienced in our clinical trials which was previously presented by a member of the agency. The adverse-event profile in the clinical trials was very comparable and it was low. But, obviously, we didn't have a million patients in the clinical trial.

We have looked at, some time ago, adverse events compared to Mycolog which is a similar combination. Our adverse-event rate was approximately half of what has been reported in the early 1990s for Mycolog. We were not able to get that data updated, however.

DR. DRAKE: I am going to go to John and then Wilma.

DR. DiGIOVANNA: Actually, I have two comments. I think they are on the opposite side of the coin. The first is that I just wanted a point of clarification. By labeling, we are really talking about what is in that little piece of paper in the box that the patients don't get. We are not talking about labeling the box or labeling the tube.

I think Fred and I were a little unclear about that. It would be of interest, I think, for me to see exactly what the tube and the box, the new version of it, looks like and whether or not there--and I guess this is really Rob's issue again--whether or not there is something that can be placed on the label to indicate to the parent.

DR. PLOTT: I have a copy of the new labeling.

DR. DiGIOVANNA: My second point was--

DR. DRAKE: Excuse me. Can I have the committee's attention all in one area? Dr. Stern?

DR. KILPATRICK: We are being chastised.

DR. STERN: We are number crunchers. I'm sorry.

DR. DRAKE: That's all right. I know you number crunchers. I am not going to let you sit together again.

DR. DiGIOVANNA: So all of this really is the package insert. The box and the tube have none of this.

The second is that the first point that Todd made, I think, really struck a cord because it recognized, to me, that I am extremely biased in this area. One of the points I made over lunch is that I probably think that the chair of my derm department would want to take back my residency certification for board certification if I actually prescribed this compound because he was one of the people who was extremely adamant against the use of combination products.

I think most dermatologists tend to feel that we treat specifically because we are trained to do that. I really would be interested in hearing the opinions of people, if there are such people, who really do favor this product because I don't think we have heard that.

DR. DRAKE: I think that was Dr. Plott's initial comment to us, that there is a whole body of experience out there that do use this product and like it. Perhaps, we are missing something.

DR. ROSENBERG: If we are going to have a general discussion, I would like to take that point of view.

DR. DRAKE: Take it. And then I am going to call on Wilma.

DR. ROSENBERG: I think one of the things that we just have to recognize, that caught me by surprise but I have thought about it, is the number of tubes of Lotrisone which are coded on well-baby visit. Let's stop and think what has happened. That baby has been there for a checkup. That baby has had a visit scheduled. It has been weighed. It has been looked at. It has been put on the growth curve. The mother has talked about how it is growing.

Her own concerns have been answered. And, on the way out, "How about this redness on Ginger's bottom?" This does not call for a referral to a dermatologist. It does not call for a KOH. It does not call for a new code or an

upcode. It calls for something that can be given that is going to be useful.

The sad thing is there is nothing--the combination rules that FDA is constrained by, have kept off the market what this pediatrician ought to be able to write for, or to suggest, something like Lotrisone/Baby, which would be the clotrimazole with half percent hydrocortisone.

It would meet that need. I have had, personally, a lot of experience at the Rx to OTC interface. It used to be one was one and one was the other, like night and day. But, you know, there is night and day but there is dawn and dusk and there is a lot of blurring.

When it come to patients, there are diagnoses, but then there is, "No, we don't need a diagnosis. It will straighten itself out, but in the meantime." I think we have got to rethink, as the practice of medicine is changing, so that more conditions are being treated by people themselves and more conditions are being treated at the primary-care level.

We have to rethink the kinds of--what the diagnoses are and move some medical diagnoses towards symptomatic kinds of things and allow the kind of product that we would have--I would write that prescription a lot if it were available and I imagine a lot of people would, too.

DR. DRAKE: I am to do Wilma, and then I have Joe.

I haven't forgotten your question. When I come to you--well, in a minute, we are going to really discuss it. I haven't forgotten you.

DR. BERGFELD: Bill, I have to agree with you. I think you have said this before this morning and early this afternoon. But I think that our responsibility here today is to look at a labeling issue on a prescription item that is already out there with a request for another vehicle.

So I am going to direct my questions to that, if you don't mind. I think, as I understand it, the lotion has a better effect on the side of health vasoconstrictive rate; is that correct? It is not as vasoconstrictive as the cream?

DR. PLOTT: In the vasoconstrictor, it was comparable.

DR. BERGFELD: Comparable? I thought the numbers were slightly lower.

DR. PLOTT: I believe the numbers that were shown earlier were maybe very minimally, but probably, I think, not statistically significantly different.

DR. BERGFELD: Thank you for clearing that up. So the studies that you presented on the cream and then you allowed to actually lap over to the lotion demonstrate that we don't have to repeat all the testing with the lotion as long as it has some efficacy that is equal as against

placebo. You did a little bit of an abbreviation of your study.

That is the first question. What we are doing is looking at another vehicle which has, perhaps, a little different elegance to it and, perhaps, a little different patient satisfaction for uses as you described.

The second question, and it is a brief question, is I am not understanding why 12 years old was chosen if we are talking about children.

DR. PLOTT: That is what our label limits--

DR. BERGFELD: I know what your label limits--but why did you chose 12? Why not 14 or 15? If we are talking skin and we are talking bones, the epiphyses are not closed until they are out a little older than that, 12. What is the basis of that?

DR. PLOTT: Unfortunately, that decision was probably made sometime before my time. However, I think that 12-year-old was probably not selected based on physiology but rather more classical age limitations.

DR. BERGFELD: It looks like it just was chosen. The last thing I would like to say is that I think that you have heard from all of us that we would like, in dealing with the label, that the label not only appear on the tube but there be some patient inserts that would be automatically given by the pharmacist to the purchaser;--

namely, probably the mother--so that they may have that information at hand about the adverse events.

DR. DRAKE: What I am going to do here in a minute, Todd, is let you sit down. I don't want you standing while we are getting into the discussion phase and we are tottering on that.

Joe, do you have a question for Dr. Plott, or is it a comment?

DR. McGUIRE: It is a comment that I would like for you to address. There are linked assumptions in this business. The first assumption is that if you print it in the PI, they will read. The second assumption is that, if they read, they will comprehend. The third assumption is if they comprehend, they will change behavior.

DR. DRAKE: You have been sitting next to Bill Rosenberg.

DR. McGUIRE: That was not my funny line. If I can get the panel serious again. It seems to me that all of these assumptions are flawed. The question of putting something in bold on the label and on the tube I think is an important one because very few of my families ever report to me anything about disturbing information in the PI.

So I think information--what is the point? The point is that a lot of information is lost in the package insert. I think it is paramount to put it on the tube and

on the box.

The second comment, and I will stop, is that I am very uncomfortable about using Diprosone or Lotrisone on genital or inguinal skin. I simply don't use those products in that location. I would hope that you would rethink the application of the product in whatever age group in genital or inguinal skin.

That's it. Thank you.

DR. DRAKE: I want to make sure that anything else, now, is a question for Dr. Plott and then we will get into the discussion phase. Dr. Chesney and then Ted.

DR. CHESNEY: Have you studied Lotrisone in children under 12 at all? Have you done any trials using it in children?

DR. PLOTT: The answer is that no; we have not conducted trials in children under 12. Our clinical trials included children up to age 12. There is, however, information in the literature on children younger than 12 and use in children younger than that.

We have summarized that information and that information has been discussed with the agency.

DR. CHESNEY: I would certainly urge you to do those studies. I think it would put you way ahead. But just one other comment--

DR. PLOTT: Let me comment there because I think

if you do studies in children under 12 but then you say that you should not use the product in that area, you are really in a Catch 22. How do you say, "Don't use it, but these are the studies." It is a difficult position for a sponsor to be in.

DR. CHESNEY: That was my next suggestion. Parents are extremely sophisticated these days. They get on the web. They come in office. They already know everything. In most cases, they know more than we do. I would urge not only labeling on the box and on the tube because, ultimately, they are the best advocate, but I would also urge that you say, number one, this has not been studied in children under 12 and that is why it is not recommended--

DR. PLOTT: It says that.

DR. DRAKE: It says that.

DR. CHESNEY: And, number two, what are side effects, not on the label but, again, a special insert for parents or on the box. What are the side effects? Just to say there are side effects is a very general term, but if they knew specifically what it might do, I think they would be very--

DR. PLOTT: The side effects are mentioned, and mentioned in the label. I would say that that labeling is in every box that goes out and is available to be read. I

don't have data on how many patients are going to read tubes more than they read labels.

DR. CHESNEY: Again, I would just like to echo what I have heard from so many people. None of us reads labels.

DR. PLOTT: Do we read tubes?

DR. CHESNEY: They are too long. They are too detailed. I am sure parents don't read the labels.

DR. DRAKE: Ted and then--just questions. And then Mary.

DR. ROSEN: I would like to get back to mycology for just one second. Not seeing many children in the VA hospital--in our wisdom, they don't serve in the armed forces, yet--what I have published and what I have seen personally in adults have been failures not in the common organisms for pedis, cruris or corporis, which would be T. rubrum, then T. mentag next, but in the animal-acquired predominantly Microsporum canis. That is what I wrote about and that is what I have seen.

My suspicion is that the initial indication, the initial labeling, was based upon in vitro data showing the clotrimazole by itself is sufficient, in vitro, to handle Microsporum canis. But it may be that this combination, in practice, may be less than optimal.

My suspicion is that, in your initial clinical

trials, the overwhelming number of patients were T. rubrum, maybe some T. mentag and very few Microsporum canis which is where I have seen failure.

Do you have any plans to address that or can you address that or can you tell me if the company is at all concerned about that?

DR. PLOTT: Specifically regarding Microsporum canis, the agency correctly points out in our lotion clinical trials, there were no patients treated with the lotion active ingredient with Microsporum canis. It was unfortunate, however, there were two patients in the lotion clinical trials that did have that organism.

They happened to be randomized to placebo, of course. So there is no experience with Microsporum canis. However, it is something that is more common in tinea corporis than tinea pedis which was studied and tinea cruris which was studied. So we didn't study the disease entity. We were not asked to do that where it might be more commonly found.

That is the data that exists. I think that we are in discussions about the remainder of the labeling and other issues regarding the lotion. That is likely to be one of the discussions that we have with the agency.

DR. DRAKE: Mary?

DR. SPRAKER: Todd, I think we all here in this

room in agreement that we would like to see the drug used as it is labeled. You indicated, in your presentation, that your company would like to reinforce among physicians the use as labeled. What concrete suggestions do you have of reinforcing that, or educating primary-care physicians further?

DR. PLOTT: We believe that the type of usage that we are most concerned about is in the area of the pediatrician where there are several things. It is under age of 12 where we are not labeled. It is diaper dermatitis or diaper rash where we clearly state, "Do not use this."

The pediatrician is the most likely person to see that patient. For example, the well-baby visit kind of thing. We think that education of the pediatrician probably needs to be augmented. Ways that we can do that are in our ongoing efforts where we are trying to educate physicians, all physicians, not to use it, but specifically target pediatricians, by our sales reps by also in direct-mail campaigns, focusing on physicians that are writing this prescription and communicating with them.

DR. DRAKE: That is really good. I am glad you asked that because I think it helps us get our attention back on--it helps us when we address the labeling. But our duty, our job, here today is to talk about labeling and get to the questions which I am going to do as soon as Bill

Rosenberg asks his last question.

DR. ROSENBERG: I want to ask about labeling. Have you had an opportunity to look at the computer-generated printed little story that is being generated at the various major drug stores when this is now being dispensed. My experience is pharmacists tell patients more than I want them to know about the side effects of the prescriptions I write.

Have they picked up on it? Is that coming out now, and so forth?

DR. PLOTT: That type of information that is handed out should be picked up out of the current labeling with the bolded print as we have indicated here. Unfortunately, that is variable depending on the pharmacy where you get your prescription filled. But we would expect that that is becoming more common where that is done.

DR. ROSENBERG: It's getting to be that there are not that many drugstores. They are all big chains.

DR. DRAKE: I am going to ask if there are questions from people who have not spoken.

Eduardo?

DR. TSCHEN: No.

DR. DRAKE: John?

DR. DiGIOVANNA: No.

DR. DRAKE: Fred?

DR. MILLER: No.

DR. DRAKE: Bob?

DR. JORDAN: No.

DR. DRAKE: Wilma?

DR. BERGFELD: No. Any more? Rob?

DR. STERN: No.

DR. DRAKE: Jim?

DR. KILPATRICK: I simply want to compliment you in keeping your cool under all of this barrage.

DR. PLOTT: Thank you.

DR. DRAKE: That was very nice. I agree.

Bill?

DR. ROSENBERG: Nothing.

DR. DRAKE: Joe?

DR. McGUIRE: Nothing.

DR. DRAKE: Joel.

DR. MINDEL: No.

DR. DRAKE: Jon? No questions?

I would invite you to stay because we may call upon you as we get into the discussion. So thank you, Dr. Plott. You did a great job. We appreciate it. I agree with your comment about being a little skewered, but we like you anyway and we appreciate all Schering does for us for our patients. So we are just trying to help you here to make the labeling a little better, or maybe reign it in just

a touch, as they would say in the South; "Let's just reign it in just a touch."

**Questions for the Committee**

DR. DRAKE: We are going to go to the questions right now. We have six questions to answer and we have about forty-five minutes to do it in. So I think, with your permission, we could start unless somebody feels the need to discuss something.

Joe, I haven't forgotten you. Before we start the questions, I am going to bring up your question you asked a long time ago because we are on the discussion phase. I think, before we hit Question 1, I would like Joe to restate his question because he wanted a sense from this committee. What was that again, Joe?

DR. McGUIRE: I just wanted to get some idea from the committee, realizing that it is a very special group of physicians and does not represent other specialties and generalists. But I would like to know if any of the committee use the product.

DR. STERN: I hate to say it, but I do; usually just the samples but, for example, when someone has got tons of lichenification in an intertriginous area, I will give them enough for three or five days if I have some samples. If someone has LSC right around the ankle and has tinea pedis, I will use it down there. I will give them a choice

between using two things or this, usually as a starter.

I often do combinations empirically by writing two scripts, but if I have some Lotrisone samples, I admit, I am a sinner.

DR. McGUIRE: I wasn't putting that litmus test on it. I just wanted to get some idea of what the frequency of use is.

DR. DRAKE: Does anybody use it very often? I think we are not the primary users.

DR. ROSENBERG: I ought to be pointed out that I think at least a couple of years ago, Lotrisone outsold all other topical antifungals combined--all other topical antifungals combined, a few years. Todd is nodding. So there really is a need for a product like this.

DR. DRAKE: Todd, what did you say?

DR. PLOTT: That is still true that it outsells all other single-agent antifungals combined.

DR. DRAKE: So people like it. I am going to say this, too. I am a big believer in treating what you know you are treating. I think you ought to have a diagnosis before you treat. I can just see my old chief. I see my chief shaking his head at me a little bit. But, in most instances, I like that.

On the other hand, there is something else you taught me and that is that patients are empirically smart

and if something works, they use it. And, if they don't like it, they let their doctors know and it doesn't get used again. So the fact that so many people are using this tells us something, I think, in one form or another.

I don't have any magic answers. I would ask you to keep that balance as we go through the discussion. There is a balance. There are a lot of people who like this drug and I don't think all the doctors and all the patients who use it are dummies. There are a lot of people using it for some reason.

On the other hand, we have a set of different concerns so I want to keep a balance as we move through the questions. And our task here is not to approve or disapprove this product. Our task here is to look specifically at the labeling to see if there are ways we can refine it and help to address our concerns, or the concerns that I have heard raised by this committee that, frankly, as I gather, shared by the company, also.

So, with that, I think what we will do is we will start the questions and try to go through them. Question 1 is what would be appropriate indications for Lotrisone Lotion.

Jon, may I ask you a question? Does the committee have an option of saying the same as the Lotrisone Cream or the same as the Lotrisone Cream with these changes? Would

you give us some guidance on this?

DR. WILKIN: Sure. At the end, we are going to ask the question, everything that you recommend for the lotion, does that also apply to the cream.

DR. DRAKE: That is what I wanted to ask you.

DR. WILKIN: What would be the appropriate indication, in part, is to address the aspect of, I think, how you have described it as symptomatic inflammatory tinea. I think you have addressed this in part, but, of course, you can rethink that now that you are thinking about a--

DR. DRAKE: Do we want symptomatic inflammatory tinea.

DR. WILKIN: Do you want those sorts of things. Currently, you will find that the labeling is for tinea and then it describes the different areas, pedis cruris, pedis corporis. The question is is there a need to modify that. In this case, it would be somewhat restrictive, restricting it to symptomatic inflammatory tinea, or any other phrase.

But the question is not meant to be limited to that. It is based on all that you have heard, you have recommendations, in general, related to the indication.

DR. DRAKE: So why don't we start with some generic comments then. I think, from our previous discussion on the first question, what would be appropriate indications for Lotrisone Lotion, clearly inflammatory

symptomatic tinea.

DR. STERN: But the other thing that came up this morning is that in virtually all of the studies that have been done of these combinations agents, it is in first five or eight days. So the question is should the indication be for symptomatic inflammatory tinea for up to eight days use with the recommendation that, for continued usage, just a monotherapy be continued.

Like I say, I use this agent actually often for three or four or five days in exactly that setting and am very comfortable with it. But I don't use it for 30 days because there is no advantage for the last 22 of them.

DR. DRAKE: What I am going to do, then--I have the same trouble with Question No. 1 that I did last time. It is very broad. I think if we go through some of the other questions and then come back to Question 1, we will have about answered it.

So I would like to go to Question 2 for the moment. If you look at Question 2, it is--possible wording for including in labeling may be--let's get the committee to respond to this--"minimally inflamed tinea pedis, corporis and cruris not requiring a corticosteroid component may be effectively treated with a topical antifungal drug product not containing corticosteroid."

DR. WILKIN: Dr. Drake, actually that was

misnumbered. It should have been 1a because it is really a subset of the first one.

DR. DRAKE: That is what I was thinking, it is a subset. This is not Question 2. This is 1a.

DR. STERN: That is an awful long way to say, "Don't use it in minimally inflamed." I think short, positive statements; "Use it here." "Don't use it there."

DR. WILKIN: Again, the wording that you looked at earlier and suggested symptomatic inflammatory. We are revisiting the same issue in a different--

DR. DRAKE: I think the answer here should be symptomatic inflammatory. That is what we spent a lot of time getting a general policy for and the committee was unanimous on that. Do I hear any dissension from the committee, clearly for 1 and 1a, at least in part, to just have us say symptomatic inflammatory tinea.

DR. DiGIOVANNA: It is not dissent. It is maybe clarification.

DR. DRAKE: Fine. Clarify.

DR. DiGIOVANNA: We had a discussion earlier as to whether the symptoms were from the tinea, whether the symptoms were from the inflammation because lots of times there is some itching or what not.

Do we want to say, "In tinea with inflammation sufficient to cause symptoms?"

DR. DRAKE: I would like to have you take that under advisement, Jon, you and your group because that is wordsmithing. Would you just take that under advisement as to how you think it is the most clearly presented. The concept is the same. It is just wordsmithing.

Does somebody else have anything? Wilma?

DR. BERGFELD: I think it might be appropriate to consider, in addition to this, and that is what Rob had suggested, is q question of limiting it in time of therapy, as to one week, two weeks or whatever would be decided upon.

The second part of that is what we speak of for the lotion should be true of the cream because they are so similar in their biological activity.

DR. WILKIN: If I could respond to that. The database we have is for the time period as listed in the dosage and administration section of the labeling. If we somehow cut that shorter, we really would not have a database to know what the antifungal efficacy would be in that circumstance.

DR. DRAKE: You have already got your timelines in there, basically.

DR. WILKIN: Yes.

DR. DRAKE: With those represented to us and, unless we see a need for change, then we probably should not mess with that because that means we have to go back and

redress the whole issue.

DR. MINDEL: With regard to the cream and the lotion having the same labeling or the argument for it, if you look in the PDR for different manufacturers' products containing the same ingredients, the labeling, especially the older labeling, may be quite dissimilar. So you don't have to have the same--that argument has limited merit.

I think, in this case, I want to emphasize that. The other is that we can all learn from our mistakes. So it doesn't have to be a very cogent argument that the lotion and the cream have to be labeled the same way. I would like to argue against--who is going to know? The patients? Is the patient going to pick up the cream labeling and the lotion labeling and say--

DR. DRAKE: Jon, I would like you to address that.

DR. WILKIN: I think maybe a more specific version or question would be actually two parts; give us what you think would be really good labeling for the lotion which is the product under consideration and then we would like your sense as to whether you think those would also be useful items to incorporate into the labeling for the cream.

Now, in this particular circumstance, we are talking about what we think of as a line extension. A line extension is a different vehicle for the same active ingredient or ingredients, the same concentration, the same

population, the same duration of usage, so are many relevant similarities between the two products and what they are intended for. Labeling probably ought to have some relevant similarities also.

DR. DRAKE: Would the audiovisual folks turn up these lights? Every time I look to my left, it is dreary. That sort of signifies nap time. Maybe I am just getting old and not seeing good, but I would like some light on the subject. I would like to see Dr. Epps, for example. I would like to see Ted.

Thank you. I feel like I have gone out in the sunshine. Sorry to digress with such a mundane thing. John, question?

DR. FELDMAN: I have a question for Dr. Wilkin. If we would recommend specific labeling for the lotion, would you then ask that the cream labeling be changed to meet that? Is that my understanding of what you were saying?

DR. WILKIN: Yes.

DR. DRAKE: Basically, for everybody, so you will know, we are sort of answering--at this moment, we are sort of beginning to answer Question 5. So we have kind of wandered into Question 5 here. But that is okay because if we answer it now, we don't have to do it later.

DR. WILKIN: The answer was yes.

DR. DRAKE: The answer was yes. So let's go ahead and answer Question 5. Or do you want to get the labeling for the lotion first and then decide if that is appropriate for the cream.

DR. DiGIOVANNA: I have a suggestion on the labeling. I think the labeling is great. It just needs to be moved to the outside. I think we have all agreed to that, outside the package.

DR. ELGART: We are taught early in our dermatology careers that the base makes a difference, that steroid ointments are more potent than steroid creams. Steroid creams are more potent than steroid lotions. We know here that the vasoconstrictor assay shows that this product is not as significant a steroid in a lotion form as it is in a cream form.

DR. DRAKE: No, wait. They are equivalent.

DR. ELGART: They are equivalent, but the numbers are a little less--not statistically equivalent, I know.

DR. DRAKE: They were basically equivalent.

DR. ELGART: So I think that we may want to make some change for the vehicle.

DR. DRAKE: I think the only way we would want to make--I appreciate your concern but, in fact, the major issue there would be the vasoconstriction and it is the same. So I think we would have to have some justification

for making them totally different. I don't mind considering that but I would like to have a justification that would make sense.

Wilma?

DR. BERGFELD: I would like to put on the table the consideration of a restriction in the labeling for use in the groin and, possibly, the face.

DR. DRAKE: Keep that thought because I don't want to get on the restrictions just yet. I want to look at--

DR. BERGFELD: No; it would be in the labeling.

DR. DRAKE: So you want it in all the labeling. Okay; I'm with you. Sorry. I got it.

I made whole list as you guys were talking about restrictions. I can tell you here is what came down the list was diaper dermatitis, groin dermatitis, breast, belly, face and underocclusion. So, I made a list in the earlier questions and comments. So it would quite a list of exclusions if you want to get into exclusions.

Jon, how do you feel about exclusions versus inclusions?

DR. WILKIN: Of course, one of the exclusions that you have mentioned, the groin, seems incompatible with a tinea cruris.

DR. DRAKE: That's right. But I am just saying this is a list that had fallen out on the table. Isn't it

true that if people would use these products according to the defined indications, which is five days--two weeks; right? Two weeks in the groin? Does that give anybody indigestion? If people would live with the labeling as it is, could you use this product for two weeks in the groin without getting into trouble? Why don't I just get a straw poll on that?

DR. McGUIRE: It is presumptuous for us to think that we can limit the duration of treatment. I don't know where patients get the drug but, if they start with a potent steroid and they like it, they get it. And they get it from me once.

DR. DRAKE: That is true with every drug, Joe. I don't know a single drug out here that is not abused. I can't tell you one single dermatologic drug that is not abused by people, by doctors particularly and by patients secondarily. Joe, Merve Elgart said it very nicely, what is in the medicine cabinet.

As a matter of fact, half the stuff is used for people that it wasn't even given to. It was given to your cousin or your brother or your next-door-neighbor or your brother-in-law. We can't control behavior totally.

What we are dealing with today is what is in the label. The label says two weeks in the groin. If that is acceptable, we have covered that issue. Is there anybody

who doesn't think that two weeks is acceptable in the groin?

Let's get a straw poll on that. I would like a straw poll because the labeling right now for groin restricts it to two weeks, no longer.

DR. DiGIOVANNA: May I ask a question?

DR. DRAKE: John.

DR. DiGIOVANNA: Were there not studies done that documented it was safe and effective and that has been declared.

DR. DRAKE: It has already been done. It has already been documented that it is safe and effective.

DR. DiGIOVANNA: So you are asking us if our subjective feelings are different than that.

DR. DRAKE: No; I guess I am asking if anybody feels strongly enough to ask the agency to look for a change in labeling for something that has already been proven safe and effective for that time period. In other words, we are trying to make a labeling better. We can't enforce human behavior.

What I am asking the committee to be is pragmatic. Please step away from your gestalt and your own personal prejudices and look at this in an objective manner. Is there anybody at this table who says a patient is going to be harmed by using this, is it safe and effective in the groin for two weeks? If there is, then you need to tell me

and you need to defend it, but the data suggest that it is for that time period.

Joel?

DR. MINDEL: The labeling, as it now exists, has a lot of messages in it. One of them says, "Clinical improvement with relief of erythema and pruritus usually occurs within three to five days of treatment." You could pick and choose the four weeks, the eight weeks here, the this and that, but this is a combination drug. One of the ingredients is only--I haven't heard an argument that it really is needed or useful or helpful beyond, say, a period of eight days, probably five days is maximum.

That, I think, bothers a lot of people sitting here at the table. I would like to see the labeling improved so that it restricts the length of the use of the drug.

DR. DRAKE: So you could stretch the length of the use of the drug?

DR. MINDEL: Limit.

DR. DRAKE: But it is limited to two weeks. So, Joel, what I want us to keep in mind is the labeling already says it is limited to two weeks. I think modifying the labeling is one thing. Changing the parameters for efficacy is another. This drug has already been proved safe and efficacious for that period of time.

I think the stronger issue here is defining what it is used for, perhaps. But I hate for us to go into this trying to change the safety and efficacy things because I think Dr. Wilkin, in his opening statement, says the company already has a letter that it is proven safe and effective for the time parameters as outlined in the previous studies.

That is not our charge today. We may feel that way, but that is not our charge.

DR. CHESNEY: I was just going to add to that that I don't think you can change that without doing the studies that demonstrate it.

DR. DRAKE: That's right. And that is not our task today.

Bob?

DR. JORDAN: it took me a while to find the two weeks but it is in here. I just wonder if, as a precaution, this could be bolded.

DR. DRAKE: Dr. Plott, just a suggestion for future reference; it might have been very helpful for this committee if you had had a blown-up diagram of the current labeling for every committee member so we would know how the drug is currently labeled. You can see we are grappling with trying to find it. Just a suggestion, if this comes up again. I may not be here but please--

DR. STERN: I think there are two issues. One is

what is the right labeling and the second is what is the right way to get the message across so that, in fact, there will be a substantially higher compliance with the labeling between information to the learned intermediaries and to the consumers.

So I think the labeling is not so much the issue as how should those rules be made apparent and operational in terms of the entire gestalt of education, packaging, et cetera, et cetera.

DR. DRAKE: I have a suggestion how I am going to proceed, then, as chairman because we could get bogged down in this forever. The opinions are all over the place. I want to have us vote on each question as defined to us by the agency because these are the questions they wanted answered.

And then, following that, if we have additional suggestions and comments or guidance things that we could propose to them, I would like us to do that also. Would that be satisfactory, Dr. Wilkin, to you guys, because you always take into account what we say.

So let us address your questions as requested and then we shall add any additional suggestions and recommendations that haven't already been offered. Reasonable? Okay.

I think Question 1 has been answered by the policy

discussion we had early on. Question 2, I am going to ask you--1a: thank you, Wilma--remember Question 2 has been changed to 1a. The thing I am going to ask you to vote on is this wording acceptable to you. Forget the second paragraph there. I want to talk about just, "Minimally inflamed tinea pedis, corporis and cruris not requiring a corticosteroid component may be effectively treated with a topical antifungal drug product not containing corticosteroid."

Yes; question, Joe?

DR. McGUIRE: I think the thought is good. The sentence needs a lot of surgery. It just sort of tumbles over itself.

DR. DRAKE: It is awkward, isn't it? It is an awkward sentence; yes.

DR. WILKIN: Actually, I thought you had just addressed this. This was where we got the response of symptomatic inflammatory and then Dr. DiGiovanna gave a rearrangement of those words--

DR. DRAKE: And I said we were going to let you wordsmith it.

DR. WILKIN: And we are going to--

DR. DRAKE: Thank you, because I already said does the committee approve it and everybody did. Thank you, Jon. Let's go to Question 3. Question 3 is, "Should Microsporum

canis be deleted from the list of dematophytes for which Lotrisone Lotion is indicated pending phase IV studies to demonstrate clinical efficacy in the treatment of M. canis?"

Comments? Let me just ask a question. How many of you say yes. The vote would be yes versus no. How many of you want to vote yes on this?

DR. BERGFELD: Is it in the list of the--is it there?

DR. JORDAN: It is here. I can see Microsporum canis.

DR. DRAKE: It is already in there. Bob, thank you for having that in front of us. That is very helpful.

DR. JORDAN: I have really got to magnify to see it.

DR. DRAKE: That is why I suggested to Todd that the next time you give us a big thing. But it is there. It is already in there as an inclusion; right--that is indicated for the treatment of M. canis. Our job here, today, is do we want to keep it in there or do we want to delete it.

The question from the agency is do we want to delete it from the list of dermatophytes for which Lotrisone Lotion is indicated, pending phase IV studies. Other comments or questions?

All in favor? Anybody who wants to vote yes to

delete M. canis, pending phase IV, please raise your hand.

[Show of hands.]

DR. DRAKE: Eight. It passes.

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

DR. DRAKE: Yes.

DR. ROSEN: Remember that you are already concerned about the labeling and the assumptions that physicians will read the label, understand the label and act appropriately. I would suggest to the voting panel that you consider something about labeling, "Caution should be used in those dermatophyte infections suspected to be acquired from animals," because I have a feeling that some of the prescribing physicians wouldn't know the difference between Microsporum canis and Superman.

This may not mean much to them. They must understand that this is animal-acquired fungus somewhere in common language, somewhere in the labeling, not "Don't do it," but, "Caution."

DR. DRAKE: That is a suggestion for the agency to take under advisement please.

I am going to move to Question 4. "Is the labeling for pediatric use of Lotrisone Lotion as proposed by the sponsor sufficient?" That, and correct me if I am wrong, says basically it should not be used for dermatitis and it should not be used in those under age 12. That is

the current labeling; is that correct? It says, "Should not be used for diaper dermatitis or under age 12."

Is that sufficient? Let's ask that. Or, the next part of the question, "Should the label be further strengthened; i.e., via alternative language, additional statements in the Warnings or Contraindication Section and placement of warnings on the product tube, itself?"

That is a big one. Fred?

DR. JORDAN: Actually, I am just going to be reiterating, I think, what has already been said but when we talk about an educational process and you are going to reach physicians, so many people slip through the cracks. It is impossible to have an ongoing campaign where you truly get everyone.

New physicians come on board. People are not there when the process takes place. People don't read the literature that comes through. The one thing that we have gotten from this is that this is not approved for pediatric patients and it should not be used in children under the age of 12. We have heard that plea, I think, from the expert panel.

The only place it is really going to have any effect is on the tube, itself, "Not to be used in children." And then parents will see it and they will certainly bring it to the attention of the physician.

DR. DRAKE: We have certainly heard that around the table today. other comments?

DR. McGUIRE: I would include box.

DR. DRAKE: A black box?

DR. McGUIRE: No. On the box and the tube.

DR. DRAKE: Oh; on the box and on the tube. I am certainly hearing a consensus. Maybe I could kind of take this backwards. Can we take the last part of this question first?

DR. STERN: Why don't we have a motion.

DR. DRAKE: Please.

DR. STERN: I move that we recommend to the FDA that it be clearly indicated on the container and the tube or bottle that use under age 12 and for diaper dermatitis are contraindicated in lay terms.

DR. DRAKE: Is there a second to that motion?

[Second.]

DR. DRAKE: Is there discussion on that motion? Bill?

DR. ROSENBERG: Perhaps an amendment that could say, "See Lotrisone/Baby for such use."

DR. DRAKE: Is there a second to that amendment? No?

DR. KING: Part of why you don't speak up is you try to get the sense of it. My sense is, having worked with

the federal government for a long time, that regulations have the force of law. When you deal with law, you deal with lawyers, having recent experience.

So what you are really talking about is if a pediatrician writes a prescription for this, inadvertently or whatever, then they are going to be held to standard practice and sued. So, in a contrary observation, I have noticed that when we deal with research people from China and all around the world, in our laboratory, when we have skill and crossbones on there, they don't read, but they can see that and they know exactly that is poison.

So I guess my question is how can you get across the information in a visual way not depending upon English as a primary language. If you have an X through there--I was trying to draw a diagram of what a diaper would look like and put an X through it but I couldn't quite get there.

It seems to me that the question is how are you going to get that because, in our experience, creams get handed around from mother, father, across the back door, shared. So I think if it is not on the tube, itself, without a skull and crossbones on the chemical thing, you are going to just pass it around anyway. Nobody is going to read that label. That is just wasted.

DR. DRAKE: Lloyd, you have brought up two separate points, both which are important. One is that

words are inadequate; you need a picture.

DR. KING: Absolutely; highway signs.

DR. DRAKE: The second thing you brought up that is equally important is on our zeal here today to try to make this language sterner, even Mary Spraker, our pediatric dermatologist--what is the matter?

DR. STERN: Sterner?

DR. DRAKE: Excuse me; no pun intended. My meetings are never boring, Rob. You have to say that. You guys haven't been taking a nap down there today.

I want to go back to Mary Spraker's comment. Even in the best of times, knowing the best of information, when it is your eight-month-old son screaming because he is miserable, you may, in fact, decide that, in this particular instance, for a day or two, it is appropriate and useful in this particular situation.

We, as physicians, have always had the ability to use something if, in our best judgment, we thought it was appropriate. What my question is is do we want to be absolute in this and fix it so that nobody can ever use this for any reason and take that decision-making power away from the physician or do we want to try to word this in a softer manner.

When I was writing guidelines of care for dermatology, we tried to write it so that we gave the best

recommendations and advice we could give, but we tried never to restrict the physician's ability to make an independent decision about what is best for their patient based upon a government regulation.

Now, if somebody's life is at stake, then we may want to be that absolute. On the other hand, I think we want to be very careful, as we set this policy today, that we don't restrict a physician's ability to make an independent decision regarding their patient and what is in their patient's best interest.

There is a difference between education and mandated forbiddance.

DR. KILPATRICK: Madame Chair, we are not setting policy.

DR. DRAKE: We are if we vote this.

DR. STERN: The company has already, in the Lotrisone Cream, actually said it better and, in fact, it was on the slides as well, "Not to be used under the age of 12 and not to be used in diaper dermatitis." Plain English. Bold type.

In fact, my original question is--

DR. DRAKE: I hate it when you are right.

DR. STERN: So, therefore, all of the legal implications are already here because this is the official document. Everything else is window dressing, as I

understand it with the FDA.

DR. DRAKE: But, does this mean anybody who uses it goes to jail?

DR. KILPATRICK: Madame chair, Rob is not only right but he is also stern.

DR. CHESNEY: I think there is a difference between contraindicated and should not be used. Contraindicated suggests fear and damage. Although we have evidence for that, I think the vast majority of the time, there is no side effect of this. So I think "Should not be used" is good, but I still would think about the caveat, "Because it has not been studied in children."

We use a lot of drugs in pediatrics, as you all know. We have to talk to the parents and say, "This is not indicated but it is only because it hasn't been studied. And these are my reasons for thinking that this is a drug that we should use anyway."

DR. DRAKE: That is a very nice way of softening it so that it still leaves that independent choice to the physician and yet tells them not to do it. I would like to ask, from the other pediatricians in the room, what is your reaction to that?

Dr. Epps?

DR. EPPS: I agree. Most of the drugs in the PDR haven't been tested, necessarily, in kids under 12. But we

use them, and it is my understanding from the rules, that if it is approved and, of course, there is compassionate use and reasons and indications to use it in children and in other situations. So those are instances when it occurs.

DR. DRAKE: Dr. Spraker?

DR. SPRAKER: I have been sitting here thinking about the pediatrician who induces striae and then goes to court. I was thinking about that actually before Lloyd mentioned it. It seems to me that we don't want that kind of difficulty. That is what Schering is talking about. They don't want to be in the middle between the physician and the indication.

But I was wondering if we could say, "Not intended for use in diaper dermatitis."

DR. EPPS: "Not recommended."

DR. SPRAKER: And because of those reasons. It already says, "Do not." I understand that.

DR. STERN: This label without the actions to protect it is exactly what puts the physician in danger. Here we have all agreed that here is a piece of information that the members of the committee were not aware of, let alone the practicing pediatrician, that protects Schering from suit.

They have told us, as a learned intermediaries, not to do it. So the way to protect the physicians, once

something like this is in the label, is to make sure there is every level of protection so that an unintended use is less likely to occur.

As long as this is here, anything that we don't do to get information to every level along the use chain is, in fact, putting every pediatrician with greater risk. This is basically liability proof from a company's point of view and a slam dunk from a lawyer's point of view with the kind of information system as has been pointed out by my much older colleague that is unlikely to be translated into changes in behavior.

DR. DRAKE: Can I do something for just a moment because we have drifted from the motion. We can come back to discuss the changes in the wording but the motion, as I understand it, is to take whatever wording we end up with and add it to the tube and the box.

Can we vote on that and get that out of the way and then go back to wordsmithing again? Is everybody in this room in favor of putting whatever wording is finalized by the agency on the box and the tube. I would like you to vote yea or nay on that.

How many are in favor of putting said language on the box and tube?

[Show of hands.]

DR. KILPATRICK: Madame Chair, I am a literalist.

We would have to have a very large tube to put all this wording on. So, amended, I agree with the sense of this wording, but not this wording.

DR. DRAKE: I think you have got a valid point. I can't believe where I am on this. I called for the vote. It is already voted and passed, so your comments--

DR. KILPATRICK: Will be considered.

DR. STERN: We just said appropriate warning.

DR. DRAKE: So it still can be done. Jim, the motion has passed. The motion was appropriate wording, whatever we end up with, so the agency can then finesse that down so that it does fit on the box. The sense of the committee, and the motion of the committee, is that a warning be put in the box and on the tube of some sort.

Does that satisfy the agency? Are you guys okay with that?

DR. WILKIN: Yes.

DR. DRAKE: I am sorry we were not more specific. Your comment is good. It should have just come in a little earlier because it is valid. I am certain Todd is over there dying, thinking, "Oh; my gosh, I have got to put twenty-five things on the tube." And you can't. But I think you can work with that if that is where the agency goes.

Remember, we are only advisory to the agency.

They may make a different decision altogether.

DR. PLOTT: I was just going to say, we don't mind making a bigger tube.

DR. DRAKE: True marketing over there.

I want to go back--I guess it is sufficient, since some of us want to weaken it--I didn't really want to weaken it. I just wanted to add a softening such as Dr. Chesney's suggestion.

DR. EPPS: The other issue is it is a class 2 steroid. So if you want to use a steroid, use something else. Don't use it. I think that is what the company is saying, "Not to be used under the age of 12 and not in diaper dermatitis." If you want to use a steroid, don't use a class 2 steroid there. Use something else.

DR. DRAKE: That is a positive suggestion, but that doesn't really address the label. You can't say on the label, "Use something else." No company is going to go for that. "We want you to use another product."

DR. BERGFELD: Hearing the concerns of everyone, in the PDR information, package information, under the discussion of the corticosteroid, is it appropriate, or is it possible, to place there that it is a class 2 steroid?

DR. WILKIN: The idea of describing it as a class 2 steroid implies that we have some evidence from a vasoconstrictor study in which we have bracketed the

vasoconstrictor response by that of known potency preparations. It hasn't been bracketed, is the key.

DR. BERGFELD: I would suggest that, if it was possible to do and, again, something to take back to the agency, that, under the discussion that is paragraphed on the second side of this first page, it might be helpful to those who would read it to know what class of steroid they actually have.

DR. ROSENBERG: I have a lot of patients if they read that would say they want a class 1 steroid.

DR. DRAKE: Dr. Wilkin, I want to go back to Dr. Chesney's comment. I tell you, I am still concerned. I know the company is very happy with saying this is absolutely don't use it because you will die, but there are a lot of physicians out there using it and, in some instances, it is in their best judgement for the benefit of their patient.

Is there anybody on this committee besides me and Dr. Chesney who would like to add this language here that was actually in our packet where it says the reason we are adding this language is because it has not been established in well-controlled clinical studies in the pediatric patients under 12.

Would anybody besides the two of us like to see that language added?

DR. DiGIOVANNA: I see two issues. I see that addresses the fact that it hasn't been studied and it softens it, which I feel fine about. It doesn't really address the side-effects issue as much.

Part of the reason that I feel you are making an appropriate point is because we are not hearing, as Todd mentioned, from the people who like this drug.

DR. DRAKE: That's right.

DR. DiGIOVANNA: I clearly have been biased against it. So I am wondering if we are not missing information from people who do use it and use it appropriately. I think what you are suggesting is that, by us coming out and recommending a blanket condemnation of it in that age group, we are really condemning it and not hearing from the people who appear to think it is effective.

DR. McGUIRE: John, the other side of what you just said is that many of us sitting around the table have seen the children who have been treated inappropriately and who have atrophy, who have ecchymoses. We see them after they are three months, six months, twelve months into treatment.

They got their drug somehow. We don't know how. But we are the ones who have seen the bad effects.

DR. DiGIOVANNA: I have also seen those, and that was the first part of my question, that saying that it

hasn't been studied doesn't address the side effects.

DR. DRAKE: Those people are already in violation of the label. If you used it for two weeks, like it said, it might not happen.

DR. McGUIRE: No. I was addressing John's issue with the bias of this group. I think we are biased for a reason.

DR. DiGIOVANNA: I agree. I am biased for the same reason.

DR. McGUIRE: We are the ones to whom those children come.

DR. DiGIOVANNA: But that doesn't change the fact that we are not hearing from the people who apparently have a different bias and we are apparently recommending labeling that prevents them from doing what they apparently consider effective. And I don't know how many of those 62 million prescriptions were used by pediatricians who felt that it was very, very effective and were basically coming up with an imprimatur that says, "This can't be used in that age group."

And we are not saying because it hasn't been studied. We are merely saying it can't be done.

DR. DRAKE: It can't be used. Dr. Chesney? And I am going to ask Lloyd to comment.

DR. CHESNEY: I had wanted to make this point

before that if there were any way to put an insert, and somebody else had mentioned that, in the box for the parents explaining what the side effects are--one thing that I haven't heard any of you mention but that I have seen personally, being in infectious disease, is babies, when they have severe Herpes simplex infections of the diaper area can look like a diaper dermatitis.

This is obviously strongly contraindicated. So, as an advocate for infants, I would like to put as much information out there as possible for pediatricians who I think you are all quite correct, don't know what category of steroid this is and don't always know about these side effects, although most of us understand the scarring.

But if there were something, again, to put in the box or on the label, "Hasn't been studied; side effects that should be considered are the following." I also appreciate your comment about the physician who has to go to court because of striae, but something to say that infant skin is different from adult skin and we don't know all the side effects. Some other wording that also explains what the side effects are is going to be educational for everyone.

DR. KILPATRICK: Lynn, may I add to that?

DR. DRAKE: Yes, Jim.

DR. KILPATRICK: Coming back to the label as distributed, information for patients, unfortunately, comes

at a break of a page, but there is a list of seven items there that I think are very important. I would like to see those incorporated with Dr. Chesney's suggestion and put in quite separately because, at the moment now, they disappear.

I know I am off the question.

DR. DRAKE: No; that's fine. That is an important comment. Lloyd, and then Dr. Epps. Fred, you have been awful quiet. And Bob. You guys have been quiet down at this end. Maybe I am not looking this way. Holler at me, would you?

DR. KING: My comment is quite simple. Having sat on the academic side and also on the VA side, it becomes clear to me that, in the land of the rare, the rare is common. What we are not hearing is what the pediatricians and other people, internists, are doing. So if you have a product that is beneficial to a lot of people and then, all of a sudden, you are restricted to that one population which is likely to see you, it then gets to be population genetics.

My mother almost died twice in Vanderbilt Hospital because she was allergic to aspirin. One could conclude that aspirin should be banned because it causes reaction. We have people allergic to water. You can take this ad nauseam but it seems to me the fundamental problem, as I see it, is what is the greater good and what is a physician to

do when facing this kind of process.

If we are going to make a decision on the group of physicians who use this a lot more than dermatologists, I think we have to have some input. And then, the reverse of that is that if we are going to make these kinds of things, they really do have the force of law, whether you say so or not, because, in the State of Tennessee, whatever it says on the PDR and the insert is actually what the lawyers look up, and they sue you for injecting a triamcinolone, et cetera, et cetera, because it is written there.

So I think putting it on the label and let the mothers and fathers decide even if they can't read English would be a best solution. Short of that, putting something on the tube where you don't have to read English at all and have somebody else look at it is the best solution as far as I can see.

DR. DRAKE: Dr. Epps?

DR. EPPS: Briefly. Certainly, we are not hearing both sides, necessarily. I do see some of the ineffective cases. I guess it is hard to do clinical trials and controlled studies when people are using it on something that is not diagnosed. There are a lot of people who use it and they don't necessarily have a diagnosis so it is kind of difficult to sort that out when another drug or something else would take care of it just as easily, I guess, whether