the immune-compromised individuals, especially children with AIDS, in which they are going to be exposed to azoles for many years to come and we are going to contribute to the development of resistance in those kids.

[Slide.]

I just wanted to make a few comment about Candida detection from reading the literature supplied in the red books. Candida albicans, as we have heard already today, is ubiquitous and commensal and, actually, if you look hard enough, you can find Candida commensal colonization on a variety of different skin surfaces, up to seventeen different body locations.

David Sole in Iowa can get Candida from all those locations in a normal, healthy person. Clearly, the GI tract is constantly colonized with Candida albicans so Candida albicans is not--it is difficult for me to think of Candida as not being in any particular body location.

[Slide.]

I would also like to make the point that there has been a lot of discussion about pseudohyphae. Candida albicans does make both yeast cells or blastospores and pseudohyphae. But the point is that we now understand that pseudohyphae can be and are present both in commensal growth and in disease or infection.

So it may be just a numbers game. When you see

pseudohyphae, you may associate it with disease just because the numbers are higher but, on a molecular biology level, hyphae are seen both in commensal growth and in disease or infection.

[Slide.]

In addition, I think that in the Year 2000, we have to start thinking about the fact that Candida albicans is not the only species anymore. While it was the predominant species, 80 or 90 percent in the '80's, nowadays, it is 50, 60 percent in populations, especially populations who are using azoles.

In addition, as has already been mentioned, we have two pseudohyphae-positive species; Candida albicans and Candida dubliensis. Dubliensis is a relatively new species. It is difficult to differentiate from albicans. But one of the problems with it is that it tends to be more azole-tolerant and so, in fact, you could be--one of the things that complicates the situation is that we have this species that is pseudohyphae-positive and azole-tolerant.

In addition, these other two species, glabrata and krusei, that are more azole-resistant, are increasing in frequency. These are pseudohyphae-negative. Glabrata and krusei clearly can cause oral, systemic and vaginal infections. I looked and was unable to find any documentation whether they do or do not form dermatitis or

skin infections.

[Slide.]

So, in terms of Candida detection, pseudohyphae is not a great indicator, especially if glabrata or krusei are increasing in frequency. Culture usually requires a long time and can be less sensitive. Even a KOH is going to have a problem looking for the presence of cells. Again, there is a certain amount of low sensitivity in developing a KOH.

[Slide.]

The last point I would just like to make is that we have been studying a variety of patient populations including diabetics and AIDS patients, et cetera. This correlation between number of Candida cells and disease is not always a good correlation.

We have diabetics with 5,000 colony-forming units per ml in their saliva--this is oral candidiasis--5,000 colony-forming units per ml, and they have no disease. So their commensal growth in their mouth is 5,000 colony-forming units per ml with no disease, and we have AIDS patients with as little as 50 colony-forming units who have erythematous candidiasis.

So this absolute correlation between numbers and disease is not a correlation that you can draw, at least in oral candidiasis. I don't know about dermatitis. So the usefulness of a detection tool to say Candida is present or

not, in my mind, there are a lot of issues surrounding that issue.

I would like to stop there. Thank you.

DR. DRAKE: Are there any questions? Dr. DiGiovanna?

DR. DiGIOVANNA: I found that very helpful. One question I have is you mentioned agricultural use of azoles. I wonder specifically would that include this product and what sort of agricultural use?

DR. WHITE: There are other azoles as well as other enzymes. The azoles target a specific enzyme in the biosynthesis of a sterol called ergosterol. There are a lot of agricultural products to several different steps in that biosynthetic pathway. So there are some azoles available for agricultural use, but there are also other drugs that inhibit other parts of the same pathway.

As we have looked, we see cross-resistance. When you make mutations in both the pumps and in the target enzyme, you can also get cross-resistance to these other drugs that are available for agricultural use.

DR. DiGIOVANNA: Do you know if this product is available for animal use?

DR. WHITE: I don't believe so.

DR. KO: I can answer that. It is available for animals but not at that concentration requested today.

DR. DiGIOVANNA: Is it topically available, systemically? Is it widely used or is it used--

DR. KO: Topically.

DR. DRAKE: Dr. Chesney?

DR. CHESNEY: Dr. White, this question may be for you or for Dr. Rinaldi or Dr. Witebsky or maybe the company. In the materials we were provided, it says that miconazole has activity against Gram-positive cocci, Gram-positive bacilli and Gram-negative organisms.

That was a surprise to me. I wonder what kind of activity we are talking about. Are we talking about static or cidal activity, because, although we are focusing on the fact that the Candida might become resistant, and I think most of us would agree with your summary, I am beginning to wonder whether we should worry about whether we are replacing normal flora with resistant bacterial flora.

I wondered if anybody had experience with what the MICs are. Is it cidal or static? Have there been any studies looking at the bacterial flora following miconazole use?

DR. WHITE: I can't speak to the antibacterial effects of azoles.

DR. RINALDI: Don't lose any sleep over this. In the early days of azoles, it was determined early on that there was, indeed, some antibacterial activity but

clinically, when they put it into clinical use in animals, right from the start, it was clear that this was one of the crappiest antibacterial drugs that ever was.

So this is not going to do anything to any bacteria that is going to be of any meaning to anything. So you can sleep good tonight.

DR. DRAKE: Joe?

DR. McGUIRE: Dr. White, thanks for your talk. It was very informative. But I heard two things. In the first part of your talk, you said, "It is going to be okay, Joe. Don't worry about it. An occasional exposure is not going to induce resistance."

And then, at the end of the talk, you got my attention again by talking about glabrata and dubliensis and krusei. So which part of the talk do I take on?

DR. WHITE: It is clear that, in the Year 2000, we are not just dealing with Candida albicans. We have glabrata and krusei and tropicalis and other species to worry about. I don't think there is any good data on the common commensals.

The shift from albicans to glabrata/krusei/tropicalis, et cetera, has occurred in immune-compromised patient populations and other patient populations in which azole drugs are used. I don't think there is any evidence, at the moment, that the normal

commensal colonizers are switching but, in the presence of azole drug, there is the potential to switch from--to gradually evolve towards these other non-albicans species.

Asking me to predict how that is going to happen based on this drug, I can't make those predictions. We know that that shift has occurred in the patient populations which use fluconazole, itraconazole, vorconazole, et cetera.

Did that answer your question?

DR. McGUIRE: Thanks.

DR. DRAKE: Dr. Rosen, you had a comment

DR. ROSEN: I would actually like to ask Dr. White for a comment based on a question that I am going to ask, or even the sponsor as well, since we didn't have a chance to ask questions of the sponsor directly.

DR. DRAKE: We will in a minute. Right now, I would like to address our questions to our experts, please

DR. ROSEN: Okay. Then I will ask Dr. White. The product that is under consideration is a 0.25 percent miconazole-containing ointment whereas what is available and up on the podium there is a 2 percent miconazole-containing product. There is a difference in concentration.

In your expert opinion, as a mycologist, does that percentage, lower percentage, over time, or with repetitive use, enhance, decrease or no difference in terms of the potential for resistance, understanding we are talking about

theory, now.

DR. WHITE: Let me just mention the AIDS patients and the bone-marrow-transplant patients. Clearly, the levels we are talking about are much different because those patients were treated with much higher doses.

In the AIDS patients, they were given essentially low doses of azoles and resistance occurred over--they were given low doses for long periods of times, months or years, and resistance developed.

Bone-marrow transplant patients are given high doses daily and resistance is developing within a week or two. So we have low doses developing over a long time and high doses developing over a short time. I think the answer is it is a static drug and you are going to get selection for strains or species that are more resistant.

The lower dose, it may take longer to develop resistance. A higher dose, it may take a shorter amount of time.

DR. DRAKE: Dr. King?

DR. KING: I find it quite fascinating, your last bit of data about the number of organisms in the mouth bears no relationship to disease. It leads to the question, if there is an increased number of Candida in the mouth in diabetics, is that also true for the genital area because that is a well-known phenomenon, that candidiasis of the

genital area is quite common in diabetes, and diabetic children have the same kind of problem.

That makes interpretation very difficult. The presence of candidiasis in great numbers does not mean disease.

DR. WHITE: First, I should say that diabetics do have a higher incidence of Candida infections than other patients. The fact that they have more Candida may predispose them to have higher disease. My point was just that you can have patients with a high number and no disease.

I think it is also important to keep in mind that at least orally there are two types of Candida. There is a massive overgrowth and there is a subtle interaction of Candida with the mucosal surface which we believe also happens vaginally, although it is not well documented vaginally.

So you can have a massive overgrowth, the cottage-cheese phenomenon, but you can also have a subtle interaction of Candida with mucosal surface which results in an inflammation which causes as much problem as the massive overgrowth.

DR. KING: Then is it a math problem, a numerator versus a denominator, the numerator would be the number of organisms and the denominator would be the number of cells

reacting or cytokine response? Is that what you are saying?

DR. WHITE: I think that the equation is that you have a pathogenic yeast and an immune system. Both of them are--it is a war. How they each fight the war will determine whether you get disease or not.

It could be numbers. It also can be how the fungus is actually attacking the mucosal surface.

DR. KING: It seems like if you have commensal growth, there is no war. One side has already surrendered.

DR. WHITE: Absolutely, but you can also have low numbers of Candida that are causing an immense immune response that is causing that.

DR. KING: I won't belabor it, but that is an intriguing point.

DR. DRAKE: Steve?

DR. FELDMAN: One quick question. We heard that with the topical, even in its lower concentration, we are still a thousand times the MIC. You mentioned the high dose used in the bone-marrow transplant unit. What kind of dose is that in relation to MIC?

DR. WHITE: Well, I believe the point made about the topical was the systemic level of the drug. Clearly, that is a thousand-fold lower than anything you will see with bone-marrow transplant patients.

But I think the issue is what is the concentration

of the drug at the surface of the skin, which I don't know what that is compared to the MIC.

DR. DRAKE: Seeing no other hands, I think moving right along. It is early for lunch. We might be able to go on through. So is the FDA ready to begin your presentations? Great.

Dr. Wilkin? Are you going to make some opening comments? You want to switch?

DR. WILKIN: Actually, Dr. Ko will begin the presentations.

DR. DRAKE: Dr. Ko will go first. Dr. Ko, please.

I want to compliment our expert witnesses. Your presentations were concise and informative. It was great. So thank you for taking the time to do this for us.

FDA Presentations

NDA 21-026 Miconazole Nitrate, 0.25 percent

DR. KO: Thank you, Mr. Chairman.

[Slide.]

Today we have NDA 21-026 before us with the proposed trade name Pediastat. This has not yet been approved and so I will be just mentioning the drug as the sponsor's product. The sponsor is Johnson and Johnson Consumer Companies.

[Slide.]

My presentation will be divided into the following

areas; diaper dermatitis as a clinical condition, diaper dermatitis as an indication, the sponsor's miconazole nitrate, 0.25 percent ointment, development of topical antifungal products for diaper dermatitis and the sponsor's development program.

Then I will address the risk of resistance before making the conclusions.

[Slide.]

I am going into a discussion of diaper dermatitis as a clinical condition. As you know, this condition is usually managed by parents and general practitioners, pediatricians and, really, the dermatologists may be seeing the more recalcitrant cases.

[Slide.]

I don't want to go into this slide in any detail because this has been discussed a lot in the last two days. Basically, diaper dermatitis is primarily an irritant-contact dermatitis aggravated by other factors.

Also, it may be predisposed by some underlying conditions such as atopic seborrhea or psoriatic diatheses. Secondary infections can include fungi and bacteria including Candida albicans.

[Slide.]

Concerning the role of Candida albicans in diaper dermatitis, again, we have had a lot of discussion on this

this morning. But, as you have heard, the recovery rate of Candida albicans on the skin of infants with diaper dermatitis varies a lot from 8 to 77 percent in the literature.

It may depend on the actual population being studied. As I said earlier, most diaper dermatitis cases do not necessarily go to the dermatologist and may not even go to the physician. Also, we have heard from the experts that the collection and culture methodology may affect the outcome of recovery.

We have heard discussion from the panel about the role of the Candida cells in diaper dermatitis in the absence of actual live cells. Suffice it to say, without going into detail, that the experimental data were not actually done in the diaper area and they were done using levels that are probably much higher than those expected in the diaper area.

From the sponsor's studies, Candida albicans at the rash site, can be recovered in about one-third of the patients, both in the U.S. study and in the one Australian study where a culture was done. So, in two-thirds of cases, Candida albicans was not recovered.

[Slide.]

You have actually seen the data here from the sponsor. This is from the U.S. study concerning--the data

here concerns recovery of Candida albicans in patients who had clinical suspicion of candidiasis and in those without clinical suspicion of candidiasis.

If you look at the pie chart there, again, two-thirds of patients do not have Candida albicans recovered and one third are positive in the cultures. But, with the culture-positive group, clinical Candida constituted only 8 percent while clinically not suspected of candidiasis is 25 percent.

So these 27 percent probably will represent those who have colonization but not overt clinical evidence of infection. Again, you have about two-thirds of patients that are negative for Candida culture. Then, significantly, you have 7 percent of patients who had the clinical suspicion of candidiasis even though they are culture negative.

[Slide.]

Now I am going to the area of diaper dermatitis as an indication. For the sake of time, I will not discuss with you about OTC things because the request for this NDA is for a prescription product. If you prefer, we can discuss about OTC issues later.

[Slide.]

In one of these advisory committee meetings in November of 1990, the issue of diaper dermatitis was

actually discussed. In the summary minutes, it says that the committee discussed the problems with terminology of diaper dermatitis as a diagnosis as it could include chemical irritation, bacterial or secondary fungal infection or some unrelated disease process.

At that time, the committee unanimously agreed that diaper dermatitis is not a defined diagnosis and, therefore, is not an appropriate indication.

[Slide.]

The indication requested in the proposed label is infants with diaper dermatitis. Now, I have noticed today that the sponsor's slide says treatment of infants with diaper dermatitis, so that is slightly different. According to the regulations, indications for drugs should be for treatment, prevention or diagnosis of a recognized disease or condition. The example quoted was like pneumonia due to pneumococci.

Or manifestations of a disease of condition such as use of a diuretic for edema. Or relief of symptoms associated with a disease or syndrome. The example quoted was like use of an antihistamine to treat symptoms of rhinitis.

The indication could also be for selected subgroups of the larger population with a disease syndrome or symptom which can be identifiable with specific tests

needed for selection or monitoring. I understand from the discussion that there may be a problem in dealing with Candida for this condition that we are addressing.

Or the condition may be reserved for certain indications such as cases refractory to other drugs. Again, we had this discussion earlier this morning that diaper dermatitis is a family of indications and so this proposed indication could be problematic.

[Slide.]

I am going to discuss with you about the sponsor's product, miconazole nitrate, 0.25 percent ointment.

[Slide.]

This product contains a lower concentration of miconazole nitrate than that which is currently available. It also contains zinc oxide, 15 percent, in an ointment base petrolatum. Again, I want to mention that this is an ointment base drug. We have heard earlier that zinc-oxide paste may be a preferable kind of skin barrier in this condition.

This product is approved in twelve countries but not in Norway. Again, I am not going to discuss with you about the reasoning of Norway but, if you want, we can talk about it at question time. The product is an antifungal and the proposed label under the mode of action mentions only antimicrobial activities and not any claim on the

petrolatum, zinc-oxide ointment base.

Since we have heard today a lot of discussion about the skin-barrier effect, we understand that this is present but it is not a claim for this product.

[Slide.]

I am going to talk about the development of topical antifungal products for diaper dermatitis.

[Slide.]

This is a quote from Dr. Schroeter in the advisory committee meeting in November of 1990, which I have mentioned earlier. Dr. Schroeter said, "If you are doing studies for antifungals in diaper dermatitis, you should do it scientifically and get positive cultures and identification of organisms just as we have done with other infectious diseases in studies where we were studying the efficacy of an antifungal agent."

For those with diaper dermatitis without fungus infection, indeed, they are not qualified for the study because we are evaluating the safety of an antimicrobial agent specific for fungus, yeast.

[Slide.]

Here I list those endpoints that we generally accept for the success of there for an antifungal therapy. I think this has been addressed somewhat yesterday, too. We would like to see mycologic cure, having negative KOH and

culture results and absence of symptoms and signs and complete cure with absence of mycologic positive results plus a clinical cure.

These parameters are generally evaluated at the end of treatment and at a predefined follow-up visit.

[Slide.]

This is just quoting the guidance on the study of vulvovaginal candidiasis which speaks of the same thing, that you need to set up at the baseline KOH demonstrating presence of the yeast and also culture positivity for the studies.

[Slide.]

The importance of KOH in antifungal studies on Candida infection is emphasized by Dr. John Bennett who, unfortunately, is not able to come today. In his book, he mentions that, "The demonstration of pseudohyphae on a smear of cutaneous oral esophageal and vaginal lesions is the single best diagnostic test and biopsy is not necessary."

Culture of skin or mucous-membrane lesions can support the microscopic findings but such a culture, itself, is not diagnostic.

[Slide.]

I have mentioned these data a few slides back and also you have seen it from the sponsor. Basically, even the sponsor agrees that Candida albicans is present in a

substantial number of rashes that do not have the characteristic appearance of candidiasis which may be due to colonization rather than infection then.

[Slide.]

We have heard a lot about clinical practice, both yesterday and today. The agency does not regulate clinical practice so I am not going into any discussion of that. The only thing I want to mention is that even in Nelson's textbook of pediatrics, the pediatricians have been recommended to do KOH or culture to make sure that they are dealing with Candida infection before treatment.

[Slide.]

The next topic would be the sponsor's product development.

[Slide.]

The clinical program has been discussed by the sponsor this morning. Briefly, the program consists of phase I dermal safety studies and a pharmacokinetic study in infants with diaper dermatitis. To support this NDA, three phase III studies for diaper dermatitis in infants are presented, one United States study and two Australian studies.

In addition, there is a study for diaper dermatitis in elderly hospitalized patients.

[Slide.]

I am going to discuss with you about the efficacy data. Before that, then, we need to talk a little bit about the phase III studies.

[Slide.]

The sponsor has presented the design of studies and here, suffice it to mention, these are studies done in the 1980s. Two of the three studies were done in Australia. The first study was underpowered and the sponsor also agrees with that in their presentation. It is a two-center study which did not succeed. There was some trend, but it did not show statistical significance to demonstrate the efficacy of their product.

The Australian studies consist of one single-center study that had cultures studies done and another study which had two centers but lacking mycologic data for an antifungal. Other issues are listed here very briefly. There is a lot more detail in your briefing package but we have no time to go into them.

The distinction between subtypes of diaper dermatitis is unclear and the status of Candida albicans involvement not clearly defined. As you heard from the sponsor's presentation today, the emphasis is still on endpoints that are not pertinent to antifungal studies. You have heard about the reduction in the rash scores. That may be good for a study on skin protection but we are dealing

with an antifungal here. And we don't have information on follow-up visits after the end of treatment at Day 7.

[Slide.]

The U.S. study, as I mentioned, had two investigators. There were 100 infants with dermatological manifestations consistent with the diagnosis of diaper dermatitis who were randomized to active and vehicle.

The drug was applied to clinically affected areas with each diaper change and after bathing for seven days. The treatment was to continue even if signs of the diaper dermatitis were no longer visible. There was clinical evaluation during and at the end of the study and culture on day 0 and at the end. There was no KOH or wet mount for detecting the Candida

[Slide.]

This slide shows the data from the U.S. study. At day 7, patients with clinical and culture clearing are shown as follows. As you can see, patients with baseline Candida-culture-negative, there was no significant difference between active and vehicle.

With Candida-positive-culture patients, there was some difference but not statistically significant. Again, as we mentioned earlier, this was the study submitted in 1985 to support the OTC treatment of diaper dermatitis and, since the study was no successful, this was not approved.

It is important to note that with the active group, there were only 35 percent having clinical and culture clearing. So, about two-thirds of patients did not have complete clearing and these patients would be prone to continue treatment if the prescriber feels that it is important to continue the clearing.

[Slide.]

The Australian studies were very similar. These two studies had almost identical protocols except that, in one study, we do not have culture information. Also, one study, despite having culture information, was a single-center study.

The sample size has been increased, so it has doubled the U.S. studies. The protocols were otherwise similar to the U.S. study. Also, no KOH was done.

[Slide.]

Here we have the efficacy data on the Australian single-center study since this is the one with culture information. Those patients having clinical and culture clearing did not show a significant difference between active and the vehicle in the Candida-albicans-negative group, Candida-albicans-negative at baseline.

Also with the Candida-albicans-positive group, the active treatment group, had 63 percent success. So you have 37 percent of patients who did not achieve a complete kind

of clearing. So, again, these may be patients more prone to have repeated treatment.

[Slide.]

The second Australian study does not provide any mycologic data so, for the sake of analysis of an antifungal effect, this was really unevaluable because it would not be possible to see whether the product has the intended effect as an antifungal. So we could only look at the clinical clearing. Clinical clearing occurred with 61 percent of the patients and so you still have about 40 percent that did not clear clinically and, again, may require additional treatment.

[Slide.]

This is only a summary of the information you have seen in the past few slides. Again, baseline Candida-albicans-negative, there is not significant difference between active and vehicle while for those having baseline Candida-albicans-positive cultures, one single-center study showed that there is a significant difference between active and vehicle.

But you still have a substantial proportion of patients who are prone to get further treatment.

[Slide.]

The sponsor also provides information on one Belgian study in elderly hospitalized patients with diaper

dermatitis. It is not used to support the proposed indication. I am just showing you this for completeness sake. It is a double-blind parallel group comparison of 14-day treatment with miconazole nitrate, 0.25 percent ointment or, the ointment base followed by 28 days of open-label use in these patients applied with each diaper change and at least twice daily.

The endpoints were global clinical response and mycologic culture.

[Slide.]

At the end of the blind phase, there was no significant difference between active and vehicle with regard to clinical clearing or mycologic clearing. At the end of the 28-day open phase where the initial vehicle group were also given actives, or everyone had active, really, also there was no significant difference between these patients.

Again, you can see that even after six weeks of treatment, 14 days in blind phase and 28 days of the open phase, even for mycologic clearing, it was only about one-half.

[Slide.]

Conclusions on the efficacy data. Although statistically significant finding in patients with positive baseline Candida albicans cultures at the rash sites is

noted on one single-center Australian study. The U.S. study with two centers does not support effectiveness.

The sponsor's product has not demonstrated superiority over the ointment base in patients with negative baseline Candida albicans culture at rash site. The rationale of extrapolation of the Australian data to the U.S. has not been provided until this morning we have heard the sponsor's presentation including some rationale.

Again, I am not going to go into this for the sake of time but, if you would like, we can address this in the questioning period.

Efficacy in diaper dermatitis of elderly hospitalized patients is not demonstrated.

[Slide.]

I am going into the safety issues.

[Slide.]

The patient exposure to the sponsor's product in phase III studies can be summarized in this table. The table shows the number of patients who actually received the proposed product. Even though we have 252 patients exposed in phase III for seven days, however, the groups are of greater interest, those with positive or negative Candida albicans cultures.

We have only information on 47 for the positive and 105 for the negative because, unfortunately, we don't

have information on the second Australian study.

[Slide.]

The sponsor calculates potential exposure in the application about 24 days on average and maybe up to 80 days for severe episodes and recurring in infancy. So the conclusion from the sponsor is that total exposure really is limited to approximately three months, and so the child would not have chronic exposure to the drug substance. Miconazole nitrate is for non-chronic indications only.

[Slide.]

This slide deals with potential exposure. The agency's focus on safety is on conditions of maximal use compatible with labeling. Depending on the likely projected usage, maximal use may not necessarily be for eight episodes or 80 days as suggested by the sponsor. Yesterday, you heard postmarketing data of other drugs that have been used for diaper dermatitis and could be up to many, many weeks.

Topical miconazole nitrate to the diaper area does not address the reservoir of Candida albicans which may predispose to relapse. Again, you have heard this morning about these infants who actually harbor the Candida albicans in different areas of the body, maybe up to seventeen locations.

[Slide.]

Our safety concerns may be summarized in this

slide. This is an ointment base product. The occlusive nature of petrolatum zinc oxide in Candida infection has not been explored either by the sponsor or actually in the literature. The adverse effects may be masked by the presence of an antifungal.

Patients given miconazole nitrate in the Belgian study on the elderly, there was one report there in which a patient who had left hemiplegia, that with use of the treatment, developed moniliasis genitalis which was considered severe and had to be discontinued from therapy after 24 days of treatment.

Also, in your package, there is this paper by Dr. Campbell at Baylor that shows that topical petrolatum ointment reportedly promoted increase in the incidence of systemic candidiasis in extremely low-birth-weight infants.

I am coming back to these dermal safety studies in phase I that I mentioned earlier. These were done in healthy adults. They are not done in the diaper area. So we really need a good database to insure safety in infants with diaper dermatitis, especially those with Candida infection.

Unfortunately, the adverse-event database may be incomplete. The briefing package mentions to you that in two of the phase III studies, the adverse data were actually collected in the form of treatment-related adverse events,

not necessarily all adverse events. So if the investigator did not regard the event as having relation to the treatment, it is not an adverse event.

[Slide.]

The next topic is on resistance. We have heard a lot this morning so I am going to be very brief.

[Slide.]

Candida albicans resistance was first reported with miconazole in 1978 in The Lancet by Holt and Azmi in a patient treated for urinary candidiasis. Even in that very first case report was cross-resistance to clotrimazole and econazole reported already.

[Slide.]

Here you can see the structural formula of miconazole. It is only different from econazole by the absence of one chlorine atom. Fluconazole looks very similar. It just is a difference mainly in an azole group compared with a benzine ring there. These are the other azoles that you have heard discussed this morning.

I am going to pause here and I will call on Dr. Marsik to address microbiological issue in his review.

Miconazole Nitrate, 0.25 percent, and Diaper Dermatitis

DR. MARSIK: Being the last speaker, I kind of feel like the fellow that survived the Johnstown Flood. You are all becoming experts and you know the little story about

he was one of the few survivors of that flood and he really was proud of himself for being an expert on survival of floods.

Of course, when he got up to the Pearly Gates and St. Peter was there, he was expounding on his survival of this flood. St. Peter looked at him and said, "I'm sure that Noah would be very interested in your story."

[Slide.]

What I am going to try to do is address some of the microbiological aspects on miconazole and its 0.25 percent as proposed by the applicant.

[Slide.]

As we are all aware, miconazole nitrate has been used over the years as a topical treatment for fungus infection due to both yeast and filamentous fungi. Its primary use today is in the treatment of dermatological infections due to Candida albicans. Miconazole, as has already been mentioned, has minimal activity against bacteria.

[Slide.]

To treat these various infections, miconazole has been applied in various forms; creams, sprays, powders and ointments. The concentration of miconazole in these various PDR-listed products is 2 percent.

[Slide.]

Miconazole nitrate is fungistatic. It is not cidal against C. albicans as well as other fungi. It is effective only against organisms that are actively growing; that is, organisms that are in their log phase of growth. Because miconazole is fungistatic, post defenses play a major role of eradication of infection and effecting a cure.

As is true for the azole class of antifungals, miconazole acts to inhibit the biosynthesis of the membrane lipid, ergosterol. The target of the azoles is the cytochrome P-450 dependent lanosterol 14-alphadimethylase enzyme which has been found to be encoded by the ERG11 gene.

The interaction of miconazole with the enzyme results in less of the normal ergosterol end product and the accumulation of 14-alphamethylated sterols. This process induces changes in membrane structure and function which results in membrane leakiness and alterations in membrane-bound enzymes which eventually leads to the death of the organism.

[Slide.]

The information in this slide and on the next is based on nonstandardized susceptibility test methods. There is a need to obtain this type of data using standardized susceptibility test methods such as are being developed by the National Committee for Clinical Laboratory Standards.

The range for the minimal inhibitory concentration

of miconazole needed to cause cessation of growth of a variety of Candida albicans is seen on this slide. As can be noted, the range for C. albicans in the literature is quite wide being from 0.016 to 100 micrograms per ml.

[Slide.]

This is some data that was presented in the applicant's submission. As can be seen, a concentration of 1 microgram or less was shown to be required to inhibit 67 percent of C. albicans and a concentration of 10 micrograms or more was required to inhibit 33 percent of C. albicans isolates.

[Slide.]

The optimal activity of miconazole nitrate has been shown in vitro to occur in the pH range of 6.0 to 7.0. Above 7.0 and below 6.0, its activity is diminished. What effect the alkaline environment of a urine-wet diaper area has on the activity of miconazole has not been adequately studies in vitro or in vivo.

[Slide.]

Fungal infections that are refractory to antifungal treatment may be a result of the presence of a strain of organism that has an MIC greater than the safely achievable concentration of the antifungal. Some of the factors that can lead us to this are mutation, transient gene expression, alteration in cell type or alterations in

the fungal population.

[Slide.]

Molecular mechanisms that can cause a cell to be less susceptible to miconazole nitrate can be the result of any one or combination of what is seen on the slide; alteration in drug target, for instance. In this case, the amino-acid substitutions in the drug target, the 14-alphadimethylase enzyme, leads to insensitivity of the enzyme to the action of the miconazole.

Alterations in sterile biosynthesis is another example and is best exemplified by the accumulation of lipid 14-alphamethafecosterol. The accumulation of sterols other than ergosterol can result in a cell becoming less susceptible to miconazole.

Lack of sufficient concentration of active component at the target site is another molecular mechanism of resistance. This is, in the majority of cases, the result of overexpression of efflux pumps which has already been discussed to some extent.

To date, two types of efflux transporters have been recognized in resistant isolates of C. albicans. These are the ABC transporters and the so-called major facilitators. The ABC transporters appear to be more important in relation to azole resistance. The possible mechanism of efflux-pump overexpression is increased mRNA

levels that can be a result of increased transcription, gene amplification or increased half-life of the mRNA.

It has been suggested in the literature that miconazole, at subtherapeutic concentrations, may induce the activity of the CDR1 gene that mediates the activity of efflux pumps.

Finally, another molecular mechanism is overexpression of the drug target. Here, the ratio of the enzyme, 14-alphadimethylase, the drug is so great that there is not enough drug to interact with all the enzyme present. This overexpression can be the result of enhanced transcription gene-chromosomal amplification.

This method has been described in other species of Candida but has not so far been described in Candida albicans.

[Slide.]

Recent evidence also indicates that a combination of two or more molecular mechanisms is needed to cause practical resistance to miconazole nitrate. This has been referred to by some as the additivity effect. The action of only one mechanism results in reduced susceptibility that may not be of practical concern. Further research is needed to fully understand the additivity effect.

Cross-resistance between the azoles should not really be any surprise since the azoles all have a similar

chemical structure and mechanism of action.

[Slide.]

It is recognized that the 0.25 percent concentration of miconazole in the product under discussion is substantially greater than the average in vitro miconazole MIC of C. albicans. In fact, it is 2500 times greater than the MIC of 1 microgram required to inhibit the majority of C. albicans isolates and 250 times greater than the MIC of 10 micrograms needed to inhibit the other one-third of C. albicans isolates.

However, the 2 percent concentration found in currently available preparations is 20,000 times the MIC of 1 microgram and 2000 times the MIC of 10 micrograms. What the margin needs to be between the in vitro miconazole MIC and the concentration of miconazole needed in a product to eliminate C. albicans associated with diaper dermatitis is not known.

Only well-designed and executed clinical studies can provide some of that information.

[Slide.]

With the use of 0.25 percent miconazole, there is the theoretical possibility that development of resistance is greater than with a 2 percent concentration. This could be result of such things as physical factors: simple application of the product; the type of diaper that one

might using, whether it is a cloth or a paper type. Even with the different papers that are available, there might be actually different binding activities of miconazole.

Or it could be due to chemical factors such as a alkalinity at the site of application decreasing the activity of miconazole. Due to the fact that exposure of C. albicans to subtherapeutic concentrations of miconazole may cause resistance to develop and/or enhance the production of virulence factors such as secreted aspartyl proteinase, it is essential that the concentration of miconazole at treatment site be sufficient to inhibit the growth of C. albicans.

[Slide.]

We have already discussed this topic. Diaper dermatitis certainly is multifactorial in nature and microbes are recognized as playing a role in the diaper dermatitis most often when it progresses beyond a mild diaper dermatitis. Candida albicans has been implicated in the maintenance or the worsening of the condition.

As we have heard, recovery of C. albicans in the literature has been reported in anywhere from 10 to 75 percent of patients with diaper dermatitis.

[Slide.]

The literature is ambiguous as to the common approach physicians take for determining if there is a

microbial etiology to the diaper dermatitis when an infant is first seen with the condition. The literature does support the fact that the KOH wet mounts and culture can be very useful in establishing etiology of diaper dermatitis.

Results of both the KOH examination and culture from clinical studies are crucial for evaluating the efficacy of antifungal treatment.

[Slide.]

In summary, well-designed and conducted clinical studies are needed to adequately document the efficacy of 0.25 percent miconazole nitrate for the treatment of diaper dermatitis. The studies are needed to establish the correlation between microbiological outcome and clinical cure. Proof of concept must be scientifically established.

[Slide.]

In addition, the studies are needed to characteristics the miconazole susceptibility and virulence of isolates that are recovered from clinical-study patients. Such studies will also better characterize the role of microbes in the etiology of diaper dermatitis and provide a more recent susceptibility profile of C. albicans to miconazole based on standardized methods of susceptibility testing.

Thank you.

Wrap Up

DR. KO: Thank you, Dr. Marsik. I will wrap up the discussion just in a few minutes.

[Slide.]

Concerns for resistance. As you have heard this morning, low-strength exposure may promote resistance development. In fact, in your briefing package from the sponsor, Dr. Rinaldi actually says that the clinician should employ higher doses of the azole for optimal therapy to occur.

Also, patients often have a non-cutaneous reservoir not addressed by topical treatment but may be exposed to amounts of antimicrobial suitable for the induction of resistance leading to future treatment failures despite initial success.

Dr. White has mentioned about the problems in the day-care setting and also in hospitals, also in the ICU. Candida albicans and Candida species resistance to miconazoles and other azoles have been demonstrated.

Cross-resistance to other azoles used to treat life-threatening systemic mycosis may pose a more serious public-health concern.

[Slide.]

So, in summary, the safety data shows that there are small patient numbers for the target populations for evaluation. The outcome beyond seven days has not been

known. The dermal safety studies are standard tests in healthy volunteers in healthy skin, so we really need a better, larger database to have more safety information.

Potential adverse effects from the ointment base on worsening of Candida infection is not really addressed because it is possible that it is masked by the antifungal and it might need comparison with no vehicle.

Again, the issue of resistance is hard to address and has not been really fully addressed because of the lower strength, the target population being infants whom might have a more immature immune system. Again, the cross-resistance issue to the antifungals used to treat serious systemic infections.

[Slide.]

Conclusions. The design limitations of the phase III studies precludes meaningful conclusion to be drawn on the antifungal efficacy of the sponsor's product which is the 0.25 percent ointment not the 2.0 percent that is currently available in the patient population that may benefit from it.

Specifically, most of the patients in the studies were culture-negative. In this group, the benefit has not been proven. Although the sponsor's product appears to be well-tolerated, we still have the safety issues that I just mentioned in the last slide.

[Slide.]

To end my talk, I will just show you what Dr. Schroeter, the chairman of the committee in 1990, said during that advisory committee meeting. "Despite showing efficacy and with proper labeling, however, what we are saying is that, from a practical clinical approach, there may be exceptions to our approving such a product--that is, antifungal in diaper dermatitis--because it will, indeed, be used for other than the specific item of labeling, i.e., fungal infection. It will be used for irritant dermatitis and, therefore, it will be inappropriately used."

DR. DRAKE: Thank you, Dr. Ko.

Are there specific questions for Dr. Ko right now? Dr. Wilkin, do you want to finish the FDA's--are you doing a presentation or presenting the questions?

DR. WILKIN: Actually, I was going to say a few words regarding the FDA point of view.

DR. DRAKE: Would you please do it now?

DR. WILKIN: And then it is your pleasure whether we hear the questions at that time or later.

DR. DRAKE: Fine. Please go ahead.

DR. WILKIN: Okay.

Comments

DR. WILKIN: I would just like to say that I think there is actually more convergence than may be apparent

between our FDA team's point of view and the sponsor's team's point of view.

I think that all of us recognize that a product that is for the treatment of diaper dermatitis that is shown to be safe and effective for that use would be an advance for the public health. I think we recognize the goal is to have a product that will meet this need.

The question is whether we now know enough about this product to have it go forward at this time. Again, I respect the views of the sponsor and also the members of our FDA team. We all know that intelligent, well-meaning folks can look at the same dataset and, at the end of the day, come down on different sides of how they think about it.

One of the key pieces to the sponsor's review of the data is they looked at these rash scores, mean rash scores. I think one of our difficulties from the point of view of the review team is that there could be folks that would have a mild improvement that would lead to a significant difference in the rash score that might, at the end of the day, not really predict whether they were going to, at the end of seven days, have sufficient clearing that they did not need further therapy.

The other issue is it is hard for us to know how many of the folks would relapse or require treatment after seven days. So we used the more conservative index. We

looked at those who had negative mycology at the end and had a rash score of 0.

The U.S. study, it is possible that the fault was that it was underpowered, but it was not significant. It did have a signal in there. The point estimate for the group that had Candida was 35 percent were culture-negative and rash-score 0 at the end of treatment.

It occurs to us that that is kind of a low point estimate and we are concerned about the need for retreatment or relapse in that particular group. Also, in the U.S. study, there was no difference between the active and the vehicle in the Candida-albicans-negative group.

In the Australian study, that was where the largest signal was seen. 63 percent of those who had Candida cultured had a response in that seven-day period. The difficulty there is we think that is an important signal but it is a single investigator site and it is always helpful to have multiple investigators so we can see what kind of variability can occur in different kinds of practice settings.

Again, in that particular study, in the Candida-albicans-negative patients, there was not much difference between the outcome in the active versus the inactive.

In the other Australian study which had two

investigators, they did not look at Candida so, once again, it is hard to make something out of that. We are not sure who is driving the success, whether it is the Candida-positive folks, Candida-negative folks.

I think it would be great to have a product that would be good for both Candida diaper dermatitis and other varieties of diaper dermatitis in which Candida may be playing a role and possibly even irritant because I think that is hard to really tease out--I would argue that we really haven't heard today that anyone can draw a line between this pole out at one end that says there is a lot of Candida involvement and, at the other end, where we would say there is virtually no--it is kind of this inter-grade.

I think that the kind of information we need before approval really is that that subset of patients out there who have what looks clinically like Candida, that has a scraping like Candida, a culture like Candida, that we need to know that the group is sort the epicenter of the Candida diaper dermatitis folks.

I would think that we would want to know that that group got better before we would have this kind of product approved.

At the other end of the scale, it is a little--I am trying to think through this especially listening to Dr. Spraker and Dr. Paller. I recall back at the institution

that I came from, we saw a lot of young professional women who worked at the medical center and they would work sometimes half a day, three-quarters of a day, and their children would be in the day-care center.

I am probably going to get in trouble with the day-care centers of North America, but we had a phrase that we called "day-care diaper dermatitis." Basically, they just didn't change the diapers when they became soiled.

The mothers who had come in with the infants were very comfortable hearing that it really didn't require a medication. It required gentle cleansing, frequent changing the diapers and, when they got them home in the afternoon, if they could give them four or five hours with their rear ends sort of up in the air and dry, that those kinds of things, and some of the other, zinc-oxide paste, that that would help a lot.

So, at that other extreme, it would be nice to know that we are not medicalizing a kind of diaper dermatitis that can be treated in much simpler means that doesn't require an active drug.

So what we didn't see is that the standard kinds of things that Dr. Paller talked about and Dr. Spraker talked about, that they may well have been incorporated into the practice of the physicians who were conducting these studies. But if there is going to be an additional study,

it would be nice to know that it is conducted in the setting where they are doing the things that we think are sort of the cornerstone for diaper dermatitis.

Again, I think there is an important place in the public health for a product that would meet this need. But it is the position of our review group that the data at this moment falls short.

DR. DRAKE: Thank you.

What I would like to do now, before we get into the business, I want to poll the voting members of my committee for just a moment.

I have had several of you say let's just work right through lunch and be done. If you think you are close enough to making a decision on this, that is not an unreasonable proposition. It is about twenty-five after 12:00 and if everybody is reasonably close to a decision, one way or the other, then we are fine.

I had another person who said, "Well, I need to check out and maybe we ought to take a short lunch." I am really very easy on that. I don't have a predetermined notion. I guess I would like the pleasure of the committee. I just want a sense. How many would like to just continue working and finish this off.

[Show of hands.]

DR. DRAKE: How many would like to take a short

break?

[Show of hands.]

DR. DRAKE: Clearly, the short break has it. Would half an hour be sufficient? Could we reconvene at 1 o'clock? 1 o'clock gives everybody a chance to check out and what not. I will see you here at 1 o'clock.

[Whereupon, at 12:25 p.m., the proceedings were recessed to be resumed at 1 o'clock p.m.]

AFTERNOON PROCEEDINGS

[1:05 p.m.]

DR. DRAKE: I am going to reconvene the meeting now. The best laid plans go astray. I think the committee has pretty much made up their mind, at least I have gathered that--I have no idea what it is, what their mind is made up toward, but I think everybody has sort of come to a conclusion.

I will also tell you that because of the time line I outlined earlier, people went ahead and made plans with respect to pickup and cabs and what not. Now, since about three minutes ago, I was approached by the sponsor who felt like they had some rebuttal that they would like to give to the FDA's presentation.

Jonathan, do you have a problem if I give them ten minutes?

DR. WILKIN: We welcome it.

DR. DRAKE: I must tell Dr. Armstrong that I feel that if we had known that before we broke, we probably could have done something. But I understand his position perfectly clearly, and I want to make sure he has an opportunity. He said he could present his rebuttal in ten minutes.

I would like you to do that and then we will go from there. He thought maybe some of these issues could be

clarified.

Sponsor Rebuttal

DR. ARMSTRONG: I would like to thank the committee and Dr. Wilkin for the offer of an additional period of time. As I mentioned in my main presentation, some of these points were ones that we did not have an opportunity to prepare for in our briefing package.

I can address many of the things which I think are most important although I don't have time to address all of them. I would like to say that I think that the amount of emphasis that has been put on Candida infection is focusing on one of a series of contributory factors in this irritant dermatitis occurring in the diaper area.

It is a focus which I believe underestimates some of the other factors. We have heard from various consultants both that we have brought to the meeting and that the FDA has that the distinction between Candida pseudohyphae present and not present, cultures being positive, not-positive, really doesn't fully explain the role that Candida can do because it need not be invasive to be important.

I think that one of the things that derives from that is the emphasis on doing results analysis only on people who are culture-negative and cured is a difficult task to make when two-thirds of the patients don't have

Candida to begin with, and yet they clearly have diaper dermatitis. It is diaper dermatitis that we seek to have as an indication.

One of the comments that has been made was that we have not demonstrated that this product is better in the patients who have no Candida at baseline. There is, I think, agreement that when Candida is present at baseline, there is a clear benefit to the Pediastat versus the ointment base.

I actually would like to take exception of that, with all respect. I think we have shown that Pediastat treatment in the Candida-negative patient is better, and the difference is statistically significant, if you compare the end-of-treatment score with the baseline score.

I think we have also shown that there is a trend in favor of Pediastat over the ointment base in the Candida-negative patient and we agree that those differences are not statistically significant. But I would point out again that that is not a non-treatment comparison group because an ointment base, a barrier product, is, in fact, part of the current standard of care for the treatment of diaper dermatitis.

So I think we have set for ourselves a very high standard when we say that we have to be better than the standard of care, not better than a non-effect treatment.

Now, there are a number of points that have been made about the conduct of the studies. I would like to go to the USA study because, although I tried to be clear about this, I am obviously not understood.

Could we start with the first slide on the efficacy for the USA study, please?

[Slide.]

This is a study where we had a relatively low number of patients. Clearly, that created some problems with us for power. But when we look at the number of rash sites, I did not present this data to you before. This is one of the efficacy criteria, how many sites showed involvement. Here, again, you can see, advantage Pediastat, statistical significance at day 5 and close to at day 7.

[Slide.]

The next slide is the mean rash score. This is what I showed you earlier. Here you can see that there is statistical significance at day 5 and at day 7 in favor of Pediastat.

[Slide.]

This slide shows the overall change from baseline to day 7. This difference is not statistically significant. And we agree with the agency that this is not. But our concern here is that we have other variables which do show statistical significance and yet the study, we are told,

should be dismissed because this one does not make statistical significance. We think that it is a bad precedent to make for clinical trials to say that we have to disregard results on all efficacy parameters if we don't make significance on any particular efficacy parameter.

There are a number of points that have been brought up about the concerns on safety. I would say that we don't have any evidence that there is a potentially adverse event from the ointment base that would create a worsening of Candida infection. That is a point that I don't really understand why we should be discussing here because we are looking for approval of the Pediastat, not the ointment base.

Another point on the analysis is that it is clear that there is an advantage to looking at patients who achieve cure. But it is also clear that that disregards the clinician's assessment of improvement short of cure. To require both cure and negative culture in a set of patients where two-thirds of them do not have a positive culture to begin with is stratifying the database into too small a group for us to be able to achieve statistical significance.

You could argue that we could overcome that by doing another study, a much larger study, in which we could provide the numbers that would give us adequate statistical power. But I would return to you with this observation

that, like every organization, we have limited resources. I know that the amount of resources that it would take to do such as study has to be considered in the light of other things that those resources could be used to develop.

Frankly, it hard for me to see what additional meaningful information we will be able to supply to practitioners in the way they are practicing pediatrics today that they would be able to benefit from by doing an additional study.

So I don't see how I could justify taking the money from investigating a new drug, a new indication or some other use that that resource could be put to. So, with that as a quick summary, I hope that the committee will feel free to ask additional questions on any points which they believe are worth asking.

Thank you.

DR. DRAKE: Dr. Armstrong, stay there. I would be very happy to have the committee ask questions of you.

Dr. Kilpatrick?

DR. KILPATRICK: Dr. Armstrong, you should understand that I am the only non-clinician on this panel so the questions I ask are slightly different and coming from a different area.

What was the primary response in this USA study agreed between you and the agency?

DR. ARMSTRONG: I can't tell you the answer to that because the study was done before I was in the drug industry. The studies are old. The efficacy criteria were laid out and then measured, but there was no prospectively identified criterion as the primary efficacy criteria.

DR. KILPATRICK: I may want to ask the agency. Were we working under more or less the same rules at that time in terms of relationship between the agency and the sponsor?

DR. WILKIN: I can say that we really don't have that good a knowledge of what agreements were made at that time. At the time the sponsor approached those of us who are now on the review team, as Dr. Armstrong had not yet arrived that his position, we didn't even have a Division of Dermatologic and Dental Drug Products at the time these studies were conducted.

So when industry came and we discussed these sorts of things, the studies were already done at that point.

DR. DRAKE: I have three people who have questions that I have spotted their hands, four now. Dr. Spraker, you are next.

DR. SPRAKER: I have a question for Dr. Rinaldi. Are you concerned about the effect if--what if every baby in the United States was treated with this product two or three times a week for really mild or minimal diaper dermatitis

for the two years or three years until they are out of diapers?

I really think the product will be very popular and that it might be handed out to every mother with a newborn. That sounds logical to me, if I were the pediatrician. Rather than reaching in the drawer for Desitin, that, if there is a little bit of irritation, I would be putting on this product instead.

So considering the numbers involved, does that change your thinking about the potential for resistance?

DR. ARMSTRONG: Is Dr. Rinaldi here? No.

DR. DRAKE: Maybe Dr. White could help with that.

DR. WHITE: In my opinion, there is a possibility that, in a certain number of children, a resistant strain could develop in that child during that time when they have the dermatitis. Assuming that that child is otherwise healthy, the chances of that resistant strain having a consequence seems very small.

As soon as they are out of diapers, the strain will revert to a sensitive phenotype. That is, in AIDS patients, when we take them off fluconazole because of triple therapy, the strains do return to a sensitive phenotype.

So there is a small chance that resistance might develop in a small proportion of those children, but the

consequences of that are probably minimal.

DR. DRAKE: The order in which I spotted you is Rosenberg, Epps, Rosen, Eduardo, Rob and then Jon. That is the order in which I spotted your hands. So next is Dr. Rosenberg.

DR. ROSENBERG: I'm sorry; this is not a question. I just wanted to make a couple of comments. Is this not a time to make it?

DR. DRAKE: Bob, you are here. When they have another question, you can pop back.

DR. ARMSTRONG: I am happy to.

DR. DRAKE: Because I want you to have your chance. I want to make sure that you are satisfied that you have had a chance to address the concerns. I just think that is only fair.

DR. ROSENBERG: I will try not to go too long, but I want to say this. I think, first of all, this is an important issue how to manage diaper problems that may be candidal in infants.

The discussion we heard yesterday, the first discussion, we learned that many prescriptions are being written by primary-care doctors and by pediatricians for a product that even the commercial sponsor, as well as the agency, feels should not be used in that site. So there is clearly a need for this.

Miconazole is a reasonable agent. An area that I have had a long interest in and so I see things through that focus concerns in interface between Rx and OTC. I think a lot of this discussion comes to that. I think if this is to be an over-the-counter product such as it is in some jurisdictions--

DR. DRAKE: That is not what is before our committee today.

DR. ROSENBERG: I understand. But I want to make the point. Then I think, if it is an over-the-counter product, calling it diaper dermatitis is entirely appropriate. That is the way you want to be, a diaper dermatitis can be self-diagnosed by mom. It should be an OTC medicine.

The data that show that, given a group of children in whom nobody could make a diagnosis except diaper dermatitis, were given this product, their agent is better than the control is some evidence. So I think were there to be an OTC product, one could look at this data and say maybe.

If it were to be an Rx product, I think it should be labeled for candidal-associated diaper dermatitis. Candidal-associated diaper dermatitis, I submit, is not going to be self-diagnosable by moms. In order to be over the counter, the individual must be able to diagnose it

themselves and it has to be safe and effective and directions can be written that they can follow.

I was, I think, to have suggested at some OTC meetings that the imidazole vaginal products be OTC. And they are. But that is different. The point was made that women who get repeated vaginal candidiasis have had it before. They have had it diagnosed by a doctor before. They know perfectly well when they have it again for the third time or the fourth time that that is the same thing.

It is something that is going to go on and on, now and then, over some years and they can handle it. And they are all grown up. I think infants are different. First of all, they are under medical care. Infants are seeing pediatricians or primary-care doctors.

They are only infants for a limited time. They are going to have a limited number of episodes. The episodes don't last that long so I think that is an argument for the prescription.

Which would be better? One of the things that we know is that this product works better in children who apparently are candidal associated rather than not. But, as was pointed out, it is not affective in one-third of those. As was pointed out by several of the speakers, there is frequently a fecal source.

So I think the baby who does not get better, the

physician could prescribe something bland and safe and usually very helpful like oral nystatin which mom can't do. Mom would probably continue using the same product.

Also, the physician could use a different topical agent, could move up to something like gentian violet that is, perhaps, more powerful than this agent. I think the moms would just keep using it. I don't think that this is really an ideal OTC product.

The question about whether the pediatrician or the doctor couldn't do any better than saying it is diaper dermatitis, I don't believe that is true. I believe if we had enough data generated that this type of product deserves from a company such as this sponsor, so that FDA had put its stamp on this as being effective in a certainly percentage of candidal-associated diaper dermatitis, after a while, the doctor would recognize the ones that got better and the ones that didn't and would do very well.

I think if it were to be a prescription drug, obviously, this is inadequate data for something with that kind of an indication. I would just pick up on what Dr. Witebsky said that in a primary-care office, the cultures are not wonderful because lots of them are colonized with one or two and you are not going to quantitate it, and it is hard to make sense out of that.

Primary-care offices where the clinical studies

are done are not ones where KOHs are done and the KOH is really not the best test anyway. A Gram stain that smears can be made in a primary-care setting, they can be shipped to a central lab, once dried. The Gram stain is not going to be perfect either, but I think it is possible for the sponsor to do a reasonable job in a reasonably setting and come back with data that would justify a positive action by the agency.

I feel the same way we did about the second paper we had yesterday. They had an agent with a historical record of effectiveness, zinc chloride cures skin cancer. They had some bit of data. After a long talk, the committee told them to maybe go back and get some more data. So I feel the same way about this one.

DR. DRAKE: Thank you, Dr. Rosenberg. Next on my list is Dr. Epps. Joe, I have got you down now, too.

DR. EPPS: Thank you. I guess I had a few questions and comments mixed. According to our papers, the musk ambret was removed from the formula but fragrance was listed. What is your fragrance?

DR. ARMSTRONG: Simple question, not a simple answer. Fragrances are combinations of multiple compounds and the reality is that most fragrance manufacturers consider that proprietary information and don't release that.

DR. EPPS: So it is more of a masking fragrance?

DR. ARMSTRONG: Correct.

DR. EPPS: So it is not, say, fragrance-free but--

DR. ARMSTRONG: Correct.

DR. EPPS: And not unscented, either.

DR. ARMSTRONG: Correct.

DR. EPPS: Another question I would have is, according to the protocol, it was applied every diaper change. Do you have an idea of how many applications per patient per day?

DR. ARMSTRONG: We estimate six.

DR. EPPS: The reason I ask is I guess the age range was from eight weeks up to thirteen months. If you have a breast-fed eight-week old, they could theoretically have eight to ten changes a day whereas a thirteen-month old may have, let's say, four or five, to be generous.

DR. ARMSTRONG: Right.

DR. EPPS: So you are applying twice a much medication to a two-month-old than you are to a thirteen-month old. Certainly, their body-surface area is different. The mass is different. And the number of applications. So that is something also to be taken into consideration.

It would be nice of there were some kind of dose regimen that could be recommended or tested or something

like that so that if someone is going to prescribe it, apply it X number of times a day is recommended instead of every single diaper change.

The same with diarrheal, kids who are having diarrhea. Who knows how many times a day that could be. Certainly, the stool is more irritating, as we have heard from Dr. Spraker and some others. So that would be nice to know.

Second, I guess another question I had was--and it may not even be an issue or relevant--is whether or not there is an effect from occlusion. Although you use eleven sites and it was very thorough with the photo testing, most of the diaper dermatitis is where the sun doesn't shine.

I don't know whether there is an effect of cloth versus super-absorbent versus whatever. It is just a question/comment which I don't know whether it has an effect but it would be interesting to know whether it did. I don't know.

DR. DRAKE: I'll tell you what. I am going to ask everybody--we are kind of at the end of the meeting. I am going to have to get to the questions, and I am going to go to the questions. I think the philosophic discussion was held earlier. I would really keep us away from philosophic discussions, although I don't disagree with you. I think they are wonderful.

What I would prefer to have at this point are pointed, short, pertinent questions to Dr. Armstrong or to the FDA because I am going to move to these questions very quickly.

So, Dr. Rosen, having that comment in mind--

DR. ROSEN: Very short, very pointed. We have heard a lot about the theoretical risk of resistance. Theory, theory, theory. My question to the sponsor, this agent, as formulated, has been available now, according to the FDA, in twelve countries. How long has it been available in these other countries and, assuming that there are reasonably good mycologists and microbiologists in these countries, have there been reports to you from these other countries of development of azole-resistant Candida albicans?

DR. ARMSTRONG: Just a point of clarification. It has been approved in twelve countries. It is actually marketed in six. It has been introduced since the early 1990s, not on the same date in all countries so there is a bit of a variance in the experience.

I am not aware of any indication that there has been any resistance associated or reported with the use of this product as a commercial agent. I think that we already have had testimony from the National Institutes of Health that routinely they don't do sensitivity testing even in a

population that has many more possibilities of having resistance be an issue than in the general population.

DR. DRAKE: Dr.--I can't read my writing. I can't tell who is next. Rob, you have a question. Would you go next? I think it is Eduardo. I goofed up here. I can't read my writing.

DR. STERN: I guess I have a couple, three questions. One is to make sure I understood, how I read the data, that there is general agreement that even in reasonably well-controlled situations, the ability to differentiate infected from uninfected diaper dermatitis even by clinicians is low.

The prevalence of the prescription or advising of using azoles even without seeing infants is high in clinical practice and there are either 1.8 million suggestions, uses or prescriptions per year in the United States with these products which includes about 8 or 10 million infants of this age range that you would expect to be in diapers.

So if I understand it, there is a relative lack of ability on the parts of even clinicians to clearly differentiate Candida, at least in clinical practice, and yet they are often comfortable making recommendations for the use of azoles millions of times for what would be appropriate therapy.

The question I have is except for the--and this is

really to the FDA--except for 21 CFR, Part 310, which clearly indicates that you are not supposed to put an antifungal in something for diaper dermatitis--that is the 1992 rule--if you look at the criteria for what is a reasonable thing to do for this condition, does this meet the criteria; that is, can it be clearly labeled, "Diaper dermatitis persisting for more than 48 hours, more than usually severe, including involvement of the folds of bumps outside of the areas of rash," and, also, "Don't use in children who are sick with immunosuppression. Do use it more often, suspect more frequently in people who have been recently on antibiotics."

So is it clearly lableable because, in terms of prevalence of use--to me, when I came here, the whole issue, I thought, was going to be on resistance. How I have come away from this meeting is I know and understand as little about the likelihood of increased resistant strains in the community with or without this agent, but there is sure a lot of agents like this going around already, tens of millions of applications a year, even in diaper dermatitis.

So that seems like less of an issue. The other issues, to me, are what is the best way to use it and is it really that helpful as a prescription. To me, as a prescription agent, it is sort of underpowered. If you are really thinking about you know it is, you really go that

extra mile in the referral cases. This, maybe, is an underpowered agent. Is it the way people practice, perhaps, useful as an OTC agent?

But I only had one other question about safety. There was a slide presented about systemic absorption showing that everybody had less than 5 nanograms per ml, I think it was, which is one-one-hundredth to one-one-thousandth what you get when you give this agent IV.

I have no idea whether there is any concern about nanogram exposures to this agent in young children. I am wondering are there any data, does anyone say, "Oh; these low levels of exposure, especially if they are chronic, may be good or bad? Is that something we know as much about as we know about the likelihood of resistance going up substantially if this is more widely available?

That was really, from the hearings today, my big health concern.

DR. DRAKE: Jon, or Dr. Ko? Who wants to answer that?

DR. WILKIN: Of course, you can always ask the sponsor what is in their database that will respond to your questions. I would like to go back five minutes to your first question which was--it related to can you use an antimicrobial for something that is not considered to be a microbial process.

I think we have examples of that. There is a treatment for rosacea, and we don't think that there is actually an organism that is on the skin that is leading to rosacea. There is no place in the Code of Federal Regulations where it requires that we know what the mechanism of action of the pharmacologic agent is prior to approval.

I mean, we need to know about its safety and its efficacy but we may learn more about how it works, actually, after it is approved. After all, silicilates, in one form or another, were effectively used perhaps for hundreds of years before Vain, Moncada and Bergstrom got the Nobel Prize for discovering prostaglandin. So things can work even when we don't really know exactly why.

If there is an antimicrobial agent, however, in the product, then we want to know what kind of impact that might have on antimicrobial features.

In this particular case, I think we have already heard from our experts and we can read in the textbooks that there is thought to be an important contribution of Candida to diaper dermatitis. As I read the accounts, it is not one of these dichotomously separable kind of issues, that there is Candida dermatitis and then there is non-Candida dermatitis, that is it is something of a spectrum.

I was speaking to if we could look at the polar

extremes of that spectrum in the study and we had information that both polar extremes--that the use in those settings was safe and effective, that we could infer what is in the middle.

So when I was talking about clearance of the Candida, I was talking about that Candida dermatitis. I think Dr. Armstrong mentioned that the FDA might be concerned about clearance of Candida when there wasn't Candida. That is really not quite the picture. It was we were interested in a subset of the population who comes in, who has all of the features that we might think of, sort of syndromic approach to Candida dermatitis.

Maybe the satellite pustule is a good clinical impression that it is there. Perhaps pseudohyphae are demonstrated and culture-positive and what happens in that particular group. I think that was the question.

DR. KILPATRICK: Madam Chairman, Dr. Stern also asked a question of safety.

DR. DRAKE: Please. I'm sorry. You are right. Thank you.

DR. KO: Your question is on systemic absorption whether that degree of exposure is of any concern, whether there is any information. We know that miconazole nitrate has also been given intravenously. There is some information on that but not in this age group.

What you are concerned about in this age group is a very valid issue. It is one of the issues raised by another regulatory agency in not approving the product because there is no information on the effect on the P-450 system in these infants because, during the first year of life, the enzyme system is gradually maturing and they felt that this is something without information on.

So that is all I can tell you.

DR. DRAKE: Wait. I tell you what. This committee, and we will do it in order. And I am also going to go to the questions at 2 o'clock so please, unless it adds to the body of information, unless it is a question and a response, it will not be allowed because we are going to move on.

I want to be fair to everybody. The sponsor deserves to have their time to answer questions from the committee and not deal with broad policy.

I will put your name on the list, Dr. Chesney and Dr. White. Eduardo, would you please go ahead?

DR. TSCHEN: My concern is not the normal pediatric group or the healthy child who will be using the product. The issue with resistance and creating super-Candida, I don't think is a big issue in that group.

The problem is the pediatric group who is immunocompromised, who has leukemia, who is taking any

chemotherapy. This is the group who can develop a resistant Candida much easier, who can develop in patients the Candida. So I have a concern because these kids are the ones who develop more diarrhea then anyone else and, at the same time, are the children who are more likely to have serious problems as in patients with the Candida.

That is my concern; is this product contraindicated in kids who have immunocompromised situation.

DR. DRAKE: John?

DR. DiGIOVANNA: I have two questions. I will try to be as focused as I possibly can. One is for Dr. Armstrong and the other one is for the FDA. For Dr. Armstrong, you showed a slide in your presentation, a slide No. 30, that was efficacy results by culture for Candida albicans ointment base group. You had a positive and negative.

Is there a similar presentation of the data for the active agent? What I am interested in is how does the active agent perform in the Candida-negative group?

DR. ARMSTRONG: That slide is coming.

[Slide.]

DR. DiGIOVANNA: So it is the active agent is also effective in the Candida-negative group, according to that slide.

DR. ARMSTRONG: These are patients who are Candida-negative. It is effective. These are the patients who are Candida-positive. Yes; it is effective in both groups.

DR. DiGIOVANNA: Thank you. The second question is similar to, I believe, one that Dr. Stern was raising and one that Dr. Wilkin addressed to some degree and that is, in a clinical situation where the physician cannot be sure exactly how the organism is affecting condition, there may be a condition of infection or there may be a condition of colonization that flares, that actually plays a role in the disease, or there may be a different situation where the local condition of the skin encourages future colonization by Candida, that the role of the antifungal agent may be different in those three, or possibly more, subsets.

One you addressed could be characterized by KOHs or cultures, the situation where Candida is infective. But the preventive benefit is something that can't be easily assessed by that. It would seem, in this situation, to rely on cultures or indicators of infection would minimize the ability to really focus on the endpoint you would be interested in, which is the clinical endpoint.

I am not quite sure why there is so much of a focus on documenting effects on Candida when I think this would be a situation very similar to the one you raised with

respect to rosacea where the activity of the antifungal may be very difficult to characterize because of its antibacterial effect or antifungal effect, but the real bottom line is the clinical effect.

DR. WILKIN: The answer to your question is yes. I agree with the whole sense of what you are describing. I think if we had relapse data, we would know more what the signal of a negative KOH and negative culture was at the end of a trial.

It is not that we are wedded to that as specific signal. It is that we are trying to get a handle on how many of these children will need retreatment, how soon. How many really will be incompletely treated at seven days.

DR. DRAKE: I think that is the sense that everybody is feeling, that we need the follow-up data to really know, to answer that question.

Next is Joe.

DR. DiGIOVANNA: Dr. Armstrong, Slide 24. You have twenty dropouts, or you have twenty no-treatment benefits; do you know if those were infected or not infected?

[Slide.]

DR. ARMSTRONG: The slide is coming.

DR. McGUIRE: No; that's it.

DR. ARMSTRONG: The slide that answers your

question is coming. This is the slide that posed your question.

DR. McGUIRE: I am just trying to be focussed, Bob.

DR. ARMSTRONG: Yes, sir.

DR. DRAKE: And your chair appreciates that.

[Slide.]

DR. ARMSTRONG: Here are the twenty-five subjects from both treatment groups, the Pediastat group with--these patients were in the third study, the second Australian study, the study for which cultures were not done. This is the combined experience from the two studies where cultures were done. What we can see here is that Candida was positive in three of these individuals who did not get a benefit in the Pediastat group, nine in the ointment base group. But, remember, the sample sizes of the two groups is essentially equal.

DR. McGUIRE: Slide 26? You may have already given me this information, but can you stratify the infected from the uninfected in these groups?

DR. ARMSTRONG: Could we show that slide?

[Slide.]

This shows the results in patients where Candida is present. It shows the lack of response with the ointment base and the clear response in the Pediastat group.

DR. McGUIRE: Thanks. Just one sentence, since I have been so brief, the fact that there is no public advocate here today does not mean that the committee is oblivious to the public-health aspects of widespread use of antibiotics, a general perception among physicians and certainly among the public that increased resistance is somehow related to increased usage. Thanks.

A public advocate was invited.

DR. DRAKE: There were two public advocates invited. Neither one was able to make it. But we will make a concentrated effort to make sure, if we have to call six, because I feel that missing link today, too, Joe. I agree with you. I think the public advocates are very helpful on this committee.

I believe Dr. Chesney was next.

DR. CHESNEY: I wanted to come back to safety issues. I think a concern that we all have is the slippery slope. As soon as it is perceived that this is an antifungal agent, even if it is limited to use in normal infants of three to six months of age, it will be used by the immunologists, the neonatologists and the oncologists, and they will use it in premature infants, and they will use it in the very immunocompromised AIDS patients in whom resistance may develop.

I think you had made that point. So I want to

emphasize that. I think that is the point I wanted to make. But my question was that the phototoxicity, the allergy and all of those studies, were not done on infant skin; is that correct? They were all done on adults?

DR. ARMSTRONG: That is correct.

DR. CHESNEY: Is there any stipulation that toxicity studies have to be done in the age group in which the medication will be used?

DR. WILKIN: There is not really a statutory basis for that. I think it is technically difficult to actually conduct these kinds of studies in a diaper-dermatitis setting.

On the other hand, one of the ways that we compensate for that is that we have larger numbers of subjects who have been in trials preapproval. It gives us a better sense of what the upper 95 percent confidence interval might be for an adverse event once the product is approved.

DR. CHESNEY: Could I just bring up this issue of the pediatric pharmacokinetic research units again because these units are specifically set up so that the children could actually stay there for a couple of days or come back day after day and have the same observer observing the same area of skin. So they are very well set up to do that kind of thing.

DR. DRAKE: Dr. White?

DR. WHITE: This was just a quick reply to your question about azoles in the blood in children that age. I will just remind you that children with oral candidiasis are treated with fluconazole and clotrimazole at levels a hundred-fold higher, children that age.

So if there is any concern about azoles in the blood, it would--

DR. STERN: That was my scenario.

DR. DRAKE: Are there other--Dr. Kilpatrick? Steve, you were down first. I apologize. You and then Dr. Kilpatrick.

DR. FELDMAN: Thank you. My question is really probably to the FDA. I am concerned about how much your focus is on the actual data that is relevant to patient care. I thought Dr. Ko's presentation was very well organized, really laid out the data well.

But it wasn't from the perspective of what kids need in real life. Yesterday, we looked at data on a product that had a very narrow indication, data on a very narrow indication, that had absolutely nothing to do with how the drug is widely use and that has serious safety implications.

Here the sponsors come in with data that really

fits very well with what I need to know when I am seeing the patient in the clinic. The patient comes in with diaper rash, a condition that I can clearly recognize and define as a condition, diaper rash.

There may or may not be Candida there. That Candida may or may not be relevant. I think the best data that it is relevant is the efficacy of the drug in the Candida-positive patients. But I am not going to get a culture on this patient when they come in diaper rash.

I am going to treat them. It is not cost-effective for me to get a culture. I have to wait days. I am going to treat now anyway. It seems to me that this data is just what I need to say that this drug is more effective than is vehicle for that patient.

DR. DRAKE: Excuse me, Dr. Feldman. You are doing policy. I would really like you to do a question.

DR. FELDMAN: The question should be very clear; how important is it to the FDA to look at data that is relevant to actual patient care as opposed to--

DR. DRAKE: But that is policy. I will allow a brief answer it, but that is not a question pertinent to the approval of this drug right now.

So, please, Dr. Wilkin, and then we are going to move on.

DR. WILKIN: I think Dr. Feldman raises a very

important question and that is what are the sponsor and the agency trying to accomplish during phase III trials. I would argue that phase III trials are extremely artificial. How many times have you given a patient a prescription and said, "This may work for you," and yet, in most of the phase III trials, there is a vehicle or a placebo.

In acne trials, the investigators will see patients back extremely frequently, much more than in regular clinical practice. They will count individual lesions. Many things happen in phase III that really do not conform exactly to clinical practice.

I think that is okay as long as what we are getting, the information that we are harvesting in these phase III studies, is going to then inform clinical practice which may be a reductive approach to that database.

The one that we are thinking about today--I would say that if a clinician knew that this worked in both irritant dermatitis and that this worked in both candidal dermatitis, and I am talking about the epicenter of candidal dermatitis, the world-class variety, and they could infer, knowing that, that it is going to work in all the inter-grades, that the would be enough information for them to do, as I think Dr. Armstrong suggested, pass on the KOH and the culture and these sorts of things and safe the healthcare system some money.

But it would be an informed reductionism.

DR. FELDMAN: Can I follow up?

DR. DRAKE: Actually, no, Steve. This really is a panel issue now and I would like to keep it focused on our panel. Dr. Kilpatrick?

DR. KILPATRICK: As Dr. Wilkin has indicated, and I have indicated before, I am interested primarily in the phase III trials. I want to come back to Dr. Armstrong and quote, or misquote, three statements that have been made by the agency and try to get the sponsor's response to these. And then I want to go on, Dr. Armstrong, to ask questions about the Australian studies, if these are all relevant to the United States study.

One statement was that not all sites were in the diaper area in the United States study. That was one of Dr. Ko's points, I think. The other one was that endpoints were not pertinent to diaper dermatitis. A third one, which is mine, actually, it appears that there is subgroup analysis going on here, but different groups, the sponsor and the FDA are doing different analyses and there has been, apparently, no agreement.

Is this because we are dealing with a 1983 study, that you have the data and they brought it in and the agency did their own analysis? Was there any collaboration or agreement beforehand as to what you would do and how you

would interpret it?

DR. ARMSTRONG: Could we do those in series? I may ask for some help with remembering all of them because I am not certain that I would.

Could I have the slide that is keyed up, please?

[Slide.]

This is the sites that were involved. This happens to be from the Australia study but I think, aside from the fact that the number of sites is different by one, what this illustrates is those areas that are not typically covered, not typically associated with diaper, were very often not involved.

The majority, as you can see, are those areas on the inner thighs, the genitalia and the perianal region. That constitutes the high density involvement, the buttocks and lower abdomen intermediate and then these other areas are a very low area of involvement.

Does that address your question?

DR. KILPATRICK: That answers it specifically; yes.

DR. ARMSTRONG: The second question was?

DR. KILPATRICK: Endpoints not pertinent.

DR. ARMSTRONG: I think what we have done here is to show what the clinical score was. I showed you during the presentation what the definition of those values was.

We think that is a pertinent endpoint.

DR. KILPATRICK: But maybe I should be asking the agency why they don't think those are pertinent endpoints.

DR. KO: The agency analyzes the information in terms of the proposed product for its antifungal properties. So it is analyzed in terms of the antifungal endpoints which actually includes the clinical endpoints. But it holds it to a higher standard requiring also the mycologic endpoints together. I think that is what the agency does. It is not that the agency disregards the clinical endpoints.

DR. WILKIN: If I could add to that. I think, in part, why we are focussing on this particular endpoint of those who had complete clearing of the rash and culture negativity at Day 7 is that is our best way to try to get at some inferences about relapse and need for continuation of therapy.

DR. KILPATRICK: You made that point, Jon. Thank you.

DR. ARMSTRONG: Could I just say that the concern that I have about that is that, in a condition where two-thirds of the patients do not have a culture to begin with, have no evidence of Candida being present, doing cultures at the baseline as a selection criteria essentially disregards the experience of two-thirds of the patients.

The practical consequence of that is that we have

to increase the size of the study that we do if we are going to follow that kind of definition, and it creates an enormously complex large and expensive trial to do.

DR. KILPATRICK: I think that has come across quite clearly. I would like, with your permission, Madam Chair, to turn now and ask Dr. Armstrong about the origin of the Australian studies.

One interpretation could be that Johnson and Johnson did a randomized double-blind study in the United States in 1983 and then went to Australia and did one in 1989 and one in 1988. But that is probably not the situation. Why were the two Australian studies conducted? Who conducted them? Why were they conducted?

DR. ARMSTRONG: They were conducted for two reasons. First, the application, the NDA, in 1985 was rejected for two reasons. One was the systemic exposure. We have provided data to address that. The second was that, as the agency in 1985 looked at the study experience in the United States, they said it needed to be combined in order to be adequately powered for a statistical conclusion and they would accept that study if it were presented as a single study.

But then there was a need for a second study to confirm the results, so there was clearly a decision, either one goes with another study or one abandons the NDA.

The choice of where to do the second study is a more complex one and, as I mentioned earlier, I was not at the company at that time so I can't give you more than a speculation about the choice of where to do that study. But I do know that drug development is a very expensive undertaking and there is a general desire to try to do studies in different geographic areas to support registration in more than one geographic market.

DR. KILPATRICK: If I may come back. I was wondering whether this was done because of Australian mandates. I have no idea what they demand, if they have an equivalent to the FDA. But I was wondering whether this was dictated by other concerns about manufacturing in Australia. You don't know about that?

DR. ARMSTRONG: No; my understanding is that it was done in Australia and the results were then available for the registration in Australia as well as the registration in other jurisdictions.

DR. KILPATRICK: But, again, that was done with very little interaction with the current agency.

DR. ARMSTRONG: Certainly, it was done with no interaction with the personnel that are in this room, from either the company or the agency.

DR. KILPATRICK: I understand. So then what we are doing is analyzing and interpreting old data.

DR. ARMSTRONG: That's correct.

DR. KILPATRICK: Okay. Thank you.

DR. DRAKE: Thank you. Other questions for the sponsor? Other questions for our experts from the panel? Dr. Armstrong, do you need to make any closing comments or petitions? Are you satisfied?

DR. ARMSTRONG: No. I would like to thank the committee for their time and for their questions and the agency for giving us opportunity to speak.

DR. DRAKE: Because I wanted to make sure--you guys spent a lot of money to come here. I want to make sure you have enough opportunity to respond and answer questions. So you are satisfied at this point?

DR. ARMSTRONG: I am much obliged.

DR. DRAKE: You are welcome. Is the committee satisfied? Can we take up the questions now? Whoa; we are there.

Questions for the Committee

DR. DRAKE: Question No. 1 is just like Question No. 1 yesterday. It is a hard one. I am tempted to move to Question 2 and 3 and then come back to this one. Do you want to do that? Deja vu. Could we go to Question 2?

DR. ROSENBERG: I think that is central to the whole thing, that Question No. 1.

DR. DRAKE: Then go back to 1; sorry.

DR. ROSENBERG: They raised it and I agree with them.

DR. DRAKE: Okay; let's go with it. This Question No. 1 is open for discussion. Jon?

DR. WILKIN: If I could just point out the Question No. 1 is more general. It is for products of this type. So, in this case, we want to hear about the placement of this product but, in addition, we would like to know, just in general, for diaper dermatitis as an indication in case other products come along.

DR. DRAKE: Okay. I think I am still right to do it in reverse order because, while the information on the product that we have is fresh in our minds, because we could get bogged down for two hours or a half day or three days on Question 1. So what I would like to do is answer the questions that you need for today regarding this product.

I want to go to No. 2. Bill, I'm sorry, but I am going to go to 2 first because I think the issue here is to answer this question.

Dr. Chesney, you had a comment?

DR. CHESNEY: My question was for 1.

DR. DRAKE: Here is what we are going to do, then. I am going to back up. I am not backing up to 1. We have looked at 1. Look at Question 2. I want to make sure everybody has read all the questions. I am going to have

you read Question 3. I am going to have you read at least 1, 2 and 3 so that, then, I will start with 1 and we will go through it systematically but everybody, please, read Question 2 and somebody be so kind, now, to put Question 3 up there. Good. This is Question 3. So at least we will have all three questions in our mind when we begin discussing Question 1. How is that for a compromise?

All right. Back to Question 1. Dr. Chesney? Thank you for rescuing me. I was wallowing around there in a hole, so thank you.

DR. CHESNEY: You did that very well. I want to be sure I understand this question. You are asking whether it is appropriate that diaper dermatitis be the indication for an antifungal agent. Is that--you said a drug of this type.

DR. WILKIN: Yes; for a drug of this type, is diaper dermatitis--in part, it relates to Dr. Feldman's question and that is how should it be studied. In other words, is diaper dermatitis really a composite of demonstrating safe and effective use in Candida diaper dermatitis and irritant diaper dermatitis, or is diaper dermatitis not an appropriate indication at all? That is kind of a discussion point.

DR. CHESNEY: One comment, which makes me say would it be appropriate to recommend amoxicillin for all

diarrhea. In other words, I think if we are dealing with an antifungal agent, then we should probably be dealing with a fungal infection. I probably didn't explain that very clearly.

DR. DRAKE: Joe?

DR. McGUIRE: Lynn, my concern about Question 1 is that it is so encompassing that--

DR. DRAKE: I know.

DR. McGUIRE: --if you say "yes," to this, then you endorsed the use of this product.

DR. DRAKE: That is why I wanted to do the other questions first.

DR. McGUIRE: For which it is not particularly any better than, shall we say, Desitin.

DR. DRAKE: With all due respect to the agency, the problem with this question coming before the other two, it puts in a position of approving something blanket before you think about the product and we have had all this evidence this morning on the product.

Which would you prefer us to address?

DR. WILKIN: Actually, I think you get the spirit of what our interest is and there is a fine tradition that chairs have exercised with this committee where you actually change the question.

DR. DRAKE: Good.

DR. WILKIN: So if you would like to modify it in a way that you think might be responsive or break it into several questions--

DR. DRAKE: Then I am going to modify it by going to Question 2 which was my original instinct. Question 2, we are going to take up right now. That was my original instinct and that is what we are going to do. I am a very concrete thinker, Jon. You give me task A, B and C and I will do it.

So, Question 2 is open for discussion. Rob?

DR. STERN: I have a question about 2b. It seems to me that, in my somewhat limited experience with diaper dermatitis that certainly the issue of b is really how long do you label it for for any given use. We certainly would anticipate that after a period of time people who have had it before are likely to have it again. So I guess, to me, the question for b is is it seven days, is it 14 days? What is a reasonable time that you have advice that, if it hasn't worked, it is time to stop it and it is reasonable to label that if it comes back within a certain period of time, you probably shouldn't it again.

So, to me, that is really a clinical judgement question, just as you would do if you were prescribing, in fact, a topical antifungal for someone with diaper dermatitis. You would say, "Well, I think this is Candida.

If it is not better in X days, or so much improved in X days, give me a call and we will try something else. If it reoccurs within Y days, give me a call because I might want to treat you orally."

So, to me, b is really a labeling issue which is important to be negotiated and I think to be very explicit in the label both with respect to what is a reasonable length before you improve, before you reconsider other therapy and what is a reoccurrence; in other words, how long is it before you can safely use it for a new episode as opposed to the exacerbation of an insufficiently treated, priorly treated, immediately prior episode.

DR. DRAKE: Eduardo?

DR. TSCHEN: I don't think that, with the information that we have, we can make any assumptions on beyond seven days. The information that we have is with other products, like the 2 percent of people who have used it longer. We don't have any information regarding resistance in the specific subgroups, or any other groups. So I don't think it is a labeling issue. I think it is a lack-of-information issue.

DR. DRAKE: Bob?

DR. STERN: I agree with that.

DR. DRAKE: You agree with that. Dr. Chesney?

DR. CHESNEY: I am uncomfortable with knowing the

absorption through the skin in only ten children when I know that this will be used in infants. We certainly learned about Lindane the hard way in that regard. It will be abused. It will be used more than seven days.

So I would be much more comfortable having more information on systemic absorption, particularly in young infants.

DR. DRAKE: Amy, I am really into the panel. Did you have a response that is directly to her, because if it is policy discussion, I won't allow it. But if it is a direct response to her comment, I will.

DR. PALLER: I would respond to Rob. I have a problem with seven days because my traditional use, for years and years and I learned it from Nan Esterle, is I treat and I tell the moms, "Go for seven days after it looks clear." It may look clear in seven days and we go for longer than that. So I am uncomfortable just telling somebody--and I wouldn't use it for just seven days.

So that is an answer to that.

DR. DRAKE: Thank you. Now, seeing no further hands from the committee, per se, so we move on, the Question No. 2, "Is additional information on safety needed for the proposed product such as the following:" I am going to try to group--do you want to take each one individually or as a group?

DR. DiGIOVANNA: I think individually.

DR. DRAKE: So the first vote will be on, "Is additional information on safety needed for the proposed product such as the following: a, potential adverse effect of the ointment base on lesions with Candida infection?" So you will vote yes or no as to whether you think we need additional information on the ointment base.

How many thing we need additional information on the ointment base?

[Show of hands.]

DR. McGUIRE: Lynn, there was a point that may be prejudicing the committee and that is the Campbell which showed systemic candidiasis in babies of birth weight around a thousand grams. That is the only adverse effect of ointments that has been reported. That is a very special population.

DR. DRAKE: That's okay. I think the committee understands that and knows it. We are voting. I am going to repeat the vote at this point. I am repeating it for a reason. It is not because you all are stupid and can't hear me the first time. I have been specifically asked by our executive officer to make sure the statements are very clear on the tape so that when they transcribe this that is it absolutely clarified. So please bear with me while I repeat this.

So we are going to now repeat the question, "Is additional information on safety needed for the proposed product such as the following: potential adverse effect of the ointment base on lesions with candidiasis infection?" People who say yes, raise your hand.

[Show of hands.]

DR. DRAKE: Five yes. All opposed?

[Show of hands.]

DR. DRAKE: Six opposed.

Now, then, the second vote. "Is additional information on safety needed for the proposed product such as the following: prolonged treatment beyond seven days and repeated usage for relapse." If you think it needs to be longer than that, please raise your hand if the answer is yes.

[Show of hands.]

DR. DRAKE: Eight. All opposed? Rob, I am in the middle of a vote. It is out of order. Please; how many are opposed to this? And then I will let you ask a question. Two opposed. Any abstentions?

[One hand raised.]

DR. DRAKE: Now, Dr. Stern?

DR. STERN: To me, beyond seven days means from seven days until you get out of diapers. And repeated use means all the time. So I think one has to think about some

parameters of what is prolonged use and some parameters of how soon you repeat the dosage and how often because certainly if you are saying is it okay to use this for two-and-a-half years, the average time you are in diapers, I would say I don't think there is sufficient safety information to make it a replacement for Desitin.

If you are talking about using it up to 14 or 15 days and using it at least with a month's break in between, I think I am not so concerned. So it is a funny question for me to intelligently vote on.

DR. DRAKE: Are you down as an abstention, then, Rob?

DR. STERN: Yes; I am down as an abstention for that reason.

DR. DRAKE: So then the FDA, I would advise you to please take his comments under consideration. For the voting committee, I will not allow interruptions in the middle of a vote. When we are doing a vote count, that is inappropriate. When I ask for a discussion right after I put the question on the table, you must raise it then or afterwards, but not in the middle of a vote count.

We are not intelligent enough up here to count 1 through 7. It is as fundamental as that, Rob. It is called counting.

Okay; here we go. The third part of this

question, "Is additional information on safety needed for the proposed product such as the following: c, antifungal resistance development in infants using this product?" All those who are concerned about that, please raise your hand saying "yes."

[Show of hands.]

DR. DRAKE: Eight. Opposed?

[Show of hands.]

DR. DRAKE: Two opposed. Abstentions?

[One hand raised.]

DR. DRAKE: One abstention.

DR. STERN: Same reason.

DR. DRAKE: Same reason; good. So well advised. Now I am going to Question 3. Question 3, "Is additional information on effectiveness needed for the proposed product to support an appropriate indication. Any comments before we vote? Joe and Dr. Kilpatrick.

DR. McGUIRE: That is so open-ended. Could it be, or should it be, "Is additional information such as a, b, c, needed for a proposed product?" This is a pretty open question.

DR. KILPATRICK: And this is really what I was responding to, also. I would like to, again, encourage the sponsor and the agency to work together to have an agreed protocol which would bring a real convergence between the

two parties.

DR. DRAKE: John and then Fred.

DR. DiGIOVANNA: I think there may be, as Joe said, much too much in this question that needs to be dissected, one of which is whether additional clinical endpoint information is necessary and whether additional bacteriologic information is necessary and what that may be.

DR. DRAKE: Fred?

DR. MILLER: I do think that we do have to know more about the effectiveness. When we look at the studies, we have, what, a total of 47 patients who had positive Candida cultures. This whole debate is based on 47 patients and data from 15 years ago. So I think that is significant.

If you look at diaper dermatitis, the vast majority of diaper dermatitis will respond to triple paste. Most diaper dermatitis is transient. It comes up very quickly and you can control it. I say that from my experience as a dermatologist and also as a father of five. I have changed many diapers. I have always been impressed with how quickly kids can develop dermatitis and then how quickly it usually goes with just triple paste. Occasionally, you use a little bit of hydrocortisone cream, but most of the time, you don't need it.

So I think that this is a specific indication. This is an antifungal preparation and I think we do have to

see what is the efficacy and we need more numbers than just 47 positive cultures.

DR. DRAKE: Other comments? I think, hearing both sides of the case, I am going to respond by voting on this question as the agency posed it because we have heard people say that it should be modified a little bit and others say they are comfortable with what it is.

But I would hope that the agency would take into mind that there was a little bit of concern that perhaps it should be better defined as an endpoint, or whatever. But I will call for a vote on the question as it is worded. "Is additional information on effectiveness needed for the proposed product to support an appropriate indication?" Please raise your hands.

[Show of hands.]

DR. DRAKE: Twelve. There were no negative votes, I assume, because the committee is twelve.

Now, then, back to Question 1. We can do that. Steve, I cut you and Dr. Epps both off a little bit earlier because I was trying to track on a specific question and item issue. I think now your comments, with respect to this question, would be most particularly appreciated. Would you mind--Dr. Feldman and then Dr. Epps, would you mind finishing your trend of thought that you were pursuing so eloquently a minute ago that I was interrupting.

I think it is very appropriate for this particular question.

DR. FELDMAN: That is very kind of you. I think Dr. Wilkin makes an interesting analogy of looking at the two extremes. I feel confident that this product has some efficacy in that group at the one extreme that clearly involves Candida. The data shows that. I think, equally true, we can say pretty much with assurance from this data that this product does not have any greater efficacy than vehicle in those patients who don't have candidiasis.

But neither of those things are what I am facing in the office. What I am facing in the office is a kid who might have candidiasis and I am going to treat him now--I'm sorry; I am facing a child who has dermatitis, diaper dermatitis, that may or not have candidiasis. I want a treatment that is effective as a barrier and will control the Candida is Candida is present.

That is what I have right there and I am not going to do any culture studies. I think it would be helpful if the FDA can recognize that as a condition, which I think is the question is 1, and would recognize that this data supports that indication.

DR. DRAKE: Thank you. Dr. Epps?

DR. EPPS: Thank you. I will be brief.

DR. DRAKE: You were doing fine. It was the

wrong--this is the time for this discussion. So if you would do it now, it would be very appreciative because what you have to say is important.

DR. EPPS: To conclude, I guess, what my comments were, I was concerned more about the dosing regimen, depending on the age of the child, you are applying it more in a young child versus an older child if you apply it every diaper change.

There are concerns about absorption, if you are applying it those ten times versus five times in an older child. If there is fragrance and other components, could there be sensitization from fragrance or whatever when you are applying it ten times a day, especially in a younger child who has eczema or some other entity.

I guess when you are applying it frequently, I guess some people have alluded to resistance. I was also interested with the potential for nursing home and other patient populations who may benefit, people who have chronic incontinence, whether it is from spinal-cord injuries or whatever. That may be another population or another route to take as well who could really benefit. They don't necessarily become toilet trained. Those people may need it intermittently for long periods of time. So that is just, I guess, a comment.

DR. DRAKE: That is very helpful. John?

DR. DiGIOVANNA: Just a short comment. I think my view is that the bedridden population, diaper dermatitis population, may be very different. One of the presentations of Candida in that group is a granulomatous disease where it becomes very invasive. So I would suggest to the FDA that that not be blended in with the rest of the studies automatically.

I think that those individuals may benefit from this but I think the irritancy potential with the occlusion and being bedridden sometimes may complicate it.

DR. EPPS: As we know, diapers come one, two, three and large, now. They have large sizes. Diaper dermatitis could be assumed to be diapers. So maybe there should be some stratification, whether it is ages or whatever, that maybe have to be addressed also.

DR. DRAKE: Rob?

DR. STERN: May I make a suggestion about altering this question for the committee.

DR. DRAKE: I would be grateful, actually.

DR. STERN: "For a product of this type, is diaper dermatitis excluding cases where the primary clinical opinion is irritant contact dermatitis, bacterial infection, atopic dermatitis, seborrheic dermatitis or psoriasis, an appropriate indication?" To me, knowing that a person has one of these conditions, it is not plain diaper dermatitis.

I think the indication for this is, as Steve has said, it is essentially not one end of the pole where you think a person has seborrhea or atopic eczema not infected by Candida but rather those very prevalent cases where there is ambiguity, you are pretty sure it is not psoriasis, you are pretty sure it is not atopic eczema, but you think, well, maybe there is an irritant component, maybe there is a Candida component, so let's--it is really a diagnostic of exclusion of certain things that represent a small but important and clinically recognizable thing, and it is that mish-mash of things.

So I would rather put it that way because this is a little bit--the way it is phrased is a little bit like one of these, "When did you stop beating your wife?" questions. Of course, it is not appropriate for dermatologists or clinicians to use a product that isn't likely to be very effective for atopic dermatitis or psoriasis if they have that clinical suspicion.

But if it is that great mass of stuff and they have excluded those things with reasonable probability, I think it is not so bad.

DR. DRAKE: Write it down. John?

DR. DiGIOVANNA: I just want to reiterate that. You have said it a little better and I am not going to waste time on wordsmithing. But I think that diaper dermatitis of

uncertain etiology--I am sure there is a better way--where one excludes the more clear-cut conditions that can be identified such as atopic dermatitis, psoriasis, seborrhea and such.

I think, clearly, as Steve has pointed out and everyone else has pointed out, there is a group of patients where the diagnosis is not clear. I think it is reminiscent of the discussion we had yesterday of those red, scaly areas that you want something for that given the fact you don't have a specific diagnosis.

DR. DRAKE: I want to do something. I am going to call on Joe and then Bill, but then I am going to call on Joel because I haven't heard from you in a while. You have been way too quiet.

DR. McGUIRE: This will be brief because it is repetitious. I think that we have to be careful that the committee does not endorse a product for indications that the company has not provided evidence for and the small amount of positive data that we have is for Candida infections in a clinical pattern of diaper dermatitis.

I think that is the only indication that we can approve. I don't want to walk out of here feeling that we have endorsed a Desitin-plus.

DR. DRAKE: We haven't because we have voted not to approve it. We voted more information was needed before

we go forward, so I think we haven't. But, Joe, I would echo that. I think the sponsor should take this--they heard it back in 1990 from the chair of the committee and I think they should hear it again from this committee as a whole. You have heard it now from two different sources, that we are pretty precise when it come to the committee.

We need to know exactly what you are going after and you need to present us with data supporting the indication that you are going after. If it is anticandidal, then we need to see anticandidal data.

If it is antiirritant, then we need to see that. So I would encourage the sponsor to be real specific. We, at this table, tend to--I have seen it happen for many years off and on in this committee, is this committee is quite literal. We tend to take the data we see and act upon it. We are not good at extrapolating nor are we good at extending, nor are we very good at defining things, particularly.

So I think, before I call on other people--I just want to tell you I think this is a wonderful notion. I think a product like this is needed. I think if you come back with some additional information that answers these questions you are hearing, that, certainly, this committee is interested in approving something like this.

I think the FDA probably is, too, for what that is