DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

MEETING NO. 52

OPEN SESSION

Friday, June 30, 2000

8:30 a.m.

Holiday Inn Bethesda
Versailles I
8120 Wisconsin Avenue
Bethesda, Maryland

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C O N T E N T S

NDA 21-026 (miconazole nitrate, U.S.P. 25 Percent) Ointment
Johnson and Johnson Consumer Companies, Inc.
for Treatment of Diaper Dermatitis

P R O C E E D I N G S

Call to Order

DR. DRAKE: I would like to call this committee to order. Welcome, panel members and FDA officials. I would like to welcome our sponsor and our guests and our experts for the panel and all of those of you in the audience. We appreciate your attendance.

For the panel, just so you will know, as a bit of housekeeping before we begin the official part of the meeting, I have had lots of inquiries about time out of here. Jonathan, is it okay for me to comment on this, about the timing of the meeting?

Okay. What we are going to do try to do is I am going to ask the speakers to be respectful of the time, keep your comments as concise as possible because there has been a lot of concern from people that this is a holiday weekend, a lot of traffic, if they miss their flight, they can't get other flights.

So we are going to try to finish not only on time but we are going to try to finish early. I think we can if the committee and the experts and everybody will be very cognizant of time. As we get into each session, I will let everybody know about how long, but I can tell you we want to be very concise.

I will hold you to the time. That goes for both

the invited experts as well as the sponsor presentation. I am just telling you up front I am going to hold everybody to the time. How you divvy up your time is up to you, but I will hold you to it just because of these constraints. I want to make sure that we finish and we have time to answer the FDA's questions.

What I have seen happen in the past is once in a while, people will start slipping out the door to catch a plane if we are running late. And then we don't have a full committee to properly address the questions. And that is our goal.

Now, then, if there is no further housekeeping, please allow me to introduce myself. I am Lynn Drake. For the next two days, I am still at the University of Oklahoma. The first of the week, I return to Harvard Medical School as my affiliation.

I would also, then, like to introduce our Executive Secretary. As soon as I introduce you, I am going to go around the table and have everybody introduce themselves before I have you give the opening statement. But we have a new Executive Secretary, Jaime Henriquez. Welcome.

MR. HENRIQUEZ: Thank you.

DR. DRAKE: This is our first meeting together and he has done a terrific job, and I want to compliment him.

We have been organized and it has been a good meeting. So, thank you for all your able assistance.

With that, I would like to start with Lloyd. Please introduce yourself and your affiliation. We will go around the table.

DR. KING: I am Lloyd King. I am from Vanderbilt University and Nashville V.A. Medical Center. I am a dermatologist and a dermatopathologist.

DR. SPRAKER: I am Mary Spraker in Pediatric Dermatology at Emory University in Atlanta.

DR. FELDMAN: Steve Feldman. I am Associate Professor of Dermatology and Pathology at Wake Forest University School of Medicine.

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

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

DR. WHITE: Ted White, Assistant Professor, Department of Pathobiology at the School of Public Health at the University of Washington.

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

DR. DiGIOVANNA: John DiGiovanna, Department of Dermatology, Brown University School of Medicine and National Cancer Institute.

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

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

MR. HENRIQUEZ: Jaime Henriquez, FDA.

DR. CHESNEY: Joan Chesney, University of Tennessee in Memphis. I am in Pediatric Infectious Diseases.

DR. STERN: Rob Stern, Dermatology, Beth Israel Deaconess Medical Center and Harvard Medical School.

DR. KILPATRICK: Jim Kilpatrick from the Medical College of Virginia in Richmond, Virginia. I am a biostatistician.

DR. ROSENBERG: Bill Rosenberg, Dermatology, the University of Tennessee College of Medicine, Memphis.

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

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

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

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

DR. KO: Hon-Sum Ko, Dermatologic and Dental Drug

Products, FDA.

DR. MARSIK: Fred Marsik, Review Microbiologist with the FDA.

DR. DRAKE: Welcome.

Mr. Henriquez, would you do our conflict of interest statement, please.

Conflict of Interest Statement

MR. HENRIQUEZ: The following announcement addresses the issues of conflict of interest with regards to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

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

In accordance with 18 USC 208-B, a full waiver has been granted to Dr. Joel Mindel. A copy of this waiver statement may be obtained by submitting a written request to the FDA's Freedom of Information Office located in 12A-30 in the Parklawn Building.

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

participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

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

DR. DRAKE: Thank you.

With that, I would like to invite Dr. Wilkin to give some opening remarks about our process and our goals today.

Introductory Remarks

DR. WILKIN: Thank you, Dr. Drake. I will attempt to be responsive to your requirement to be efficient with my our use of time.

If you look in the last part of Dr. Ko's presentation, you will find three questions. The first question--I will not read the question but I will give you some of the thinking behind the question. The agency is interested in whether diaper dermatitis, per se, is an appropriate diagnosis. If it is an appropriate diagnosis, what is the database which should be developed to support that.

One possibility would be that the sponsor would study all patients with diaper dermatitis not

differentiated--that is, not evaluated. The other possibility is that the sponsor would need to demonstrate the effectiveness of the product in both Candida diaper dermatitis and also in primary-irritant dermatitis which would then allow for an informed reductionism in the clinical practice.

The second question is regarding safety. Some of the issues that we would like to know about is what happens with treatment beyond seven days. It is clear in the dataset that not all of the children have their diaper dermatitis clear by seven days, so what happens with longer treatment. What is the rate of relapse, some other areas there related to safety.

And then, finally, after hearing about the dataset from the sponsor's point of view and from the agency's point of view, we would ask whether there is sufficient evidence for effectiveness or whether additional information on effectiveness is needed for this product.

DR. DRAKE: Thank you, sir.

If I had just about one more piece of paper up here, I would probably drown in it but I am about half organized here this morning. I have about got the right pieces of paper where they belong.

I think, now, we will move to the Open Public Hearing.

Open Public Hearing

DR. DRAKE: Mr. Henriquez, do we have any formal requests for--

MR. HENRIQUEZ: No; we have not received any formal requests from the public to speak.

DR. DRAKE: Having received no formal requests from the public, I would still like to make that opportunity available for anybody in the audience. Is there anyone who cares to comment or speak at the mike during this session? Seeing none, we will move forward, then.

I would like now to ask the sponsor, which is Johnson and Johnson, to begin their presentation. Ms. Uhl, thank you. Welcome. There is a mike and podium and please begin.

Sponsor Presentation

Introduction

MS. UHL: Ladies and gentlemen of the advisory committee, the FDA and the audience. Thank you for letting us have this time this morning to give you some information on our product, Pediastat miconazole nitrate 0.25 percent diaper rash ointment.

[Slide.]

The presenting speakers from Johnson and Johnson Consumer Companies will be myself, Diana Uhl, Manager of Regulatory Affairs and Dr. Robert Armstrong, Vice President

of Medical Affairs.

[Slide.]

The order of presentation today will be Introduction; Clinical Overview by Dr. Armstrong; Resistance in Candida albicans by Dr. Michael Rinaldi, a consultant; Clinical Perspective by Dr. Amy Paller, a consultant; Current Clinical Practice and Summary by Dr. Armstrong.

[Slide.]

Our product is a 0.25 percent miconazole nitrate in an ointment base of zinc oxide and petrolatum. The indication which we seek is treatment of diaper dermatitis in infants.

This product has been marketed OTC for diaper dermatitis since the early 1990s in Australia, Belgium, Denmark, Luxembourg, Russia and Venezuela. Miconazole nitrate has been used in the United States both Rx and OTC for over twenty-five years.

Some indications include vaginal infections, athlete's foot and other skin infections.

[Slide.]

The original NDA for this product was submitted in 1985. At that time, we submitted as an OTC product. The FDA determined that it was not approvable as an OTC product. They suggested that if we had data on systemic exposure from percutaneous absorption and one additional study that we

could refile as an Rx indication .

The reason that we needed an additional study is because the two U.S. studies were not statistically robust and had to be combined. Today, we will show you information on both of those requirements.

[Slide.]

The fundamental questions for approving this product are: is there sufficient evidence to establish that Pediastat is effective in diaper dermatitis; is there sufficient information to assess the safety of Pediastat; is the benefit of Pediastat greater than the risk.

[Slide.]

We believe that the evidence that we will show you today support the conclusions that Pediastat is effective and safe and is a valuable treatment option. In the U.S. today, there is not FDA reviewed and approved treatment for diaper dermatitis. We also want to show you information from which you can conclude that Candida albicans continues to be susceptible to miconazole after extensive use over twenty-five years.

Dr. Armstrong will now talk to you about some clinical aspects of diaper dermatitis.

Clinical Overview

DR. ARMSTRONG: Good morning.

[Slide.]

While I am adjusting the microphone, I would like to thank the people in my group, my colleagues, who have helped me with this presentation and you are the beneficiaries of it because it is better now than it would have been if I had done it by myself.

I would like to start, as Dr. Wilkin has suggested, with what are we talking about today, what is diaper dermatitis. Some of the remarks that Dr. Wilkin made in opening are reminiscent of some of the reasons that they gave us in their reason for not approving this.

[Slide.]

The first point is there was a need for a clear-cut definition of the indication so that the product could be recommended for a target population that would receive the clinical benefit without introducing the risk of drug restriction through indiscriminate use.

I expect that, as we present our information today, we will address the question about what target populations could be considered and why we think that would be a benefit for them. We will also address this issue of restriction which we think is theoretically valid even though we think there is a substantial amount of experience to show that, in practical terms, it hasn't been a difficulty to date.

[Slide.]

The second comment made in the letter that we received stating that we would not get approval for the product is presented here. This has to do with identification of different types of modifiers of the indication that might be considered, for example the severity of diaper dermatitis and the possibility of including some reference to the association with Candida albicans.

[Slide.]

Again, I think that the next slide may be the best definition yet. It is actually a definition provided by the FDA and presented in their tentative final monograph for over-the-counter drug products in the category for diaper rash. This definition is that, "Diaper rash, or diaper dermatitis, is an inflammatory condition in the diaper area caused by one or more of the following factors: moisture, occlusion, chafing, continued contact with urine or feces or both, or mechanical or chemical irritation."

We think this is an apt description and we would be very happy to take this as an indication and, if that would resolve some of the areas where we have had discussion with the agency about the references to Candida or the severity of the disease, I think we could easily resolve those labeling issues.

[Slide.]

There is, however, one factor that we recognize as being important in diaper dermatitis that is not included in that definition and that is Candida albicans. Candida albicans can be an important contributor to diaper dermatitis. It is present in many but, by no means, all cases. Depending on which report you read in the literature, you can find incidences of as high as 80 percent. In our studies, 30 percent of the patients has positive baseline cultures showing Candida albicans.

One of the reasons that we can find it so frequently is that Candida is a part of the normal flora of the lower intestinal tract. This, then, leads to a lively debate about what is the significance of Candida when cultured. Is it a colonizing organism? Is it an invading organism? Is it clinically significant?

Many textbooks of dermatology and pediatrics suggest that there be a presumption that Candida is present and an important contributor if diaper rash persists for more than three days. In general, when there is a suspicion that Candida is present, recommendation is for specific treatment for that condition.

[Slide.]

There are a couple of experimental studies that I think are worth reviewing very briefly because they relate to this issue. One is an experiment in which Candida was

cultured, applied to the skin under occlusion for 24 hours. The occlusion was then removed and the sites observed to see how the area would progress over the next two to three days.

What was observed was a progression from erythema to papules to pustules in a fashion that is quite reminiscent of cutaneous candidiasis. It also was found in these experiments that the incidence and/or the severity of that reaction could be increased by increasing the number of yeast cells in the inoculum, by increasing the duration of the occlusion and by stripping this stratum corneum before the inoculation. We believe that the stripping is a kind of mechanical comparison to the enzymatic effect of the enzymes present in feces.

[Slide.]

A second study also involved Candida grown in culture. But, in this case, the Candida were killed, disrupted and an extract supernatant prepared as well as a sediment. Both of those two preparations were used to try and reproduce the clinical appearance of candidiasis by applying them to the skin.

In both instances, it was possible to reproduce both the clinical and the histologic features of cutaneous candidiasis in 75 percent of subjects.

[Slide.]

Now, this leads us to two implications from these

experimental series that we think are relevant to the situaton in diaper rash; first, that Candida albicans, introduced as part of the fecal flora, has the potential to become invasive. Secondly, Candida can be irritating to the skin without being invasive and without, in fact, being viable.

[Slide.]

With that as an overview for reference or orientation, if you will, I would like to review a bit about the way the clinical development program was done for this product.

[Slide.]

First, the formulation is one which consists of petrolatum and zinc oxide. It is really quite like some of the standard products that are used, but there is an important ingredient that is added and that is miconazole nitrate. As you can see, it is a very simply formulation, one which does not pose any clear ingredients with a potential for irritation.

[Slide.]

The three trials that were submitted as part of this NDA. One was done in the United States. That was the initial trial. In two subsequent trials, both done in Australia with a total of 252 patients in the Pediastat group, 253 in the ointment base group.

It is important to notice that most of the patients completed this trial. 96 percent of the Pediastat patients, 90 percent of the ointment base patients--very good compliance.

[Slide.]

Having provided the FDA's definition of diaper dermatitis, I wanted to share with you what the entry criteria, the inclusion criteria, for these three protocols, what those criteria are. They are presented here verbatim from the protocols. They were identical for all of the protocols.

As you can see, it was open to male or female patients, age 2 to 12 months, and the clinical manifestations had to be consistent with a diagnosis of diaper dermatitis.

[Slide.]

The treatment was assigned to one of two treatment groups by a random, double-blind process with patients receiving either the Pediastat preparation or the ointment base. The dosing regimen was to be applied after every diaper change for a period of seven days.

Cultures were done for Candida albicans at baseline and at Day 7 for two of the studies, the U.S. study and the first of the two Australian studies, and assessments were done for efficacy as well as for safety at baseline,

Day 1, Day 3, Day 5 and Day 7.

[Slide.]

It is also worth noting that, out of this group, KOH was not done in any of the studies. So if, in fact, you consider that it is critical to be able to divide things by the presence or absence of pseudohyphae, it is clear that these studies will not be able to make that distinction. The test was not done.

[Slide.]

How did we measure efficacy in these trials? There were several criteria that were used in common through all of the trials: an overall rating, which was how is the patient today compared to an earlier status; how many sites of the patient's body are involved with rash; and what is the severity of rash at each of those sites and then what is the total of those at the sum of the sites for the patient.

An additional criterion was added for the two Australian studies and that was the use of the global clinical impression. Again, Candida cultures were done for the U.S. and the Australian studies.

DR. DRAKE: Excuse me, Dr. Armstrong. There was no Candida study done in B, the Australian B study?

DR. ARMSTRONG: That's correct.

DR. DRAKE: Just one of the studies?

DR. ARMSTRONG: That's correct; there were no

cultures done in the second of the Australian studies.

[Slide.]

Each site that was assessed was scored on a 0 to 4 scale for the degree of diaper dermatitis at that site. So it could be 0 for none, 1 indicating a mild erythema with minimal maceration and/or chafing. It could be moderate erythema with or without satellite papules, maceration or chafing. And then more severe manifestations got the numbers 3 and 4, as you can see.

[Slide.]

What sites were looked at? Where were data recorded? Well, in the U.S. study, they were recorded from ten sites and, in the Australian studies, from eleven sites. The sits are indicated here in these diagrams taken from the case-report form.

One of the comments make in the FDA's briefing document was that, in fact, some of these sites, the chest, the back, the outer thighs, are not typically covered by the diaper. That point is well taken. It is accurate and, in fact, less than 5 percent were involved in our studies.

However, since we have a total score that we are using for comparison, we don't believe that it has compromised the conclusions that we can draw from these studies.

[Slide.]

I mentioned that we had a high degree of patients who completed the trials, but I wanted to review with you those patients who dropped out before the trial was over. Importantly, none of the patients dropped out because of an adverse experience which was clearly attributable to their treatment.

The largest group was the group that dropped out because they hadn't received and clinical benefit. There was no treatment benefit appreciated and they discontinued for that reason. There is, otherwise, a pretty similar agreement between the two groups but this no treatment benefit is clearly more common in the ointment base treatment group.

[Slide.]

With that, I would like to proceed to a discussion about the efficacy. In respect to your request for conservation of time, I am going to talk only about the total rash score criteria, but we have data available and would be happy to share any additional information which you would like.

I think it is pretty supportive of the same conclusion, so I think we can use this as a shorthand in the interest of time.

[Slide.]

This is the first study, two centers done in the

United States. The same type of graph is used in each of the next five slides, so I would like to point your attention to the Y axis being the mean rash score. So each patient has a rash score assigned to each site, summed over all the sites and then an average of that determined to come up with this number.

On the X axis, we have the day of the student and we have presented here the results for the Pediastat treatment group compared to the results for the active base group.

The pattern that you see in this slide is actually quite similar to the one you will see in the next two slides for the next two studies. What it shows is that there is progressive improvement over each assessment point for both treatment groups, that Pediastat shows a greater degree of clinical improvement and that that difference between the two treatment groups is statistically significant in this trial at Day 3, 5 and 7.

One of the points that was noted in the briefing document you received from the FDA was that, in this trial, one of the other efficacy criteria, the overall criteria, did not achieve statistical significance. So, in this trial, the number of sites involved, the mean rash scores, were statistical different between the two treatment groups but the overall score was not.

We think that this is not uncommon in clinical trials for there to be some parameter out of the mix that does not achieve statistical significance, but the FDA has suggested that we disregard this trial as not being valid. We would take exception to that and point out that we believe that there is a reasonable conclusion that can be drawn from this and, in fact, a reasonable action step that can be taken from it because we increased the size of the next two studies that were done and then, in that instance, were able to show statistical significance for all categories of efficacy which were measured.

[Slide.]

I would like to proceed to the first of the two Australian trials. This is the Australia-A trial and, again, the same pattern, progressive improvement over a seven-day treatment course for both groups, Pediastat showing an advantage over the ointment base and that difference being statistically significant at both Day 7 and at Day 5.

[Slide.]

Finally, for the third study, the Australia-B study, same pattern, progressive improvement, Pediastat better than vehicle, Pediastat statistically significant in that difference on Day 5 and Day 7.

[Slide.]

That is one way of looking at the data but there are others. I am going to present, again, only the data from the Australia-A trial as the larger of the trials for which we had culture data available. I can show you the results from the U.S. The pattern is quite similar.

This is in a subgroup of patients who had positive cultures at baseline for Candida albicans. What it shows is that the ointment base patients, the patients who received the ointment base, when they had Candida present at baseline by culture really did not show any improvement over the seven-day treatment course.

We think that this is a significant point and one which we will need to come back to shortly.

In contrast, there is progressive improvement in the response in the Pediastat group and, in this instance, the statistical significance seen in this clinical response is present as early as Day 3 and persists on Day 5 and Day 7.

[Slide.]

Yet another way that we can look at this is to now subdivide the Australia-A study and look at only those patients who are treated with the ointment base. Here you can see the same result. This is the same data on the top line. When Candida is present, there is no improvement. When Candida is not present in the baseline culture, you can

see a progressive improvement in the clinical score.

We think this is actually a very significant component of the clinical trial because this ointment base is really the standard of care as a barrier ointment, the standard of care mentioned in all the pediatric and dermatology textbooks as being an important part of the treatment of diaper dermatitis.

This is not a "no effect" comparison group. When we can show that we have performance that is superior to an accepted standard-of-care therapy, I think we have met a higher standard of proof than if we were doing a comparison to a treatment which would be expected to have no therapeutic benefit.

[Slide.]

What conclusions do we take from this study? We believe that this shows that Pediastat was both clinically and statistically superior to the ointment base for diaper dermatitis, that the benefit of Pediastat was most pronounced, it was most advantageous in the subgroup of patients who had baseline cultures that were positive for Candida.

Both Pediastat and the ointment base provided clinically and statistically significant improvement in patients whose baseline cultures were negative for Candida. Then, finally, as I have said before, the ointment base

provides barrier protection and it is part of the standard of care and it could qualify for marketing today under the FDA's tentative final monograph for skin protected drug products for diaper dermatitis.

[Slide.]

That brings us next to a very important consideration and that is safety. I would like to share with you the reasons why we believe this is a very safe product.

[Slide.]

First, I would like to review the adverse experiences that occurred in the studies. This is a combined dataset that pools results from all of the studies. What you can see is that 23 patients in the Pediastat population developed an adverse experience compared to 54 in the ointment group.

The total number of adverse experiences was 25 in Pediastat, 63 in ointment, so about two-and-a-half times as frequent in the ointment base group as the Pediastat group. As you would expect for a group of infants, otitis media, upper respiratory-tract infection and gastroenteritis were the most common side effects that were noted.

Only those that were included in the skin and appendages had any that were considered to be possibly related to treatment. None of these were considered to be

serious adverse events and most of them were considered to be coincidental by the investigator.

[Slide.]

In 1985, the original NDA submitted was not accepted because there was no data on the systemic exposure in patients treated with this product and how much miconazole would enter their blood stream.

So we have done a study that involves 18 infants who were hospitalized because they had a severe gastroenteritis with diarrhea and, as a consequence of that, had developed diaper rash. These infants were treated with a dosing regimen that is essentially identical to the three studies that we have presented.

When blood values were tested for, in 15 patients, any miconazole absorbed was below the limit of detection, the limit being 1 nanogram per ml. In three patients, there was detectable miconazole but it was present at a concentration of less than 5 nanograms per ml.

Just for a point of reference, blood concentration in children who had been given intravenous miconazole in doses of 7 to 10 milligrams per kilogram, blood levels were obtained that ranged between 400 and 3,600, obviously very much higher than we experience in these subjects.

[Slide.]

So we conclude from this that Pediastat is safe.

It is safe because there were no clinically significant adverse experiences reported with Pediastat during the clinical trials. Less than 1 percent of adverse experiences were actually attributed to treatment. All of those occurred in the skin. All of them resolved without complications.

Adverse experiences were about half as common in the Pediastat group as the ointment base group, but these adverse experiences were generally regarded as coincidental and, with the exception of a few of the cutaneous ones, not related to treatment.

The next point I have not presented you with any data, but I am prepared to do so if there is a question which you would like to ask. But tests in volunteers indicated little or not irritant, allergic, photoallergic or phototoxic potential. As I have said, there is little or no systemic exposure following the use of this product topically.

[Slide.]

Nor, resistance has been a part of our discussion already and we are about, now, to move into a more detailed discussion of that. But I thought it would be worthwhile to review with you a little bit of information about susceptibility of Candida albicans.

[Slide.]

These are results provided by another one of the Johnson and Johnson companies, a company which markets products for the treatment of vaginal yeast infections. These represent baseline isolates from a study of a new dosing regimen for a treatment for vaginal yeast infection.

It totals 448 Candida albicans isolates from the entrants to this prospective study. Then they were tested for MICs to miconazole. What you can see is that the most common group, 70 percent, were sensitive at the lowest MIC shown here of 0.05 micrograms per ml.

The highest was sensitive at 6.25 micrograms per ml. I would like to point out to you that the concentration of miconazole in the Pediastat formulation is about 1,000 times higher than these concentrations here, so in significant excess over these concentrations.

[Slide.]

Having talked about susceptibility, I would like to conclude with this point, that the briefing document from the FDA contends that using miconazole in patients who do not have evidence of infection could select resistant Candida albicans.

This is something that is, in a way, curious to us because if there is no Candida present, presumably there is no possibility to select for a resistant organism. But it is also relevant, and, perhaps more important, to note that

miconazole resistance has not been a clinical problem despite widespread use over 25 years of marketing and we have not seen, to date, any reason to indicate that Pediastat would contribute to the emergence of miconazole resistance.

With that, I would like to introduce another one of our consultants, Dr. Michael Rinaldi, a member of the Subcommittee on Antifungal Susceptibility Testing for the National Committee for Clinical Laboratory Standards. I am going to ask Dr. Rinaldi if he would address issues of resistance as it relates to Candida.

Dr. Rinaldi.

Resistance in C. albicans

DR. RINDALDI: Good morning. As we say in San Antonio, "Buenos dias, y'all." Nice to come up here. The folks at Johnson and Johnson asked if I would say a few words about restriction in fungal problems in contemporary medicine.

[Slide.]

As all of you are well aware, we have had a period of time, now, over the last, say, fifteen years where these organisms went from components of microbiology infectious disease that were of very little interest to anybody to now some of the most critical problems in medicine.

This is all because mostly we keep creating, by

what we do to these patients we take care of--we keep making this ever-growing population of living Petri plates. We just kind of keep making all these Petri dishes. And then, into these Petri dishes fall these fungi which, up until the time we were doing this, were of very little interest.

That, in turn, spurred interest in the pharmaceutical industry to make new antifungal drugs. So we have had also, in addition to all these increased number of Petri plates with fungal disease, we now have the most antifungal drugs we have ever had in the history of medicine.

So then that always results in the question about what is the story with restriction to antifungal drugs. So let's take a look at this.

[Slide.]

If one hears this business about fungal resistance, I think the very first thing you always might want to ask is when people say this word, "resistance," what kind of resistance are they talking about? Do they mean here that the fungus is genetically, innately microbiologically resistant to the antifungal drug, true microbiologic resistance?

Are they talking about, rather, that after the patient has experienced therapy with the antifungal drug that there is then the development of resistance which is

actually also genetically acquired; that is, has true resistance developed after therapy or during therapy?

Lastly, is this a situation where the doc is using an antifungal drug to treat a patient who has a fungal infection with a drug that is supposed to work at the dose that is recommended and yet they don't see a clinical response; clinical resistance?

Chances are high that when you review the literature and you talk to any docs that treat fungal infections on a routine basis that the vast bulk of all this resistance business is clinical. Not to say that there isn't microbiologic resistance because there certainly is, but the vast bulk of the problems that you see when you talk to practicing docs taking care of patients with mycoses turns out to be clinical resistance.

[Slide.]

Let's look at that a little bit more. In the case of the question under discussion here today, namely Candida and more specifically, Candida albicans, let's concentrate, then, on candidiasis in this instance.

When you look at the total experience in the literature over the last, says, twenty-five years resistance issues to antifungal agents and Candida, in generally, is just basically about somewhere in the neighborhood of about 1.5 percent.

It certainly has not emerged as an overwhelmingly major problem in contemporary medicine like you would expect to see with the MRSAs in the bacterial world or the problem that we all know about with tuberculosis and its resistance to antibiotics, and so forth.

Now, if you look at specific drug/fungus interactions, there are certain fungal drug interactions that everybody that takes care of patients that has used these drugs certainly knows those well; for instance, this little yeast, Candida lusitaniae, which, from time to time does get in people's blood.

There is no doubt about it. This fungus is genetically resistant to amphotericin B about 20 percent of the time, so one would want to know that in that instance. All the more reason why you always need to do good microbiology.

The same could be said for fluconazole and the yeast fungus, Candida krusei which is just basically right out-of-the-box resistance to fluconazole no matter what one would do.

Those are two good examples of well-known interactions. But, in the case of Candida albicans which is, of course, the major fungal pathogen of all mankind and, in this instance today, is the agent under discussion, there has really been, of all the antifungal drugs that have ever

been used to treat Candida albicans, one group of patients that has demonstrated, again and again, this resistance issue and it has formed the crux of almost everything that has ever appeared in the literature about resistance to antifungal drugs, and that is our friends who have HIV disease, who have Candida albicans in their mouth and their throat and their esophagus and develop, basically, resistance to fluconazole.

That has been the single biggest resistance issue. In fact, that has triggered, I think, more than anything than has ever been, any discussions of resistance to antifungal drugs.

If you look at this business more closely with fluconazole and candidiasis, and I think Dr. White, on your panel, is one of the great guys that has elucidated this at a molecular level, you can see that these interactions are pretty interesting.

There has been both microbiologic and clinical resistance. There have been instances where people have Candida albicans in their mouth where one strain is resistant and the next strain that you grow out from the same area in the mouth is not.

There has been switching back and forth between which ones become resistant and ones that don't become resistant. It has turned out to be a far more complex

problem in that patient group than anybody would have ever imagined. But the bottom line is that still, even with AIDS and thrush in the mouth, almost all of those cases, when you look into them, have been clinical resistance where the doc is not happy with the outcomes from the therapy with fluconazole at doses that they think should work in these kinds of people.

Basically, if you raise the dose of fluconazole, in virtually all these cases, then you start to see response. Then, after while, that does not respond so you raise the dose of fluconazole again. These have all been really essentially used as the springboard for discussions of resistance to antifungal drug.

[Slide.]

Now, what about the product that you are considering here today. In the past, with the advent of miconazole back in the early days of the '70's and '60's and then later sort of son of miconazole, ketoconazole, also a Janssen product, there came to be a couple of docs that noticed that they had some patients with chronic mucocutaneous candidiasis and that they were using miconazole and keto to treat these people.

As you derms in the room certainly know, ketoconazole turned out to be really the major agent to treat chronic mucocutaneous Candida.

There was a guy in Colorado, Dr. Charles Kirkpatrick, who noticed in a little gal who had chronic mucocutaneous Candida, that she didn't seem to respond to keto and miconazole the way that these people normally did. So he was a guy that was very perceptive and he kept the pre-treatment isolates. He kept the inter-treatment isolates. And he kept the post-treatment isolates.

Lo and behold, it turns out that, with these--I believe in the literature, they were well characterized and passed around from lab to lab for years, and there were three of these strains of Candida albicans. These were actually genetically microbiologically resistant to miconazole and ketoconazole.

Those have been the three strains that I have been constantly familiar with all these years that have been involved with resistance that is truly genetic to keto and itra.

[Slide.]

So, now, if we take a look at what is going on with the modern azoles, and with the older azoles like miconazole, I think it is pretty clear there is cross resistance. You can test them in the test tube and you can see, if it resistant to one, you will see an increased MIC to the other.

But the bigger question is what dose the

cross-resistance mean in terms of the clinical business. It turns out that, in the cases where there is cross-resistance, from a clinician's point of view, the cross-resistance is so below the MIC or the amount of drug that you give can so far exceed the MIC that it becomes clinically sort of irrelevant. It really still comes down to being clinical resistance issues.

So, as near as I can tell, having tested these fungi for twenty years now, with the exception of this group of AIDS guys who have Candida in their mouth and get low doses of fluconazole, and I guess you could say this is the deal. Is there anybody who doesn't think that the fungi aren't as smart as the bacteria, that if we keep giving these azoles at teeny doses to people who don't have any immune systems over long periods of time, that these fungi are not going to figure out how to become resistant to some of these drugs.

That is precisely what happens with the AIDS group who get low doses of fluconazole over long periods of time.

The exception to that; I can't think of any times, now, that I have seen in dermatology-type fungal disease, dermatomycoses, or dermatophytosis--I can't think of any of the vaginal strains that we have ever tested and I can't think of any big studies of invasive fungal isolates which is mostly what my lab does is deep fungal disease.

I can't think of any issues that we have ever seen with miconazole resistance with the exception of those three patients with CMC and AIDS guys who have thrush in their mouth.

So, as far as I can tell, this is an issue that just hasn't ever surfaced and I am not really sure why there is concern about this. We just haven't seen this and I am not sure what reason we would ever see it.

So, with that, I will stop and thank you for your attention. I'm sorry. I am supposed to pass this on to our next consultant for J&J, Dr. Amy Paller from Northwestern University in Chicago who is going to talk to you about her therapy of diaper dermatitis.

Clinical Considerations

DR. PALLER: Thank you very much and hello.

[Slide.]

What I am just going to talk about is kind of a clinician's perspective of diaper dermatitis.

[Slide.]

I am going to start by just reminding all of you something that you well know which is that diaper dermatitis is a very common problem and it usually is managed not by us in dermatology but by pediatricians or family practitioners. The referral to the dermatologist or the pediatric dermatologist is usually only in those cases that are

recalcitrant to therapy or are unusual and there might be a question about the diagnosis.

[Slide.]

The majority of infants with diaper dermatitis have what we would call irritant-contact dermatitis.

[Slide.]

This largely results from a combination of the wetness in the area leading to the epidermal swelling and increased tendency, then, for irritation and percutaneous absorption as well as those stool lipases and proteases which we know can be activated by the increased pH in the area.

[Slide.]

Candidal infection does occur more easily in damaged skin of irritant dermatitis and we think that it is contributory towards that inflammation.

[Slide.]

How do we manage diaper dermatitis? Standard of care includes frequent diaper changes, avoiding excessive water exposure and harsh cleansing agents.

[Slide.]

And, very importantly, the application of zinc-oxide-containing protective paste with each diaper change. That is standard of care whether we are talking about irritant diaper dermatitis alone or with candidal

diaper dermatitis.

[Slide.]

If we think that there is a candidal infection, we will include an anticandidal agent as part of that treatment. So we do use these anti-candidal agents if candidal infection is suspected and, on occasion, we will use a mild, usually non-fluorinated, topical steroid for no more than a few days, and we are very careful about the use of topical steroids if the choice is made to use them at all.

[Slide.]

Currently, the topical agents are applied a few times daily when they are medications and then topped with the protective paste which, again, is used with each diaper change. So the main decision that needs to be made by a physician is about the presence of Candida.

That is where I think the difficulty comes in. The diagnosis of candidal diaper dermatitis versus irritant diaper dermatitis is largely made outside of dermatology offices based on clinical judgment.

[Slide.]

We have used some standards such as the intensity of the erythema, the distribution on convex areas, as you would probably see with an irritant diaper dermatitis from exposure, versus fold areas which we attribute more likely

to candidal infection, and then the presence of satellite papules and pustules which would be more specific of a candidal infection.

Unfortunately, these clinically based decisions about Candida albicans versus irritant diaper dermatitis are often wrong. I know this has been a source of consternation by my colleagues in pediatrics and I can admit, for myself, when we go do the KOH, I am often wrong based on my clinical judgement.

I will just show you some examples.

[Slide.]

This is a case, a very clear-cut, relatively mild-to-moderate irritant diaper dermatitis. You notice that the convex areas, here, are most severely involved, the areas in contact with the wetness, the areas subject to friction. On the other hand, this is very typical, candidal diaper dermatitis with fold area involvement and papules and pustules in the area, a more intense erythema, very often.

[Slide.]

I show you these two examples. Here is a case of irritant diaper dermatitis, lots of convex-surface involvement but also fold involvement. Here is one which is proved to have Candida on KOH examination; again, fold-area involvement but even more intense convex-area involvement. We don't really see satellite papules and pustules. That is

because so many of these patients do have an associated and often underlying irritant diaper dermatitis as well.

[Slide.]

Just another example. Here is a case of irritant diaper dermatitis. The folds are spared, but there are quite a few of these satellite lesions. And here is a patient with candidal diaper dermatitis with relative sparing of the fold areas.

So there certainly are situations where the rules are not followed if one is just making a decision based on clinical characteristics.

[Slide.]

The best way to make that diagnosis is KOH examination. That requires scraping of the skin, treatment with potassium hydroxide and then waiting for scales to dissolve and microscopic examination. All of us who do this know that that takes time.

We also know that, in primary-care offices, time is extremely valuable. Many patients need to be seen in a short period of time. These primary-care office practices are really too busy to allow doing KOH on babies who have diaper dermatitis.

In addition, primary-care physicians really do have limited training in performing and reading KOH examinations. Even those of us who do them on a regular

basis frequently come cross them that we will call equivocal and that we are really just not sure on the basis of the examination.

I would mention, too, that I know we had to get a CLIA waiver in order to do KOH exams in the office and that takes extra effort.

[Slide.]

Cultures are not terribly useful largely because you have to make a decision there in the office. As we know, candidal cultures may take up to a week to grow out. So that is not a very useful, although simpler, test to perform.

In addition, I will say, from my experience, anticandidal agents are often prescribed even if the KOH is negative if you have a strong clinical suspicion.

[Slide.]

Unfortunately, what is too often used in primary-care offices is what I call the shotgun approach. That is the prescription of combination anticandidal agent and topical steroids to decrease the inflammation that is seen. Unfortunately, the available combinations include those with more potent topical steroids including a moderate-strength one, triamcinolone, and a more potent one, betamethasone diproprionate.

[Slide.]

I think we all know that these are inappropriate for diaper-area use and they are associated particularly with continuing use with a higher risk, then, of atrophy, of striae, and even of systemic absorption, particularly since they are in an area of occlusion and then, on top of that, you are slapping protective paste which may further occlude and increase absorption.

I also worry, too, about prescriptions even when patients are warned by the physician about use for a short period of time because I see too often patients continuing to use products or coming in having used them repeatedly despite warnings.

[Slide.]

So I think if there were a combination of zinc oxide paste with miconazole that were very effective against Candida, it would be very useful to us. First of all, we need to use a protective paste anyway, at each diaper change, over the medicated product and at each diaper change to decrease exposure to wetness and stool.

We all know, in this day and age, anything we can do that makes it easier for moms is great. The combination of a protective paste which, again, is standard of care and an antifungal would increase the ease of treatment and, thereby, increase compliance.

I think it provides an alternative agent that

treats both irritant diaper dermatitis because of the protective paste and Candida albicans and, very importantly for those of us in pediatric dermatology who are concerned about the safety of children, it lacks this moderate to high-potency steroid and thereby would eliminate the risk of steroid abuse and increase safety for the infant.

Thank you.

Current Clinical Practice

[Slide.]

DR. ARMSTRONG: I would now like to take a trip away from the clinical-trial setting and into what is the actual practice in common use today.

[Slide.]

Let's start with textbooks, in a sense, to define with the standard of care is academically. We know that these tests can be done, the culture and the KOH, and that a positive KOH showing pseudohyphae is generally agreed to be an indication of an invasive Candida infection.

It is also possible to get a positive that does not show pseudohyphae; it shows other fungal elements. This is a situation where people would be making the diagnosis that this is colonization, at least based on that site, and does not exclude the possibility that there would be pseudohyphae at a different site and it certainly does not preclude the possibility that what is currently a colonizer

could become an invader at some time in the future.

It also does not exclude the possibility that there is some irritant contribution from those Candida when they are present; then, of course, the negative KOH, whether that is a true negative or a false negative.

[Slide.]

What we wanted to do was to take a look at what the actual practice of some pediatricians was in their hospital. So we did a survey. This is a kind of an informal survey chosen from the population of board-certified pediatricians in an office-based practice with a minimum of 100 patients per week being seen.

The list was developed as a randomized list to get some appreciation that we might take as representative of the greater population of pediatricians.

What we did was to ask a number of questions, the first one being what kind criteria will you use to make the diagnosis and determine treatment. What we found was that over 99 percent said they would make the diagnosis on clinical grounds alone in some patients.

44 percent said that, for selected patients, they would add to that clinical assessment a culture. About 25 percent said in selected patients they would add a potassium-hydroxide examination. And, in about 17 percent, they said they would, in fact, do not only the clinical

assessment but also a KOH and a culture.

So, clearly, this group of pediatricians, about 45 percent of them, indicated that they would do laboratory tests to confirm their clinical diagnosis in selected patients. That led us to the next question which was how often do you select these patients for additional laboratory testing, in what percentage of cases do you use these tests to make your diagnosis.

Here is something that actually was not what I had expected to find; it is even higher than I had expected to find. 96 percent of the time, these pediatricians told us they made the diagnosis based on the clinical appearance, alone. Less than 2 percent of the time would they do a KOH or a KOH and culture as part of their assessment.

So, 98 percent of the time, they are making the therapeutic decision based on their clinical impression without resorting to any laboratory test for confirmation. I am not advocating that as being the most intellectually precise or satisfying diagnosis. I am simply presenting it as an indication of what is part of the current practice.

[Slide.]

As Dr. Paller has already indicated, one of the difficulties with that is that the clinical diagnosis is good but it is not perfect, by any means. So what we have done is to take one of the studies, the study done in the

United States, and ask the pediatrician to make the judgment, was Candida likely to be present or was Candida unlikely to be present on clinical grounds.

We then could correlate those answers with the results of the culture for Candida which could either be negative or positive. What we found was about two-thirds of the time the culture and the clinical prediction were in agreement. Candida was expected to be present and the culture was positive in 10 percent. Candida was felt to be unlikely and the culture was negative in 60 percent.

So far, so good. The difficulty comes in this group of patients, these 29, where Candida was felt, on clinical grounds, not to be present but, in fact, the culture was positive. If you recall back when I was reviewing the efficacy, this is exactly the population, those people who were treated only with a barrier protection but had Candida present at baseline who showed no improvement over a one-week treatment course.

We think that this is the group of patients that constitutes the need and the appropriate use for a product like Pediastat. Not necessary--a distinction can be made if a precise diagnosis is being made, but since a precise diagnosis is not being made in the overwhelming majority, we think making this distinction is a distinction that does not make a difference to these practitioners.

[Slide.]

That brings us to what is the standard of care. If we start with textbooks, there is a consensus standard of care; that is the frequent diaper changes and barrier creams. Every textbook of pediatrics and dermatology recommends that.

There is a complimentary standard of care, if you will, and that is the treatment of Candida albicans and, depending on which book you read, some will favor a KOH, some will favor culture, to determine the clinical impression but, as Dr. Paller has already pointed out, only the KOH can be done in time to determine initial treatment.

[Slide.]

A number of authors in these text books, including some text books of mycology, submit that when diaper dermatitis has been present for a period of 72 hours, it is appropriate to make a presumptive diagnosis that Candida is important in contributing and treat on that basis.

Having given these kinds of criteria for identifying candidal contribution, there is quite a bit of agreement on the treatment of choice. It is either an imidazole or nystatin.

Then, finally, there is a controversial standard of care. That is the use of corticosteroids for the inflammatory reaction and all of the textbooks recognize

that this is something which is rarely warranted because they introduce a new element of risk that is not present with the antifungals or the barrier creams; that is the risk of atrophy, striae or HPA suppression.

[Slide.]

I would like to take a step back to the survey which we did. We asked 45 percent of pediatric practitioners, "If you have the results of the KOH and it shows to you that pseudohyphae are present, or it shows to you that pseudohyphae are absent, what kind of treatment would you recommend?"

These are the options that these practitioners presented us with. The thing that I think is relevant to notice here, there are two important points on this slide. Number one, whether pseudohyphae are absent or present, every one of these patients is being recommended to have treatment with an antifungal agent.

I think that the rationale or the take-home message from that is, at least in the judgment of these physicians, not treating a colonizer provides an opportunity for a colonizer to become an invader and create a prolonged case of diaper dermatitis which can simply be preempted by the use of a very safe topical antifungal agent like miconazole.

The second point that I would direct your

attention to is when pseudohyphae are present, these practitioners said they would increase their use of an antifungal-steroid combination by two-and-a-half times, from 10 percent to 23 percent. Clearly, that represents a way to try and cope with the diagnostic ambiguity that the clinician deals with in the office.

[Slide.]

What are our conclusions from this survey? Our conclusions are that 96 percent of treatment decisions were being based on clinical criteria alone. These practitioners do use antifungals. They use them in the majority of patients. All of this use is, in fact, off label because none of them are approved for this population or this indication.

These practitioners reported that pseudohyphae would cause them to double their prescribing rate for antifungal-steroid combinations and those combinations contain steroids that can induce skin atrophy.

You could say, and I would certainly agree with you, that this is, by no means, a perfect study and it is not a rigorously projectable study. We think that it is a valuable study, nevertheless, and we think that it is corroborated by the information on this slide which is derived from marketing data in which the number of prescriptions by pediatricians--now, this does not include

family practitioners and dermatologists--but pediatricians for diaper dermatitis.

It indicates almost 2 million prescriptions in 1999. Out of that--and these are prescriptions for antifungal agents--so that is a significant amount of antifungal agents being used for diaper dermatitis cases. Out of that, 4 percent using a product called Lotrisone and 22 percent using a combination of nystatin and triamcinolone, that represents over 25 percent of these prescriptions, almost a half a million prescriptions being written for these agents for this condition.

With that as background, I would like to proceed to the questions which the FDA posed in their briefing document. These are the questions but, in the interest of making sure that I do not omit any of the points that I wanted to make, I am going to present them in the next five slides with the question as a header and the points that we think are relevant to follow it.

[Slide.]

First, is diaper dermatitis appropriate as an indication for an antifungal. Here, we would like to point out that Pediastat, in our view, is not simply an antifungal. It is an antifungal in a protective barrier preparation where the protective barrier is, in fact, a part of the standard of care recognized by textbooks.

[Slide.]

We reinforce our argument here that the treatment decisions are commonly being made without laboratory testing. Indeed, our data would indicate that 37 percent of these cases were estimated by the pediatricians that we talked to as presenting by telephone. Clearly, a case presenting by telephone offers no opportunity for testing.

The clinical assessment of Candida involvement agrees with the culture result most of the time but 30 percent of the cases in the study done in the United States had undiagnosed Candida albicans.

The trials that we did demonstrated that Pediastat was superior to ointment base in all patients with diaper dermatitis whatever their culture results at baseline were and the addition of miconazole to the ointment base provides important coverage in those instances where Candida is present but undiagnosed and possibly even unsuspected.

[Slide.]

Should an antifungal be considered in the absence of an infection if a benefit can be demonstrated? Well, we think that is a risk/benefit decision, consideration, so we would like to point these things out.

First, Pediastat, as I said before, provides barrier protection as well as antifungal activity, and Candida is frequently present but not suspected on clinical

grounds. These patients, as our data show, do not benefit from barrier protection alone. We believe that Pediastat would decrease the duration of diaper dermatitis in these patients with unexpected Candida because those patients would have to persist for long enough to have additional treatment selected.

Finally, as it relates to the risk/benefit consideration, we have not seen any cause for concern about miconazole being topically. So, for a very safe product, it is easy to understand why a practitioner might say that it is worth adding $6.99 worth of antifungal purchased across the street at the CVS this morning instead of doing a $10.00 KOH to provide not only treatment for Candida when it is present but protection against Candida should it be introduced subsequently.

[Slide.]

Should an adverse effect of the ointment base on Candida albicans infection be sought? This, in a way, is a curious question because, in fact, barrier ointments are part of the standard of care that is recommended by textbooks so there is kind of already, if you will, an academic position well established and not controversial on this point.

Indeed, there are formulations that are quite similar to the ointment base--here is one--that are marketed

and available without prescription now.

The next point, I think, that is worth pointing out is that we have actually applied for approval to market Pediastat. We are not applying for permission to market the base. In fact, under the tentative final monograph, we could market the base today.

Finally, and this I think is the most important point, if there were an adverse effects of the ointment base on Candida albicans that, in our view, would be an argument in favor of approving Pediastat. That is the very population where Pediastat would add an advantage.

[Slide.]

Next, is development of resistance by Candida albicans a serious consideration for a relapse for the public health? There are a number of points to bring out here. First, the concentration of miconazole in Pediastat is one-thousand times higher than the MICs in Candida albicans, even among those that are relatively less susceptibility in the data which we shared earlier.

We have not seen evidence that clinical problem with resistance by Candida albicans exists. Indeed, the only three cases that have been presented to you in your briefing documents and so far today are the three cases which Dr. Rinaldi has brought out, three cases over almost three decades.

Since resistance by Candida albicans has not been a problem over twenty-five years, we don't see any reason to believe that it would become a concern either for the patient or for the public.

[Slide.]

Finally, are the studies that were done in Australia applicable to U.S. patients. We think they are. The first reason that we think they are is that the three clinical trials, the one from the United States, the two from Australia, all show very similar results; the reaction pattern to treatment is quite similar.

Secondly, the quality of medical practice and the clinical investigation done in Australia is generally recognized as being high. Clinical practice; the population and the products used in both countries are similar. I say that from the perspective of the company that is the leading marketer for baby-related products in Australia and the leading manufacturer of baby-care products in the United States. That is us. That is Johnson and Johnson.

The products that we use in both countries are frequently the same formulation and sometimes a very similar formulation. Finally, Australia is recognized as a Tier 1 country by the FDA.

[Slide.]

There are a number of issues that were raised in

the FDA's briefing document that we did not address in our briefing document and I am not going to address here. The reason that I have not addressed them in the briefing document is a very simple one; the deadline for submitting the briefing document was a week before we received this information from the FDA.

I don't have time to address them now, but I would ask you, please, in the interest of fairness, if you believe that any of these issues having to do with the adequacy of the trial, the conduct of the trials or the evaluation of efficacy is central to your decision as to whether this could be approved today with the information that is available, that you ask us about those reservations because we are certainly prepared to talk about them.

[Slide.]

We believe that Pediastat is a valuable treatment option for diaper dermatitis in infants. We believe that because it proved superior to the ointment base in the overall population and also in the subpopulation that had baseline cultures positive for Candida. When Candida was not present, it produced benefits that were comparable to the ointment base.

Pediastat offers barrier protection, activity against Candida albicans and it provides an alternative to steroid antifungal combinations with the greater degree of

risk that has been associated with those.

Two additional reasons that we think are worth consideration are is that there is no prescription medicine approved for diaper dermatitis and there is no topical antifungal that is approved for infants under the age of two years.

[Slide.]

So what I have presented for you today has been focused primarily on the clinical trials which we have done. From that information, we have provided information that Pediastat is effective, that it is safe and that it is a valuable treatment option.

In addition to that information, you have at your disposal the information that the kind of care that Pediastat provides is recommended in virtually every textbooks of pediatrics and dermatology. So, not only are we convinced that this is a reasonable form of treatment, but authors of textbooks have and were publishing that well before these clinical trials were made available.

Finally, Candida albicans continues to be susceptible to miconazole after extensive use for more than twenty-five years.

[Slide.]

I hope that the presentation that I have presented to you will convince you of the conclusions that we believe

are justified, that this is a safe, effective and valuable treatment option. If we have, we would ask your support in concluding that there is an adequate amount of information to label this drug today in a way that will be clinically meaningful to the practicing pediatrician, dermatologist or primary-care physician.

Thank you very much.

DR. DRAKE: Thank you for your presentation. You just went a little over. My compliments to you. You kept it concise. Because we are about ten minutes over, I think what we will do is move--and we will save our questions because we can get bogged down in questions. I would ask you to please stick around.

DR. ARMSTRONG: I intend to.

DR. DRAKE: I think we will move to the next segment so that we don't get too lost. I guess there is not much chance of you not sticking around, is there?

I think we will just move on. Do we need a break right this minute, or do you want to go to the first part of the next one. Let's go to the first part of the next one. Everybody is willing to do that.

We are going to the section of our invited speakers. We are very pleased you came. I would ask you to remember that your presentations, I hope, are twelve to fifteen minutes so that we have adequate time to ask you

some questions. I would invite Dr. Witebsky to take off.

Presentations - Invited Experts

Problems in Laboratory Diagnosis of Diaper Dermatitis

DR. WITEBSKY: Good morning. I was asked to say a few words about problems in laboratory diagnosis of diaper dermatitis. Actually, I think I should tell you from the outset that I have really had no experience in the diagnosis of diaper dermatitis, per se. I come from the diagnostic lab at the National Institutes of Health where, for all practical purposes, there are no infants at all.

I have had some experience, a fair amount, I think, in the diagnosis of cutaneous candidiasis and, in particular oropharyngeal candidiasis. What I really want to do is just give you some general principles that we use in the laboratory to show you that this is really a rather complicated business.

[Slide.]

I have some rather crude slides that I think, in a room this well-lit, won't project very well. But what I first wanted to show you was a Gram smear showing what I would presume is Candida. Unfortunately, you can't see it very well, but there are, in here, both budding yeast-like cells and what we would call pseudohyphae.

One thing you haven't heard is that the Gram stain, which is a quick and really quite simple stain, is

very useful in the diagnosis of the presence of Candida. It is not very useful for the diagnosis, usually, of other kinds of fungi, but Candida tend to stain blue; that is to say, Gram-positive, with this stain and it is something that we use regularly when we are specifically looking for Candida as opposed to other sorts of fungi.

But, even here, there are lots of problems. Just because you see budding yeast-like cells doesn't necessarily mean that you are dealing with Candida. If you see things that look like pseudohyphae, then it is probably Candida. But sometimes there are even problems, even in the hands of an experienced technologist or pathologist, in trying to be sure that what you are seeing really are pseudohyphae as opposed to true hyphae.

Candida doesn't often form true hyphae, but it can. But this is a reasonably good example of pseudohyphae and some budding yeast.

[Slide.]

You have also heard about the use of a KOH stain which, I guess, at least some laboratories still use. We much prefer a calcofluor or a fungifluor stain because it is much more sensitive. It is also much more expensive because it requires the use of a fluorescence microscope. But, basically, this material binds to certain carbohydrate linkages in fungal-cell walls.

It is not specific for any particular fungus but it is very useful in finding organisms quickly, particularly in direct patient specimens, much easier to read than a traditional KOH prep. Here, again, you see examples of some budding yeast and some pseudohyphae.

[Slide.]

This is difficult to see, but if you don't see many organisms, particularly in inexperienced hands--what I have got here is a slide of some staphylococci in a neutrophil. But I have even seen some confusion in the hands of even, I guess, moderately experienced individuals as to whether something is a bacterium such as these staph or a fungal structure such as a Candida.

I must say, that is particularly likely to happen in the case of physicians who only look at these kinds of things very rarely.

[Slide.]

Just because, I have said, you see these things, you can't be even sure that you are dealing with Candida. If you really want to be sure what you are dealing with, you have to grow the organism. This is an example of the way Candida look when it is grown on a culture plate.

I had another intent here, but I think you can--well, maybe some of you sitting close, at least, can see it. You have heard a lot about Candida albicans this

morning, but Candida albicans is one particular species of Candida. It is far and away the most common Candida involved in human infections, but there are others.

To be sure that it is Candida albicans, not only do you have to grow the organism but then you have to make sure that what you have got is specifically Candida albicans. An experienced tech, looking at this, would say that this is virtually certainly Candida albicans because many of the colonies have these little projections--feet, we call them. That is almost always only Candida albicans.

But, right now, I should tell you something else about problems in the identification of these organisms if you want to bother to do it. That is a big "if" because, I think, often, it really isn't necessary.

But there are several things such as even this colonial appearance that we have had, well, for decades, I think, really thought indicated that we are definitely dealing with Candida albicans. But there is now another species of Candida very closely related to Candida albicans which many mycologists feel should be considered a separate species, something called Candida dubliensis.

There are a number of so-called phenotypic tests that the lab can do that will make the discrimination with considerable reliability but, as far as I can tell, the only way to be sure is actually to resort to molecular methods,

to be sure that you are dealing with albicans versus dubliensis.

Obviously, no physician's office could be expected to do something like that.

[Slide.]

This is what Candida looks like when you only see budding yeast grown up in culture.

[Slide.]

Here is an example. Actually, this is not Candida albicans. This, I think, is Candida tropicalis, but you can see some incipient pseudohyphal formation here. But all these things are really quite consistent with Candida.

[Slide.]

What most diagnostic laboratories, I think, even now, are using is a test like this to determine that something is something is Candida albicans. Again, this won't tell you that this is not Candida dubliensis.

This is a positive germ-tube test. After you have grown the organism up, it generally takes in the neighborhood of forty-eight hours, although Candida can sometimes take a little longer to grow up in culture. Then this test take a couple of hours more and requires microscopic examination.

This germ-tube test, which you look for, is this round cell which is the organism and this tube coming

straight out from the cell without any indentation at its point of emergence. When you see something like that, that tells you that it is Candida albicans.

But, again, this requires a fair amount of experience and training in order to interpret this correctly. It is not something that someone can do who does it very rarely with any degree of reliability, I think. Now, there are other tests, some enzymatic tests and a variety of other biochemical assimilation-based tests that will tell you what specific species that you are dealing with.

There are a lot of other problems besides these related to determining in the laboratory whether Candida really is involved in a disease process or not. Some of these considerations apply with any organism that can be a colonizer as well as a pathogen.

Just because we don't see it, first of all, doesn't mean it isn't there. That is one of the big problems, really, in microbiology as a whole, what really is the sensitivity of whatever test that you are using. Those concerns relate to exactly how the specimen is collected, how it is transported, how it is cultured and how the culture, itself, is handled.

Really, we have, in clinical lab, no very good--actually, I guess we don't have any criteria for being

able to say when we get a specimen on a swab from the surface of a lesion, that this is definitely due to Candida or this is definitely not due to Candida or really almost anything else, for that matter.

If you see a lot of organism, or if there is a lot of organism growing up in the culture, I think that significantly increases the likelihood in the appropriate clinical setting that the organism that you have isolated is a pathogen. I am not sure it ever, unequivocally, proves it. So all these things really need to be taken into consideration.

There is also the issue of the significance, at least in my opinion and you should understand that, essentially, everything I am telling you is just my opinion, the significance of the presence versus the absence of pseudohyphae; we do report out the presence of pseudohyphae when we see it but I, frankly, don't know how much significance to attribute either to its presence or its absence.

We usually see pseudohyphae only if we see more yeast as a whole in the preparation. I think it is reasonable that an organism is more likely to be invasive if we see pseudohyphae but I certainly wouldn't want to say that the organism could be disregarded, or that Candida could be disregarded if you don't see pseudohyphae.

Again, I have seen, sometimes, when we do both a Gram smear and a wet mount, a calcofluor--we just call them wet mounts--that they don't necessarily always correlate from the same site. It relates to how much organism is present, which swab was handled when, how.

So all these things are really rather difficult issues, at least in my view. Probably the best way of doing this is to do a biopsy. But, obviously, nobody is going to do a biopsy for the diagnosis of diaper dermatitis, at least I presume not in 999 out of 1000 cases.

So the clinical lab, I think, can, in my view, just provide some supporting evidence that, in the appropriate clinical situation, it is quite likely that what you are dealing with is something that Candida is at least playing a role in. It is difficult, in my view, if not impossible, for the lab to say absolutely, with 100 percent certainty, that is or is not due to Candida.

I think that is really all that I have to say. I would be glad to answer any questions. Would you rather we wait, if there are any?

DR. DRAKE: I think while you are at the mike, I would ask the committee if there are any very specific questions for him right at the moment.

DR. DiGIOVANNA: Do you have any sense as to whether some of the other species of yeasts that commonly

you would see recovered from skin infections would have the same sort of sensitivities? In other words, if there were other yeasts that you might occasionally see that might actually be present and causing disease--

DR. DRAKE: John, I hate to interrupt you; can you use your mike a little more.

DR. DiGIOVANNA: If there are some other organisms, yeasts, that might potentially be causes of diseases that, let's say, are more difficult to culture, may come out in culture less frequently but may actually be causing some degree of disease, do they seem to have the same antibacterial sensitivities, or do you have a sense of that?

DR. WITEBSKY: There are really a couple of things here. I think virtually all Candida species--that is to say, all the species in the genus Candida, are equally easy to isolate. It is easy, generally, with these fairly simple tests to say that something is Candida albicans or is not Candida albicans. You have to do, generally, some more time-consuming tests to identify these other species.

To my knowledge, most of these would have essentially equivalent sensitivities except for the examples, the specific ones such as Candida krusei and fluconazole that you have already heard about.

We don't generally do susceptibility testing for

Candida unless there is some reason specifically to be concerned.

DR. DRAKE: Eduardo?

DR. TSCHEN: I understand, also, that in the diaper dermatitis, there are other pathogens present, other bacteria, anaerobes and micrococci and others. What is your experience in this, or is just Candida the only one that we see, period?

DR. WITEBSKY: As I said, I cannot pretend to be an expert in the specific issue of the etiologies of diaper dermatitis. I have never seen a case. There are problems, however, again, when you are dealing with any surface such as the skin which has a wide variety of organisms that are just sitting on it. So it can be very difficult to decide whether something is a pathogen or not.

There are some well-recognized pathogens such as Staphylococcus aureus that can be on the skin, or, occasionally, Group A betahemolytic strep. I think, most of the time, if you culture a Group A hemolytic strep from the skin in the appropriate setting, you would assume that it is a pathogen in any amount.

Staph aureus is a little bit more of a problem because it can just be sitting there and not doing anything. So, under those circumstances, the quantity becomes important. When you start talking about most other bacteria

under, so to speak, ordinary circumstances in a nonimmunocompromised patient, it can become very difficult.

A lot of anaerobes are part of the normal flora of the skin. You very rarely, without a really good clinical indication, would even do an anaerobic culture from a swab from the skin surface because you just don't know how to interpret what you get.

So, again, there are all these interpretive problems. Also, what you culture for--different laboratories will do things differently. If you ask specifically, in many settings, for a fungal culture, particularly from a contaminated surface--that is to say, contaminated with bacteria--for fungi, it is likely to get planted on media that won't allow bacteria to grow up because, if there a lot of bacteria and just a few Candida, say, they could overgrow the plates and make it harder to find the Candida if it is there.

So, generally speaking, at least in our setting, if you really want a reasonable sensitive examination done for both bacteria and fungi, you have to ask for cultures for both separately because they are done by somewhat different methods.

The advantage of something like a Gram stain is that it will allow you to see the range of bacteria that are there as well as Candida. It is not good at all if you are

concerned about other dermatophytes because then either a KOH or a calcofluor stain would, I think, have considerably more sensitivity.

DR. DRAKE: Dr. King?

DR. KING: It is clinically said that diabetes and topical steroids, particularly potent ones, encourage the growth of Candida. Is there any direct or indirect data to correlate that with the kind of information you have?

DR. WITEBSKY: I just don't have any information on that.

DR. KING: That has been my experience. It is so, but no proof.

DR. DRAKE: Dr. Stern?

DR. STERN: So, how often at the NIH do you see resistance to miconazole among your patients who you have Candida cultures on?

DR. WITEBSKY: We never test it.

DR. STERN: You never do?

DR. WITEBSKY: No. That issue never comes up, the specific one of miconazole. Furthermore, at least to my knowledge, the NCCLS has, at the moment, no published criteria for break points for miconazole sensitivity or resistance specifically.

DR. STERN: Let me put it another way. Is azole resistance a big clinical problem at the NIH with its very

specialized kinds of patients?

DR. WITEBSKY: No, not really, except, again, as you have heard. There are a few specific species that you presume are resistant to certain agents, and there is some problem with--we have a large population of HIV-positive patients. In some of those, there is a significant problem with the specific issue of mucocutaneous oropharyngeal candidiasis.

DR. STERN: But not cutaneous.

DR. WITEBSKY: No. Not that I have seen. Again, that is my opinion. We don't see that much. We see a lot of disseminated candidiasis in the immunocompromised patients, but that is really a quite different issue.

DR. DRAKE: Thank you, sir. I appreciate it.

Dr. Spraker.

Overview of Diaper Dermatitis and its Etiologies and Treatment

DR. SPRAKER: Jonathan asked me to give you a little perspective on the problem of diaper dermatitis.

First, I will begin by saying that, for the last eleven, almost twelve, years, I have been happily distracted by my children and have done a lot of diapering.

DR. DRAKE: We might mention, she has triplets. So she has had a little diapering experience.

[Slide.]

DR. SPRAKER: First, my son.

[Slide.]

And then the triplets, one of whom is Dr. Drake's goddaughter by the way.

DR. DRAKE: The most beautiful child in the world. The one in the middle.

DR. SPRAKER: That is Louise, over there on the right.

DR. DRAKE: Excuse me; on the right. Louise is on the right. That was a different picture. I didn't look carefully. I am not proud of her or anything.

DR. SPRAKER: I estimated that our family has spent $5,000 on diapers just for the triplets. Diapers are big business.

[Slide.]

I might also say that, in addition to the experience with my family, I have been fortunate enough to be a consultant for Kimberly Clark, the makers of diapers, because their research headquarters are in Atlanta. So it has given me opportunity to learn a lot about the subject and participate in a lot of meetings, et cetera, and continue to learn more.

So here they are. At any given time, 12 to 15 percent of infants in the United States have a significant enough rash that the parents need to do

something; i.e., more frequent changes. About 6 percent of them have enough of a problem that the physician or parent treat it with either an antifungal or an barrier cream. This is in-house Kimberly Clark data.

[Slide.]

As Jim Leyden has pointed out, it is not just infants who have a diaper dermatitis problem. The elderly is a big market.

[Slide.]

Interestingly, diaper dermatitis does not occur in less developed societies. Why is that?

[Slide.]

In some societies, diapers aren't worn at all. This is a slide from my colleague, Bernice Krafchik, in Toronto who kindly lent me some of these. Here is a child in Peru.

[Slide.]

Here is a child in South Africa.

[Slide.]

There are these wonderful stories.A nanny from China was telling me that, in China, the infant is trained to urinate on command, that from early infancy, the legs are held in a certain position right after feeding and a sound is made, "Shhh, shhh, shhh, shhh." That is a signal that now it is time to urinate.

If the baby happens to do that, by coincidence, then there is a lot of positive reinforcement, "Yea," clapping. That reinforcement continues and, eventually, the child is trained. So, in China, diapers and diaper equivalents just are not necessary.

[Slide.]

In other societies, there have been more primitive diapers. The absorbent--they usually have two layers. If you think about it, the diaper has an absorbent layer that can be moss, grass, linen, silk, cotton, cellulose now. The diaper cover; animal skins, wool, linen, cotton.

[Slide.]

For example, in many societies, infants were wrapped in swaddling clothes. Just what does that mean? It is a long, narrow band that is wrapped around and around in different styles according to country. But, notice; this is one of the sculptures, the famous sculptures, by della Robbia. I like this one because it shows that there isn't much underneath those swaddling bands.

It is almost like the hip casts that are used for children with congenitally dislocated hips, that there is a cast and a hole in it. Buttock clothes were tucked underneath. So even the infant wrapped in the swaddling bands, the bottom breathed.

[Slide.]

Could go on and on about the history of the diaper because I have become intrigued by the whole subject. But it was once a triangular piece of cloth and then with a diaper cover of knitted wool. Diaper pins changed the style of diapering and reduced injuries from hat pins that were used before that.

In the 1920s, there was literature about cotton is better cloth than linen because it absorbs better. In the 30s, commercial laundering services became available. In the 40s, and before the 1940s, diaper dermatitis in the United States was relatively uncommon, it seems.

In the 1940s, rubber pants were introduced. In the 1950s, plastic pants were introduced. In 1957 was the first reported case of Candida diaper dermatitis. At one point, I was trying to make the point that it is the rubber and plastic pants with the occlusion that was really causing all this Candida problem, but then Jim Leyden pointed out that that is about the same time that amoxicillin was being more widely used and it is true that amoxicillin fertilizes Candida. It increases the Candida concentration in stools by two-fold.

[Slide.]

The incidence of diaper dermatitis is decreasing over time. This is a slide from Proctor and Gamble showing, in the left, 1982 to 1983 and with 1995 in the right column.

Down in the bottom, severe diaper dermatitis, 5 percent going down to 2 percent. Next from the bottom, moderate, 22 percent going down to 7 percent.

So we are seeing less moderate and severe diaper dermatitis. Accordingly, we are seeing a little more slight dermatitis, so it is going up from 36 to 58 percent.

So that is good. Most clinicians, both pediatrics, dermatologists, everybody, will say they are not seeing the bad diaper dermatitis that we used to see except for Candida.

[Slide.]

Probably the change in the last decade has been the introduction of what has called the superabsorbent diapers that have those cellulose--they have the gel cores that absorb up to 50 times its weight in urine, lock the urine away from the skin and don't allow it to leak back, although they still associated with some humidity in there.

[Slide.]

Here is showing a graphic example of just how much these superabsorbent diapers hold. On the right is a dry diaper. On the left is one that is filled with water. You have seen kids at the swimming pool that sink to bottom when they jump in.

[Slide.]

Let's think about the problem of diaper

dermatitis. I like this definition by Janet Weston, who is Bill Weston's wife, who is a pediatrics professor at Colorado. What is it? Well, it is a problem in the diaper area that is caused by wearing a diaper. We learned earlier that, if you don't wear a diaper, you don't get diaper dermatitis, and also that it is unrelated to any underlying skin pathology.

[Slide.]

What are the known causes of diaper dermatitis? Moisture. The average newborn urinates twenty times a day. It is totally impractical to expect a mother to change the diaper that frequently. The average infant's diaper is changed six to eight times per day so it is going to be moist.

Hydrated skin is more easily abraded. You all know that if you are trying to flip pages, if you moisten your finger, you increase the friction and it is easier to turn the pages. Hydrated skin is also more easily penetrated by microorganisms.

Additionally, hydration swells the horny layer enough to occlude eccrine ducts and cause miliaria. It kind of intrigues me; what does miliaria have to do with diaper dermatitis, does it play a role.

Secondly, heat; the heat causes sweating and enhances the growth of microorganisms. Third, irritants;

detergents, aggressive cleansing of the area. There has been a pediatrician in my area calls that "polishing the apple."

Other irritants. It is not ammonia and it is not urine. You can put patches of urine on infant skin and it does not induce irritation. So, therefore, a diaper doesn't have to be changed every time it is wet. However, soiled, fecally soiled diapers, are extremely irritant.

In the early 80's, the folks from Proctor and Gamble did the studies that we all wish we had been clever enough to do. They put little patches of stool on infant skin with a little diaper patch on top, occluded it and proved, very beautifully, that stool causes diaper dermatitis.

If you boil stool, it doesn't cause diaper dermatitis. If you take boiled stool and add fecal enzymes to it, you get diaper dermatitis again. If you add urine or increase the pH to that stool sample that has fecal enzymes in it, the irritation factor is even greater. Bile salts probably has something to do with it and increased pH.

Then microorganisms. The microorganisms that are usually talked about are Candida and Staph, but there is a recent paper talking about anaerobes in the diaper area. In 19 percent of patients; Bacteroides, for example. It is unclear what the significance of that is.

[Slide.]

Let's look at a few clinical slides. Here is an example of what I would clearly call Candida diaper dermatitis; beefy red, lots of satellite pustules. But notice that the inguinal folds are spared in this example. So it shoots a hole in that way of defining Candida diaper dermatitis.

[Slide.]

It is often said that if the dermatitis is beefy red and the scrotum and the periurethral area are involved, that is a good indication that the patient has Candida diaper dermatitis. This child also has satellite pustules.

[Slide.]

This must be irritant diaper dermatitis. It is symmetrical, very erythematous, no satellite pustules and not as much erythema on the peri-anal area. This is a child who had diarrhea and sat in a diarrheally soiled diaper for a while. It doesn't take very long, by the way. Stool, especially diarrheal stool, is extremely irritating.

[Slide.]

Here is what is probably irritant diaper dermatitis with some ID reaction up there on the abdomen. Who is to say that there isn't some Candida in there also that might be playing a role.

[Slide.]

This one I find somewhat confusing. It is smooth, similar to a chafing dermatitis on the buttocks and the inguinal areas yet the scrotum is beefy red.

[Slide.]

Up there, on the topical, there are satellite pustules, so it probably is Candida.

[Slide.]

But, what about this one? This is the typical diaper dermatitis. It is not really pustular. Is this miliaria? There is erythema in the perianal area so maybe that means it is Candida. But chances are this would do fine just with a barrier cream. But then, it might not.

So, to me, this is the patient that the pediatrician is often seeing and has to decide, is this Candida is it not.

Let's lets turn to the first overhead, please.

[Overhead.]

Now let's talk about Candida and its role in diaper dermatitis. One study, this is the study by Rebora that other people have quoted, also; 30 percent of diaper dermatitis was culture-positive to Candida. Now, you can percentages all over the map. These are somewhat representative and I present these just for argument. That was compared to 3 percent of normal controls.

14 percent, in Krakowski's study of diaper

dermatitis was Candida according to clinical criteria. So there is this difference between 30 percent and 14 percent. Therefore, because of that difference, there must have been some irritant, clinically irritant dermatitis. Therefore, not all irritant diaper dermatitis is culture-negative.

Only 63, according to Dixon, or 80 percent--this was Leyden and Kligman's study of clinically Candida diaper dermatitis is culture-positive. So even dermatologists sometimes clinically did not suspect Candida when the cultures later were positive.

Is that significant? Does the baby really need to be treated with an antifungal agent? That is another question.

Leyden and Kligman's study, 0 out of 20 of their patients which classic chafing or irritant dermatitis were Candida culture-positive, but lots of other studies, the clinical diagnosis of the irritant is made that there is culture Candida in some percentage.

30 percent of clinically Candida diaper dermatitis is KOH-positive. That is only 30 percent. This is Al Lane's study but we have recently heard something comparable.

So, odds are, even if you think it is Candida diaper dermatitis, their KOH is not very helpful. It is useless unless it is positive. Then 40 percent of severe

diaper dermatitis in this study was culture-positive compared to only 26 percent of mild diaper dermatitis implying that severe diaper dermatitis is more likely to be associated with Candida than mild. I think most of us would think that that is a sensible conclusion.

So Candida diaper dermatitis can be difficult to diagnose which is the reason--let's go to the second overhead.

[Overhead.]

The reason for the practical treatment algorithm that has been popularized by Bill and Janet Weston and Al Lane in their article, that if the diaper dermatitis persists more than 72 hours, Candida is likely playing a role.

We will just digress a minute with pathogenesis of Candida diaper dermatitis. The GI tract is probably the reservoir. In Candida diaper dermatitis, the stool culture for Candida is usually positive, so skin cultures and stool cultures usually correlate quite nicely. Ampicillin increases the fecal concentration of Candida, both Candida in the feces and on the skin. But infants without diaper dermatitis can have Candida on their skin and can have Candida in their stools.

A suboptimal epidermal barrier function increases the risk of Candida. If skin is tape-stripped, it is easier

to inoculate Candida and cause an infection. But in Rebora and Kligman's study, when they tried to inoculate the Candida on psoriatic skin and on atopic dermatitis skin, it was harder for the Candida to grow unless they cleaned the skin with alcohol.

So it seems as if, if the skin is secondarily infected with bacteria, if it is dermititic, then the Candida does not prosper.

[Slide.]

High relative humidity in the diaper area enhances the growth of Candida. In this slide, up there on the topical on the left, the relative humidity is 100 percent. When Candida is inoculated on skin, the percent survival was 100 percent. If you can get the relative humidity down to 60 percent, there on the bottom, the survival of Candida drops down to 17 percent.

So in the diaper industry, there has been great movement to try to produce diapers that breathe better to get the humidity down. There has also been movement to try to better protect the skin so it is less easily macerated and possibly penetrated by organisms.

So here are measurements of diaper.

[Slide.]

The diaper patches where Candida is being applied, with saran wrap, with new diapers versus old diapers.

[Slide.]

An example of the eruption that occurs when Candida is inoculated.

[Slide.]

Indeed, in some of these drier diapers, there seems to be less diaper dermatitis. Over on the left, is saran wrap occludes a Candida inoculum, that there is a lot of dermatitis. Way over on right, if open gauze is placed over an inoculum of Candida, the Candida does not grow. In between those two columns, the bars, is when various diapers are used.

[Slide.]

The treatment for diaper dermatitis is barrier paste, antifungals if you suspect Candida. It usually worked quite successfully our treatment. We do have a problem, the Candida problem, and our other problem is babies who have chronic diarrhea. Usually, it is an irritant problem and, even with our best treatment, the kids with Hirschsprung's disease, for example, who probably have abnormal stools, we have a long ways to go to be able to successfully treat those patients.

[Slide.]

So I conclude that diaper dermatitis incidence is going down where Candida remains a problem. Candida has something to do with humidity. Candida has something to do

with wearing diapers. We need better treatments and it would be nice to have better treatments out there that don't contain potent topical steroids.

Thank you.

DR. DRAKE: Dr. Spraker, thank you. I want to draw your attention, again, to Louise in the middle. Most beautiful child. And smartest, too.

Dr. Spraker, thank you. Do we have questions for Dr. Spraker? Dr. McGuire and Dr. Chesney.

DR. McGUIRE: Mary, you got very close to the question I have wanted answered for years. I don't know if the information is out there, but what is the incidence of Candida in normal infants without diaper dermatitis, of fecal Candida?

DR. SPRAKER: I can't quote you a figure, but I know it is in those articles. I can get that information for you. It has been in a number of studies that there is a certain, a given, percentage of infants who have fecal Candida who don't have diaper dermatitis. That has been looked at.

DR. McGUIRE: Is it your recollection, and if you don't remember, fine; we will look it--that the incidence of fecal Candida is higher in the infants who have diaper dermatitis?

DR. SPRAKER: Yes; that's true.

DR. CHESNEY: This is all very intriguing. I am beginning to wonder if Candida diaper dermatitis even exists. I have several questions for you. In the adults who had Candida cultures put on the skin, and we have heard that Candida products can induce this kind of reaction, are there any good histologic studies that show that Candida is, in fact, invading the skin in either diaper dermatitis, which I am sure has never been done, but in your human models?

DR. SPRAKER: I believe that the Rebora study, that biopsies were done on that skin and it reproduced beautifully, the histologic picture of Candida diaper dermatitis. So I think the answer to question is yes.

DR. CHESNEY: Where was that again?

DR. SPRAKER: I think that is the Rebora and Kligman study reference.

DR. CHESNEY: What did it show?

DR. SPRAKER: It showed that the experimental model inoculating the Candida, that clinically showed beautiful pustules and an erythema like we would see in the clinical situation with Candida dermatitis. It could be reproduced experimentally, and histologically, the findings were identical, also.

DR. CHESNEY: Were there actual organisms in the skin? Again, if the products can do the same thing as the

organisms, do you actually have to have invasion by the Candida, itself?

DR. SPRAKER: It is complicated because, apparently, if you put the inoculum on the skin, it won't grow and survive and the cultures will be negative if the skin is not occluded. So you have to occlude it.

Now, if you put the organism on, occlude it for 24 hours and then take the saran wrap off, I believe it was after an hour, as I recall is what Jim Leyden has said--after an hour, the organism is dead and you can no longer culture the skin. But the erythema is still there.

So presumably, then, you could have Candida diaper dermatitis that gets dried out and is no longer Candida-positive but the patient still has an intense erythema from the Candida inoculation that was present yesterday.

DR. CHESNEY: I think I understand that, and that is fascinating. But if there are no Candida subcutaneously, then why would we need to use an antifungal?

DR. SPRAKER: The Candida is never subcutaneous. The Candida doesn't invade unless your immune system is abnormal. The Candida is located up there in the stratum corneum. Part of what we are getting at here is that a normal human being with normal functioning skin, if you get a fungus on your skin, your skin gets scaly. By scaling off

your stratum corneum, you shed a lot of the fungal organisms.

DR. CHESNEY: So there may not be any fungi under the stratum corneum, or do we know if there are Candida under the stratum corneum?

DR. SPRAKER: The Candida are in the epidermis, usually the stratum corneum; right?

DR. DRAKE: First John and then Bill.

DR. DiGIOVANNA: Mary, I don't know if you know the answer to this, but as our resident expert in diapers and Kimberly Clark, do you have any sense as to what the types and the usage of diapers in the U.S. and Australia might be and how the products may have changed since some of these studies were done, I believe, in the late 1980s, more than ten years ago, over time, and your sense of how that might relate to the issues related to the particular product under discussion.

DR. SPRAKER: I don't know about diapering practices and what diapers are being used in Australia. That is a very complicated question, actually, because these diapers, the companies are continually improving their product so, every year, there have been incremental improvements.

The machines that make these diapers are really expensive. It is a big machine the size of a huge building

that takes a role of paper and spits out umpty-ump diapers per second at the other end of the building.

So the new machines are usually introduced in the United States and then other countries get the newer machines later so that it is hard to know in any one given year just which quality of diaper a particular grocery store is selling.

But, in general, certainly in the United States, the diapers that are being used now and were being used a couple of years ago are much better than they were ten years ago as far as better absorption. They are thinner and more comfortable. They breathe more so that they are not as hot, for example.

DR. ROSENBERG: I would like to speak a little about questions that Dr. Chesney raised and others in the sponsor's presentation about colonization, invasion, infection, irritation and reactivity. I have never worked with diaper dermatitis specifically, but in our psoriasis work, I have certainly become acquainted with what the British call "napkin psoriasis," which is the spread of psoriasis over the skin, the abdomen and then the rest, in infants who have a family history of psoriasis who go on, when adults, to develop psoriasis and who have Candida albicans in their diaper area at the time.

I think the relevant scientific papers are the

ones from Kirkpatrick's group at National Jewish Hospital and then Sohnle, later, who is now at Medical College of Wisconsin in Milwaukee. These are starting with patients who have no t-cell reactivity whatsoever against Candida, who have chronic scaling skin disease, sometimes with some erythema but never have invasion. They demonstrated that it is activation of the alternative complement pathway which is responsible for the inflammation and scaling which is protective.

Our work in psoriasis has paralleled that. Sohnle has written papers in which has had made mice leukopenic down to, I think, 700 white cells altogether, put Candida albicans on them under occlusion and the leukopenic ones scale a little bit more than the t-cell-healthy ones. Nobody gets invaded, but there is a lot of reactivity.

So I think these are meaningless. We have enough scientific basis for saying that the presence of Candida in numbers on skin will produce inflammation and a reaction and diaper dermatitis. I think we know enough about how maceration and so forth not only, perhaps, makes them grow, maybe not, but increases the penetration, as was brought out.

So I really think that there is quite enough scientific justification for saying if Candida are present, we know that Candida are present in the stool and the lower

bowel, and, in susceptible individuals, Candida can play a role in diaper dermatitis.

There are two other things. I was pleased to hear Mary mention zinc paste. I had always thought that paste was better than ointment, but you fellows don't use the paste. You use the ointment.

Then just a word about nystatin. I spent too long with Harvey Blank not to think about nystatin. I think oral nystatin is useful if you are going to writing a prescription. I just question the sponsor's statement about there is no approved antifungal for infants. I have asked someone from the agency to look up nystatin USP. I know of no suggestion that nystatin USP is not--I know, by mouth, it is approved for--mentioned specifically, it is good for neonates and debilitated old people.

I can't believe that there is any bar to the use of nystatin topically.

Thank you.

DR. DRAKE: Thank you Dr. Rosenberg.

You know what I am going to do right now? I see people needing a quick break. I think what I want to do--we are moving pretty well. If we keep tracking, we, theoretically, could be done--if we delay lunch, we could potentially even be done.

I am not trying to push it that hard, but I want

us to keep this pace. It is a nice pace.

I am going to break. I have got twenty-five 'til. I would like to give just everybody a ten minute break. Then let's reconvene and have the third presentation.

[Break.]

Candida Resistance and Detection

DR. WHITE: I was asked today to speak about antifungal drug resistance, azole resistance, and I would also like to make a few comments about Candida detection.

Before I get to the slides, I do want to make a point that I think hasn't been made yet this morning and that is that all azole drugs are static drugs. They don't kill the cell. So the development of resistance is a potential, with azole drugs because they are not cidal drugs, they are static. So any strain in the presence of azole drugs is still alive. It will still potentially grow if you remove the azole drug.

[Slide.]

As Dr. Rinaldi already pointed out, there is essentially an acquired resistance associated with azole drugs. I would like to summarize what we know about azole resistance. Unfortunately, we know very little about resistance on the skin or in dermatitis, but I will try and summarize what we do understand about azole resistance.

First of all, there is innate resistance. In the

last ten years, with azoles being used in a variety of situations, we have seen the dramatic change in the Candida species that are most common. What we are seeing is a replacement of Candida albicans with at least two different species that are intrinsically more resistant than Candida albicans.

Those two species are Candida krusei, which Dr. Rinaldi already mentioned and which are present about 5 percent of the time, or less, and Candida glabrata, which is slightly more resistant than Candida albicans but it also has the ability to become more resistant over time in a quicker--it becomes resistant more quickly than Candida albicans.

In addition, even in Candida albicans, of course, you have resistant strains just because of a random distribution of the MIC in a particular strain or species.

[Slide.]

In terms of acquired azole resistance, we see quite a lot of it, especially in AIDS patients in which a patient's strain, his resident commensal strain, develops resistance over time after it is exposed to azole drugs.

In addition, we have documented instances where a resistant strain can be transferred from one patient to another. Usually, those conditions are when one of the patients has disease--and we have seen both oral

transmission and genital transmission--so that a resistant strain is transferred and becomes the colonizing strain or the resident strain on the recipient.

[Slide.]

Now, I am a molecular biologist, and we understand a lot about the molecular mechanisms of azole resistance and they can be briefly summarized to say that when resistance develops, what we see is a change in the target enzyme, either mutation or overexpression of the target enzyme.

We also see an overexpression of efflux pumps. These are pumps in the plasma membrane that pump azoles drugs out of the cell. These efflux pumps are related to the MDR genes in mammalian cells that pump out chemotherapeutic agents.

The point I want to make about from this slide is that when all of these things occur, what we see is a generalized cross-resistance to all azoles. So fluconazole-resistant strains are going to be cross-resistant to itra, flu, vorconazole, ketaconazole, miconazole, clotrimazole, all of the azoles we see cross-resistance to.

[Slide.]

So where have we seen the most resistance? Clearly, that is in the AIDS patients where AIDS patients were given low doses of fluconazole, 100 milligrams per

week, long-term prophylaxis for months or years. Usually, what we see is azole resistance developing after an AIDS patient has been administered a dose of about 10 grams.

After that point, roughly, an AIDS patient would start to develop a resistance.

[Slide.]

What we now see is that in various patient populations, 10 to 30 percent of AIDS patients have an oral isolate that has a high MIC and is resistant to azole drugs. Usually, that resistance has developed as the result of fluconazole therapy but it is cross-resistant to all the other azoles.

In addition, oral candidiasis in AIDS patients is the most common opportunistic infection with AIDS and it is very common in children. I will return to that in a minute, talking about clotrimazole resistance as was recently reported.

But AIDS patients are not the only place where we have seen azole resistance. We are also seeing azole resistance in the bone-marrow transplant patients where azoles are now used to prevent systemic candidiasis. These bone-marrow transplant patients are given 400 to 800 milligrams per day starting on the day they enter the hospital for their bone-marrow transplant.

In a recent study by Kieran Marr and myself, 10 to

15 percent of patients that start undergoing azole therapy for bone-marrow transplant--10 to 15 percent of them will develop an oral isolate that is resistant to azole drugs. That resistance can develop within two weeks and in as short as one week.

[Slide.]

In terms of azole use with vaginitis, obviously, over-the-counter azole drugs are available. There is not good indication that resistance has ever developed in vaginitis patients. I did give the FDA a paper where I came across the abstract and it is in the red books that were distributed. But I hadn't actually looked at the paper. It came across my desk as an abstract.

When I inspected the paper, it reported 50 percent resistance in vaginal isolates. However, there are problems with the data and the way that the MICs were determined so, to date, as far as I know, there is no good documentation for azole resistance in vaginitis.

Several of the molecular mechanisms imply that because there are differences in the pH of the vaginal mucosa, those pH differences affect these pumps in the target enzyme and so the pH differences may be the reason that we don't see azole resistance in vaginitis patients.

[Slide.]

Another worrisome situation is that, right now,

azoles are used extensively in surgical wards to prevent ylocal and systemic infections associated with surgery. At the moment, there are no studies to ask if resistance is developing this patient population.

[Slide.]

Also, in terms of azole use with dermatophytes, obviously, the azoles are available for athlete's foot, jock itch, et cetera. Obviously, these azoles are used at relatively high concentrations compared to what we are talking about at the moment. And there have been no reports of resistance. I looked through the literature and could not find any reports of anyone actually looking to see if resistance had developed in this patient population.

[Slide.]

Finally, azoles are used in agriculture and, as far as I am aware, there are no studies on the azole resistance that could be associated with azole use in agriculture by the people handling those agricultural products.

[Slide.]

The last patient population I want to talk about is thrush or oral candidiasis in children. I know of no instance where resistance has ever been reporting otherwise normal, healthy children. However, in children with AIDS, the major opportunistic infection that these children have

to deal with recurrently is oral candidiasis. Resistance in these children is a major issue.

[Slide.]

The next slide is a report by Tom Walsh that just appeared last month in which he studies children with AIDS that were using clotrimazole troches to control for oral thrush. 28 percent had a high MIC against clotrimazole. That was cross-resistance to all the other azoles and these children required use of amphotericin B to treat their oral candidiasis.

[Slide.]

So, unfortunately, there are no studies about azole resistance in skin or in dermatitis. But if I were going to create a list of what things did not worry me and what things did, I would say that treating otherwise healthy children, either single-dose or multiple-dose, the chance of developing resistance in those children is probably minimal if there is any chance at all.

Situations that would worry me a little bit are situations where a resistant strain could start developing in one child and be transferred to another such a day care, intensive-care units or surgical wards where you could have the compounding of azole resistance associated with dermatitis and with other problems.

The place where it would worry me the most is in