worth. So, Joe, I am glad you repeated it. The concept has not changed over a ten-year period, basically.

Bill?

DR. ROSENBERG: I am going to try to focus on this question, if I can. Is a product of this type for diaper dermatitis and so forth appropriate? I think the answer to the agency, in my opinion, would be clearly no. This is a product which is built around an anti-candidal, antifungal drug.

I think there is every likelihood, although it is certainly not at a level that the agency would approve it at this point, but I think there is every likelihood that it can be shown to be a useful drug in candidal-associated diaper dermatitis. But they haven't shown it yet. I think for the FDA to approve a drug that is helpful in candidal-associated diaper dermatitis but without evidence for anything else, as good for diaper dermatitis would have been tantamount to approving the same company's Regranex for skin ulcers rather than, as they did, for the very precise subset of diabetic pressure-associated ulcers that have been debrided and for which support is given, and so forth.

So I would say no for this question.

DR. DRAKE: Joel?

DR. MINDEL: I agree with what has been said before about this question. But since you want me to say

something--

DR. DRAKE: I do. You have been very quiet.

DR. MINDEL: I will say something that I wanted to ask before but didn't get a chance. I wanted to know what is the evidence that--the drug is in a thousand times more concentration than the ointment. But what is the evidence that it gets out of the ointment and into the skin interface. Is there any evidence, because all the other preparations I have seen of this are solutions and lotions and powders but not petrolatum ointment which could trap that drug and keep it sequestered.

That raises the question about whether resistance would be more likely to develop and such.

DR. DRAKE: Dr. Armstrong; do you guys have any information on that?

DR. ARMSTRONG: We haven't done assays within the skin of patients who have been treated with this. I think the clinical outcome gives an indication that when Candida is present, you see a different clinical experience. We also have the conversion data for cultures that were positive at baseline and negative at the end of treatment, and the differences between those treated with Pediastat and with the vehicle base. So indirect evidence, yes. Direct evidence, no.

DR. DRAKE: Anybody else have anything to add to

that? Ted?

DR. ROSEN: Just a very quick comment. In Dr. Ko's presentation about three or four slides down, he quoted the minutes of the advisory committee meeting about ten years ago, and the last sentence he quoted was, "The committee unanimously agreed diaper dermatitis is not a defined diagnosis and, therefore, is not an appropriate indication."

I think that that quote from ten years ago relates to this question. I think the committee, the voting members of the committee, need to decide whether there is an indication called diaper dermatitis.

DR. DRAKE: I agree with that

DR. ROSEN: Psoriasis is not a subset. Atopic dermatitis is not a subset. Contact dermatitis is not a subset. It is the patients Steve was talking about who don't fit those or, as Rob was saying, it is a negative thing. But, is there an indication?

I think that the agency is very strong in showing that slide and reiterating that opinion that there is no appropriate indication for diaper dermatitis. I would argue otherwise. I think there is an indication for it, but you have to think about maybe this data didn't support this drug at this point, but that there is a clinical entity.

My last comment would be if I told you all I was

treating a patient with perioral dermatitis, you would all know what I was talking about even though some people think it is due to demidex and some people think it is due to tooth paste, some people think it is rosacea and some people think it is acne. But you would all know what I was talking about.

If we say diaper dermatitis, excluding psoriasis, seborrhea, et cetera, you all know what we are talking about. So I think there is an indication and that this position should be changed, albeit there needs to be some data to support it.

DR. DRAKE: Dr. King?

DR. KING: I guess this is my first time here. I have problems with definitions. It is kind of like the quote, "How do you recognize your mom in a crowd?" "She just looks like this."

If diaper dermatitis is a syndrome produced by diapers and readily recognized by one and all, the clinical pattern is such that if you take the diapers away, it is supposed to be get better just by air. You have seen that kind of data that Dr. Spraker showed that some cultures don't have diaper dermatitis at all.

So, again, you know what you have got in hindsight because if it does not respond in a short period of time, you have to suspect the coexistence of infection or some

early subset of primary scaly dermatitis.

We all recognize impetiginization or strep or whatever of primary scale diseases or blistering diseases so we don't have any trouble with that. So I come down to the question if it is my mom and I recognize her, it is only in hindsight that I have done this prospective treatment. I am not going to do a biopsy. I am not going to do all this stuff. I am just going to treat it.

In hindsight, I may change my diagnosis in response to therapy, and it leads me to a fundamental question to Dr. Wilkin and the FDA, does miconazole or any other antimicrobial agent have a role in preventing clinically relevant candidiasis or something that develops in the context of irritant dermatitis or atopic dermatitis or something else.

I mean, we are routinely giving antimicrobials to prevent the evolution of disease in bone-marrow transplant, et cetera, et cetera, et cetera.

I didn't hear a word about prevention of candidiasis or anything else in the context of a susceptible person. Even though they may be kids, or whatever, I submit that there is potentially a role for treating those folks if they don't respond after appropriate letting the air get to it or whatever.

And it would still be my momma.

DR. DRAKE: John?

DR. DiGIOVANNA: I would just like to second and third that motion. I think that there is a clinically relevant condition of diaper dermatitis that excludes other well-known entities and I think that it is practical, at this point in time, to have that as an indication.

DR. ROSENBERG: Can I ask a question?

DR. DRAKE: Yes, sir.

DR. ROSENBERG: If there were to be such an entity as diaper dermatitis, excluding psoriasis, atopic dermatitis, et cetera, so it had a broad indication, and if the clinical data brought back by these sponsors were that these material was useful that had an associated Candida but not in cases that did not have an associated Candida, never mind that the doctor doesn't always know by looking whether it is Candida and doesn't always want to culture.

But if that, in fact, were the data as suggested it might be, then do you think, does anybody think, that they should be allowed to say that this is a product for dermatitis rather than this should be a product for diaper dermatitis associated with Candida albicans?

DR. DRAKE: That is a very good question because it also might help the sponsor if they are going to do further work. Comments on that?

DR. STERN: I would say it depends on what the

alternative treatments are for those without Candida that one could have knowingly instituted at the time of original prescription, whether those treatments would be harmful to the subset with Candida and whether, by doing this for the people who don't have Candida, you are doing as well as you would have been doing anyway.

So the question is really what is the harm in doing it and what is the harm of the alternative actions you could have taken in the absence of other than your clinical impression where Candida maybe yes, maybe no.

So it is really for the subset. I think, as Steve says, we are dealing in an area, in clinical reality, of ambiguity about diaper diagnosis. We eliminate certain things and then we are left with the subset of patients we call diaper dermatitis--that is, a large class and a very common group of patients.

You have to think about, well, if I give this, am I going to do more harm than good. Clearly, that is conditioned on your own prior probabilities among the diagnoses. If you know it is psoriasis, you treat it one way. In your case, you might, in fact, advocate this agent if you knew it was psoriasis. And others of us might not.

If you know it is Candida, you certainly treat it in a certain way. But there are all these in between cases. To me, it would be how much worse did the people get

compared to the usual treatment of noninfected, not-related-to-anything-else, plain-old, "if you only were in a social situation where you could take off their diapers for a week, they would get better," dermatitis, did you make them any worse than what the parent would have done, which is Desitin, to use a brand name.

DR. DRAKE: I would like to do this. I have a suggestion and the committee can comment if I am wrong. I think we could vote on this question. I think that the answer to this is potentially no because I have kind of heard around the board that you don't like all this stuff in there.

So could we vote on the question as it is worded and then, perhaps, come up with a second question that might be of assistance to the agency.

I would like to vote on the question as it is worded. All in favor of this question, please raise--is that okay, first of all? Let me ask, is that okay with everybody? All in favor of this question, as worded, please raise your hands.

[No response.]

DR. DRAKE: All opposed to this question as worded, raise your hand.

[Show of hands.]

DR. DRAKE: I think you have got twelve. Wait.

Hold up your hands again, please.

[Show of hands.]

DR. DRAKE: It is everybody. It is twelve. Thank you very much.

Now, then, Rob, I told you to write that down.

DR. STERN: I tried. "For a product of this type, is diaper dermatitis, excluding subsets of patients with the likely primary alternative etiology of irritant contact dermatitis, infection by bacteria or viruses, atopic dermatitis, seborrheic dermatitis or psoriasis, an appropriate indication?"

I didn't list every disease I think makes things worse in the diaper dermatitis area but only the common ones.

DR. DRAKE: I see Mary shaking her head.

DR. SPRAKER: Rob, you didn't mean to exclude irritant, did you, chafing dermatitis?

DR. STERN: Well, not chafing. That is one I have the most problem with.

DR. SPRAKER: It is hard to know what to call that. People call it chafing, but often people call it irritant-contact. That is what Amy was calling it in her lecture, for example.

DR. STERN: That is the one I have a hard time about where to include that because so much of what is

diaper dermatitis is often irritant, chafing, heat, maceration, all those things.

DR. SPRAKER: I think that adds class diaper dermatitis, plus or minus Candida.

DR. McGUIRE: Rob, did you want to include Candida?

DR. STERN: No. I said excluding those things.

DR. DRAKE: Rob, instead of making this a negative, maybe having heard this, it may be better worded--what do you guys think about "Diaper dermatitis which could be either irritant or Candida?" Is that a more positive way to state it instead of a negative way, instead of exclusionary, more inclusionary?

DR. SPRAKER: And/or.

DR. McGUIRE: I would add the exclusions. You want to include Candida.

DR. DRAKE: Okay.

DR. McGUIRE: But you want to exclude viral, bacterial, psoriasis, atopic dermatitis, et cetera, et cetera, because you have other agents for those that you have got better data on. But you want to include chapping and--

DR. DRAKE: Dr. Chesney and Bill?

DR. CHESNEY: Can I come back to my diarrhea example? The analogy may not be perfect, but if we were to

say amoxicillin can be used for all diarrhea that is not salmonella, Shigella, all the other kinds that we know of, I think that is very imprecise.

I think there are many different things that can cause diarrhea that are not even infectious, just as there is irritant diaper dermatitis. I think what we are dealing with is an antifungal drug for a fungal infection regardless of whether it is difficult or easy to diagnose it clinically or in the laboratory, the fact remains that this is an antifungal drug for an fungal disease.

DR. DiGIOVANNA: But we, in actuality, do that. We treat traveler's diarrhea with a standard antibiotic regardless of what country people go to or regardless of when they get it, at the beginning of the trip or the end of the trip. So there are some of those clinically defined situations where we accept an unknown.

DR. CHESNEY: But traveler's diarrhea is actually a fairly precise entity. There are only about two or three organisms and toxins. It is not just nonspecific diarrhea. I understand what you are saying, but--

DR. DiGIOVANNA: Again, I don't want to belabor this because Lynn will shoot me but here we are talking about mostly Candida.

DR. DRAKE: I am not going to shoot you now. We have got all the hard work done.

DR. DiGIOVANNA: I can see the parallel.

DR. DRAKE: I had to get a certain amount accomplished today or the FDA would shoot me. We have done that. Now I am content. You can chat until--you can miss everybody's flights. I don't care. I'm here.

DR. ROSENBERG: I will just say that, for some people here who have been at Massachusetts General Hospital when I was there with Dr. Tolman watching him see patients one day, and he wrote a prescription for Ointment No. 10.

DR. STERN: I am the only other one in this room who remembers that.

DR. ROSENBERG: And I said, "Oh; Dr. Tolman, what is Ointment No. 10?" He said, "That's 5 percent boric acid and vaseline." He said that was Dr. White's prescription. He said, "Any time you see something you don't know what it is, you write a prescription for Ointment No. 10 and tell them to come back next month." He said, "I have cured more skin disease with Ointment No. 10 than you are ever going to see."

Now, that is the dream of every commercial company is to get an indication for, "This is an ointment for if you don't know what it is." I can see the appeal of this to a commercial sponsor. "We have a product that is good for--if you don't know what it is, this is what you want." But I am not sure that the agency is quite ready to operate at that

level.

DR. DRAKE: I don't think so. And, in order to bring this meeting to some kind of close, you have got the answers, the formal answers, to all of your questions. I guess what I would like to do is I am going to pose a sense of the committee, question to the committee.

The question I am going to pose, and you can raise your hand on yea or nay, is, is it the sense of the committee that, at least for the foreseeable future, instead of trying to micromanage all these definitions, that the sponsor should come forward with a specific indication such as an antifungal drug for an antifungal disease.

If you would like the sponsors to continue to be reasonably specific for prescription products, I would like you to raise your hand.

[Show of hands.]

DR. DRAKE: That is just a sense of the committee. The sense of the committee, and the majority, is that there is a comfort level with understanding we are going to treat X disease--I used to have--there is a Tennessee connection here. I trained there and Dr. Pat Wall used to day, "You go to know the bug before you can pick the drug."

He said, "If you don't treat the right bug with the right drug, you are not going to fix your patients. That is what I learned when I was in pediatrics at

Tennessee. I think, probably, the comfort level with this committee is at that point.

Jon, I would also suggest that the committee would also probably be very responsive to additional and new definitions if there is some rationale and if we can define some parameters on how to judge products along that line.

Unless there are any further comments, I am going to close the meeting here in just a second. Is there anything else anybody has a pressing need to say? Fred, please? You haven't said much. Talk all you want.

DR. MILLER: It is not really that pressing. I think diaper dermatitis is certainly--I am using the term "diaper dermatitis--" it is such a common entity and it is one that we face so much. You would hope that from a study we would get some elucidation of etiology or at least shed a little bit of light on the pathogenesis.

Again, we have so few people in this group that we really haven't shed any light on it. We have done a lot of discussing but, as far as etiology or anything precise about it, I don't think that has come out of that. That would be nice to have. I think we do need more data.

The second thing is, we can talk about subsets. And perhaps we will treat psoriasis and psoriasis and we will treat the fungal disease. However, in the world, it is going to be used for all diaper dermatitis, for the most

part. And there is the added expense that we talked about yesterday. This is a prescription medicine and it is going to cost a lot more, I would suspect, than triple paste and, in most cases, it probably won't be needed.

I think there are cases where it will be needed but, in most, it will not be needed.

DR. DRAKE: Anything else that people have to say? I would like to say two or three things. First of all, any time the committee doesn't act in a real positive manner for a sponsored product, I think it has got to be hard on the sponsor. If I was in your shoes, it would be hard on me.

But I want to encourage you. I think what you brought before this committee this time was extremely important. I think it shows that there is this pressing, overwhelming need to address some of these questions. I think you have created a great opportunity, not only for yourself, but for us, too, by pursuing this a touch.

I don't think this committee is going to require a ton of additional information from you, but I think if you come forward with some additional information to answer some of these questions, I think you will find a committee very responsive to hearing it because there is really a need for a product of this type.

So I want to compliment you for having the gumption to come before the committee with this notion

because I think it is important. It is a wide-open area that clearly needs a new product in that arena. I think all our pediatric derms would support that concept.

So I don't think this committee is trying to be unreasonable, but I sure want, at least on a personal level as chair of committee, to encourage you to pursue this because I think it is needed and I think you are on the right track and you potentially have something very positive.

With just a little bit more data, I suspect we could act on it. So I would view this more as kind of a deferral and not a rejection. I know we voted no, but we are just an advisory body. The FDA can still do what they want but I would really like to encourage you to go ahead. And I want to thank you for bringing it before the committee.

I want to thank all of our experts for taking your time and coming and sharing. And I want to thank my committee for your diligent hard work on a holiday weekend and for putting up with me. I really appreciate that.

And then I want to thank our new executive secretary, Jaime Henriquez. Thank you for your first meeting. You did a great job. I must admit, I didn't know. I had never met you before we came, but you were organized and professional and books were great. We thank you.

And then I want to thank everybody from the FDA, Jonathan Wilkin and all of you guys. These meetings are fun for me because I always end up learning so much. It is like a CME course benefit your presentations are good and they are efficient. So thank you for all the hard work in putting this information in a concise package that we could understand.

I remember years ago when I was on the committee, years ago, we used to get this many books, this high, two days before the meeting. You and I were on at the same time; remember that? We would get twenty books that high. It wasn't a critique. They were just trying to give us everything they had. But, being the humans we were, we didn't kind of get through it as easily.

So when you give us something like this, we can actually get through it. So I want to thank you because it is really hard to condense all that information. So we do appreciate it and we thank you.

Now, before I close, Dr. Wilkin, have we addressed all the needs of the FDA? Is there anything else you need from us?

DR. WILKIN: Of course, it is not only the votes that we look for at the end. We pore over the transcripts and look for all of the comments and the thoughts that are in those comments. There are many things that we learn from

this kind of experience.

I really appreciate the thoroughness with which the committee has addressed the topic. It is a Friday afternoon on a long holiday weekend. I notice that everyone is still here with the committee. It is very much appreciated. We got very good information. Thank you.

DR. DRAKE: With that, we stand adjourned.

[Whereupon, at 2:50 p.m., the meeting was adjourned.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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