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ADVISORY COMMITTEE MEETING NO. 50

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P A R T I C I P A N T S

Dermatologic and Ophthalmic Drugs Committee

Joseph McGuire, Jr., M.D., Chairman
Tracy Riley, Executive Secretary

Madeleine Duvic, M.D.
S. James Kilpatrick, Jr., Ph.D.
O. Fred Miller, III, M.D.

Special Government Employees, Consultants, and Guest Speakers

John J. DiGiovanna, M.D.
Jacqueline Goldberg, J.D.
Joel Mindel, M.D., Ph.D.
William Rosenberg, M.D.
Gerald Krueger, M.D.

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CDER

Robert DeLap, M.D.
Jonathan Wilkin, M.D.
Hon-Sum Ko, M.D.

CBER

Karen Weiss, M.D.
Louis Marzella, M.D.
William Schwieterman, M.D.

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CHAIRMAN MCGUIRE: If we can be seated, please?

Good morning. I'm Joe McGuire, and this is the 50th meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee. The agenda today includes many of the items that we covered on March 20th or 21st on psoriasis, and some of those will be summarized later this morning.

I welcome all of you, and I'm glad to see strong representation from industry.

Tracy Riley, who is Executive Secretary, will read the conflict of interest statement.

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

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

Since the issues to be discussed by the committee at this meeting will not have a unique impact on any particular firm or product but, rather, may have widespread

1 implications with respect to an entire class of products, in
2 accordance with 18 U.S. Code 208(b), each participant has
3 been granted a waiver which permits them to participate in
4 today's discussions. A copy of these waiver statements may
5 be obtained by submitting a written request to the agency's
6 Freedom of Information Office, Room 12A-3 of the Parklawn
7 Building.

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

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

18 CHAIRMAN MCGUIRE: Thank you, Ms. Riley.

19 I'd like now to introduce Dr. Karen Weiss, who
20 will give a brief overview, and following Dr. Weiss, Dr.
21 Wilkin will make his comments.

22 DR. WEISS: Thank you. Actually, it's not an
23 overview. This is just to welcome members of this committee
24 back for a discussion on psoriasis and just to say that this
25 discussion is intended to pick up and to expand on where we

1 were last March, to cover perhaps other areas. Last March's
2 discussion focused a fair amount on methods, analytic
3 methods, ways to assess efficacy in psoriasis, and there are
4 many more issues to assess in psoriasis, including potential
5 claims, including issues such as extrapolation across
6 different types of patient populations. So the idea of this
7 meeting is to expand on a broader array of issues in
8 psoriasis with the hope that we can use this advice for
9 various manufacturers, both biologicals and drugs, and
10 ultimately as another goal to develop a guidance document
11 that's going to be a joint effort between the Center for
12 Drugs and the Center for Biologics, the two centers that see
13 a fair amount of these types of products.

14 So that's pretty much my comments, and I'll turn
15 things over to Dr. Wilkin.

16 DR. WILKIN: I would just simply like to add to
17 Dr. Weiss' comments that the document that we have that
18 we're going to be working on today, the questions and the
19 narrative portions, is a joint effort of the CBER folks and
20 the CDER folks. We're looking at these products in very
21 similar modes.

22 Then the other item I'd like to mention is on page
23 2, where we have "OTC Monograph Relating to Psoriasis," one
24 item to emphasize is that the changing of the words in the
25 OTC monograph really isn't up for discussion. What we're

1 talking about today will be prescription drugs that are not
2 OTC and prescription biologics. That's really the focus of
3 today.

4 The OTC monograph indications are here just simply
5 to round out the listing of all the kinds of indications
6 that have been approved by the agency for drugs for
7 psoriasis.

8 CHAIRMAN MCGUIRE: There are a few new faces in
9 the Advisory Committee and also from the agency. I'd like
10 to go around now and have people identify themselves. Dr.
11 DeLap, we could start with you. You can be as--just talk as
12 long as you want.

13 [Laughter.]

14 DR. DeLAP: Well, I'm Dr. Bob DeLap, and I'm now
15 the Director of the Office of Drug Evaluation V. My
16 predecessor in this position was Dr. Weintraub, who played a
17 major role in many issues for the agency, but has recently
18 retired. I'm pleased to be here, and I'd like to thank all
19 the members of the committee for taking the effort to come
20 here and help us with this work.

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

23 DR. KO: Hon-Sum Ko, Medical Officer, Division of
24 Dermatologic and Dental Drug Products in CDER.

25 DR. WEISS: Karen Weiss, the Director of the

1 Division of Clinical Trial Design and Analysis in the Center
2 for Biologics.

3 DR. SCHWIETERMAN: Bill Schwieterman, Chief of the
4 Immunology and Infectious Disease Branch, Center for
5 Biologics.

6 DR. MARZELLA: Louis Marzella, Medical Reviewer,
7 Division of Clinical Trial Design and Analysis in CBER.

8 DR. KILPATRICK: Thank you, Joe. I kissed the
9 Blarney Stone at an early age, and so as a professor, I can
10 talk at length.

11 CHAIRMAN MCGUIRE: Of course, Jim.

12 DR. KILPATRICK: Jim Kilpatrick, Medical College
13 of Virginia, Virginia Commonwealth University.

14 MS. RILEY: Tracy Riley. I'm the Executive
15 Secretary to the Dermatologic and Ophthalmic Drugs Advisory
16 Committee.

17 CHAIRMAN MCGUIRE: I'm Joe McGuire, Dermatology
18 and Pediatrics, Stanford.

19 DR. GOLDBERG: Hi. I'm Jackie Goldberg, and I'm
20 the consumer rep, and I run the Health Sciences IRB at the
21 University of Missouri, Columbia.

22 DR. MINDEL: Joel Mindel, Departments of
23 Ophthalmology and Pharmacology, Mount Sinai Medical School,
24 New York.

25 DR. DUVIC: I'm Madeleine Duvic. I'm Chief of

1 Dermatology at MD Anderson Cancer Center in Texas.

2 DR. MILLER: I'm Fred Miller. I'm Director of
3 Dermatology at Geisinger Medical Center, Pennsylvania.

4 DR. ROSENBERG: I'm Bill Rosenberg, Division of
5 Dermatology at the University of Tennessee in Memphis.

6 DR. DiGIOVANNA: John DiGiovanna. I'm Director of
7 Dermato-Pharmacology at Brown University School of Medicine,
8 and an adjunct investigator at NIH.

9 CHAIRMAN McGUIRE: Thanks very much.

10 At our meeting in March on psoriasis, on March 20,
11 we had no representatives from the public and no
12 representatives from the industry, and I'm glad to see that
13 there are people who wish to be heard this morning. We'll
14 start with Dr. Alice Gottlieb.

15 Dr. Gottlieb, just tell us who you're representing
16 and which hat you're wearing today.

xx 17 DR. GOTTLIEB: I'm Alice Gottlieb. I'm director
18 of clinical research center at Robert Wood Johnson Medical
19 School, and I'm representing myself.

20 The take-home messages I would like to emphasize
21 from this are, one, I think that the FDA's concern over
22 risk/benefit ratio is appropriate and it's shared by--oh,
23 you need me to put a mike--sorry. I'm from New York, and
24 usually I have a loud enough voice. I'm sorry.

25 Can you hear me better now? Yes? Okay. So these

1 are the take-home messages. The FDA's concern over
2 risk/benefit ratio is appropriate and shared by the academic
3 community interested in psoriasis research. Although the
4 risk/benefit ratio remains constant, the numerator and
5 denominator can be varied depending on the psoriasis disease
6 severity. And by that I mean that a patient who has more
7 severe disease, one could accept more risk, and the other
8 way, people who have less severe disease will accept less
9 risk.

10 I think that we must attract traditional drugs
11 back to the United States in early phases of development,
12 and in dermatology, if you're talking about small molecules,
13 most of the early development is in Europe now. And why do
14 we care? First of all, I think the FDA has minimal input
15 into the overall strategy and study design if they get the
16 drugs in Phase 3 in the United States. Two, U.S. patients
17 get access to new therapies only late in maybe Phase 2(b) or
18 Phase 3. And, finally, psoriasis clinical research is
19 funded mostly by pharmaceutical studies one way or another.
20 So that if we lose that to Europe, you will see a drop in
21 psoriasis clinical research by, I'd say, greater than 90
22 percent in this country. And in that sense--and not to be
23 viewed as self-serving, but I think that the hope for
24 psoriasis is in research.

25 And I think that we must keep biologics in the

1 United States in early stages of drug development, and I'm
2 very worried that, as things are going, we may have a
3 problem that the companies will say, Why bother with the
4 U.S.? We'll go to Europe with our biologics, too.

5 What do I think are the challenges of psoriasis?
6 I think in moderate to severe psoriasis the therapeutic
7 challenge is actually to maintain remission effectively and
8 safely. We have drugs that say I could put 90 percent of
9 patients into remission. We don't have drugs that say we
10 maintain remission. However, for the mild to moderate
11 psoriatic, the need is different. We mainly have topical
12 treatments, and we need to find new topicals that clear
13 psoriasis without tachyphylaxis rebound, atrophy, or
14 systemic risk.

15 What's wrong with what we have now? And how do
16 pharmacodynamic markers help early in drug development?
17 Well, as you know, Type 1 psoriasis patients tend to get
18 their psoriasis in their 20s to 30s. They tend to go on to
19 more severe disease requiring photo or systemic therapy.
20 They're the ones who have the genetic HLA association. By
21 the time they've come to their middle ages, they've run out
22 of all of the FDA-approved treatments to date. They've
23 rotated through all of them. So we don't have good
24 treatments now.

25 The current FDA-approved drugs for moderate to

1 severe psoriasis are all toxic. Whether it's acitretin,
2 whether it's Neoral, whether it's methotrexate, whether it's
3 PUVA, they're all toxic.

4 And since we don't have a cure and these
5 treatments are toxic, you would ideally like to have a drug
6 whose remission time is long in the absence of continued
7 treatment. And these are data that were gotten actually
8 from a population at Rockefeller University, which is
9 moderate to severe psoriasis, and we asked the question:
10 What proportion of patients remain clear without lesions how
11 long after stopping their treatments cold turkey? And this
12 is PUVA. This is inpatient Geckerman(ph), which is tar plus
13 UVB, and this is cyclosporine.

14 As you can see, PUVA, about half the patients are
15 still clear after cold turkey stopping the PUVA, and they're
16 clear about four to six months after stopping the treatment.
17 And we would call PUVA a remittive treatment, one that does
18 not require continuous administration in order to maintain
19 clearing.

20 In contrast, cyclosporine is a suppressive
21 treatment because within one month after stopping cold
22 turkey, patients relapse and they relapse to about the level
23 they were before treating. And we would call cyclosporine a
24 suppressive treatment, a treatment that requires continuous
25 administration in order to maintain clearance. And in

1 between is inpatient Geckerman.

2 Now, why am I telling this to you? Because
3 clinically, no matter what scoring system you use, if you
4 take a look at a PUVA patient or a cyclosporine patient
5 after clearing--at clearing, except for the tan with the
6 PUVA, they look the same clinically. But they don't behave
7 the same, and the histology, the pharmacodynamic markers
8 that we use can predict that difference.

9 And what are these pharmacodynamic markers that
10 are done basically at four to six millimeter skin biopsies?
11 You can assess keratinocyte activation by using Ki-67, which
12 basically stains cells--thank you so much. Remind me to
13 give it back to you. This detects proliferating
14 keratinocytes. K-16 keratin is turned on in hyper-
15 proliferative epidermis and is a good marker for whether--
16 its absence is a good marker for normal differentiation.
17 And, of course, epidermal thickness is useful. These two
18 give quantitative data. This is qualitative.

19 Immune activation can be assessed by counting at
20 minimum the number of epidermal T-cells, but depending on
21 your reagent, you can actually sub-specialize. By looking
22 at keratinocyte, HLA-DR or I-CAM, one can get an idea of
23 gamma-interferon production. And these markers that are
24 really very useful in early drug development have been
25 validated for at least six different treatments and

1 published, and they predict whether a treatment will be
2 remittive or suppressive. So that PUVA, UVB/tar inpatient,
3 and the fusion protein, IL-2 DT fusion protein, all decrease
4 immune activation by 90 percent or more in the epidermis and
5 normalized keratinocyte differentiation and proliferation at
6 the end of treatment.

7 Now, in contrast, cyclosporine, which--you'll see
8 the PASI score drop will be very similar, 90 percent. Okay?
9 Compared to pre-treatment. In contrast, even though this
10 was a flat macule, you only have a decrease of about 50
11 percent of the T-cells in the lesions, and you don't
12 consistently normalized keratinocyte differentiation and
13 proliferation at the end of treatment. Therefore, it's not
14 so surprising that this is merely suppressive because the T-
15 cells are there and the keratinocytes are not turned off.

16 Okay. So let's talk about safety--okay?--and how
17 these pharmacodynamic markers also can help that.

18 I think psoriasis offers the opportunity to study
19 clinical pharmacology and safety in patients on single
20 therapy and distinguishes itself from rheumatoid arthritis,
21 inflammatory bowel disease, and multiple sclerosis in that
22 regard. I'm head of a clin pharm unit, and I can tell you
23 psoriasis patients are ideal for traditional Phase 1 study.
24 Why? Because the psoriasis patients who pass the rigid
25 exclusion/inclusion criteria have normal lab values; two, in

1 exceedingly difficult for patients. It's not fair to the
2 patients. in fact, I think it's unethical, and it's a very
3 hard sell as the doctor. And, in fact, our patients are
4 smart enough. They say, Doc, why should I join this study
5 early? I'm going to wait until the later doses. At least
6 I'll have a chance of getting something that might work.

7 And so I think that it's appropriate to have
8 risk/benefit being acceptable, but I would suggest that if
9 one is going to do that kind of a safety study that one uses
10 less severe psoriatics who can stand being off any effective
11 treatment for three to six months.

12 And so I'm going to get off right now, and my
13 take-home message is that the confluence of scientific and
14 biotechnical advances in understanding the pathogenesis and
15 treatment of psoriasis make these exciting and hopeful times
16 for the patient. So let's not lose the momentum, and let's
17 make sure that we can continue doing these studies in
18 America.

19 Thank you.

20 CHAIRMAN MCGUIRE: Thanks, Alice. Will you take a
21 few questions from the Advisory Committee?

22 Are there any questions? Dr. Wilkin?

23 DR. WILKIN: I was wondering about if maybe you
24 could come up with a more precise operational definition
25 that would separate remittive versus suppressive. It seemed

1 like these were really n's of a continuous spectrum, that
2 there were treatments that would give intermediate kind of
3 results between, say, PUVA and cyclosporine, that there
4 would--do you have an idea of like, you know, if it comes
5 back within one month or--

6 DR. GOTTLIEB: Well, I could explain to you why I
7 think that UVB/tar Geckerman gives an intermediate result.
8 But I was basically really at five minutes, so I didn't go
9 into details.

10 PUVA basically not only decreases immune
11 activation in the epidermis, but actually because UVA
12 penetrates deeper, actually goes beyond the thermal
13 epidermal junction, and that's where--in contrast UVB/tar,
14 the UVB does not penetrate pretty much lower than the
15 epidermis, and you still see activation in the dermis. So
16 although it's enough--getting rid of the epidermal T-cells
17 is enough to clear the plaque, I think the reason why you're
18 seeing an intermediate result with inpatient Geckerman
19 rather than PUVA is because you're not getting as far down
20 with the ultraviolet light. You're not getting rid of all
21 the immune activation in the plaque.

22 So I think that explains the intermediate value. I
23 can't really--I don't have another example to actually add
24 to your question for every single them.

25 DR. WILKIN: Okay. So there are intermediate

1 kinds of therapies that would be between pure remittive and
2 pure suppressive. But what I'm wondering is: Is there a
3 timing of relapse that you think of as sort of a watershed
4 time, that beyond that you would be willing to say if
5 there's recrudescence, this is truly a remittive kind of
6 therapy? You know what I mean, dichotomizing between the
7 remittive and suppressive, drawing a line in time and
8 patients after withdrawal of therapy?

9 DR. GOTTLIEB: If asked that question, I would
10 like to use PUVA as the gold standard for that and say
11 somewhere between four and six months would be considered
12 remittive.

13 CHAIRMAN MCGUIRE: Dr. Schwieterman?

14 DR. SCHWIETERMAN: Thank you very much, Alice, for
15 that. Could you clarify your comments on what I think is a
16 very important matter? That is, the type of patients that
17 should be studied in early clinical development of
18 biological therapies, because obviously this is something
19 that we have to deal with often.

20 I'm a little bit confused, however, from your
21 presentation because at one juncture you mentioned that many
22 of the patients didn't do well on the toxic therapies that
23 the FDA had approved and thereby needed new agents, and at
24 another point I thought the point was well taken that it's
25 unethical to take those patients off of those therapies for

1 the purposes of giving them a new biological therapy.

2 So I guess what I'm trying to get at is: At one
3 point it sounded like they weren't doing very well on the
4 therapies, and then on the other hand, it seemed like it was
5 unethical to do that. Could you clarify that?

6 DR. GOTTLIEB: Yes, sorry. As I mentioned, the
7 treatment of moderate to severe psoriasis--and I'm not going
8 into the definitions because I suspect the NPF will, but
9 let's say what you're defining in many of the protocols 10
10 percent or more. The challenge there is not clearing them.
11 I can clear almost anybody with either cyclosporine,
12 methotrexate, or acitretin plus UVB. The problem is you
13 can't stay on these treatments forever. And so the
14 maintenance of clearance safely is really where the
15 challenge is there.

16 So when I say that--so as long as we keep treating
17 them, they'll stay clear, but at that risk of toxicity. So,
18 therefore, in that population, that 10 percent, taking them
19 off the methotrexate, off the cyclosporine, off the
20 acitretin-UVB, for the considerable time periods that are
21 being required, they are definitely going to get worse
22 during that time period, and, in addition--and then we're
23 going to ask them to be two or three months--and that's
24 pretty short--you know, one single dose with a follow-up of
25 some piddling amount that everybody thinks will not be

1 effective, and here you have the poor patient, who, as
2 you'll find out from the NPF survey, there's a relative--a
3 surprisingly high incidence of major depressive episodes.
4 It impacts all aspects of their life, whether it's work,
5 sexual, and we're asking them for six months to be
6 essentially on no treatment.

7 Now, what the solution is--because you don't want
8 to just say this thing stinks. You know, we want to
9 basically come with a solution. If your goal is primarily
10 safety and you want to have the advantage with psoriasis
11 that you can get proof of concept with target lesions, which
12 are very powerful, again, with the pharmacodynamic markers
13 and clinical scoring, then I would suggest do your first
14 study in less severe patients, whether one defines it--NPF,
15 I don't know exactly what the final consent this is, but
16 remember at the IBC meeting they presented that mild
17 psoriasis was less than 2 percent, moderate was 2 to 10, and
18 severe was 10 or more. Well, then, pick the 2 to 5 or 2 to
19 10 range, and do it there.

20 You might say, okay, why expose these people to
21 any risk? Well, you know as well as I do that there are
22 companies who do their first study in men and normal
23 volunteers. So if you're willing to do it in normal
24 volunteers, why not do it in mild psoriatics and get some
25 proof of concept as the same time. And those patients can

1 stand being off their top--basically topical treatments, and
2 many of those patients who volunteer for such studies are
3 actually quite public spirited and they want to help
4 patients in the future and potential family members who
5 might have the disease.

6 CHAIRMAN MCGUIRE: The dilemma of identifying the
7 appropriate study group will come up again this morning.

8 Alice, if you would, would you pass Dr. Mindel's
9 laser to Beatrice Abrams?

10 Dr. Abrams is representing Novartis.

11 DR. ABRAMS: Good morning, ladies and gentlemen.
12 My name is Beatrice Abrams, and I'm the Executive Director
13 and global group leader for Dermatology Wound Healing at
14 Novartis Pharmaceuticals. I'd like to discuss with you
15 today some opinions that we've developed during the course
16 of studies with a number of drugs for the treatment of
17 psoriasis. And just in some broad generalities, I'd like to
18 start with just some concepts that we've had to deal with.

19 First of all, what do you measure in the treatment
20 of psoriasis? Well, we picked generally the three key
21 signs, and there's very little debate on what they should be
22 in the plaque thickness, scaling, erythema. Some people say
23 one is more important than the other, but generally, all
24 three are hallmarks of the disease and should be measured.

25 Based on some new information from the NPF and

1 some other investigators, it's certainly clear that pruritus
2 is an important component in a lot of psoriatics. At this
3 point, though, we haven't quite figured out where to put it,
4 and I am still tending to keep it out of a primary variable
5 status. But I think it should be looked at, and we need to
6 get more information.

7 For topical drugs, you can only hold a drug
8 responsible for the area it's actually being applied to, and
9 so I think indicator top lesions are appropriate for the
10 study of these agents because you can look at what's going
11 on where the drug is actually being applied.

12 I do add the caveat, though, that you should be
13 looking at a number of various anatomical sites because some
14 sites are more responsive than others, and you would want to
15 get an idea of what the drug is doing in general.

16 On the other hand, when you're working with
17 systemic agents, you need to know what is going on with the
18 whole patient, and the whole patient is defined not just by
19 the signs at an indicator lesion, but by the signs across
20 the body and, as well, the extent of the disease. And
21 because you have to look at so much, we propose the use of
22 composite variables, and composite variables are used in
23 other therapeutic areas. On a practical standpoint, a
24 composite variable does conserve the n relative to defining
25 a lot of numerous single variables as your primaries. So

1 with one primary variable, you can use a little bit reduced
2 sample size relative to multiple primary variables and get
3 an idea of what your patient looks like at a specific time.

4 Some other aspects that are important when you're
5 looking at measuring disease and the effect of a therapeutic
6 agent are to have something where you can look at intra- and
7 inter-rater variability, and I think what you need is,
8 having very--oh, what do you want to say?--ethereal words
9 that could have multiple definitions such as moderate or
10 such as he's markedly better, I think these are difficult to
11 standardize. And I think that what you need is something
12 with a little bit more concreteness to define the disease
13 and then go back and you can look at the inter- and intra-
14 rater variability in assessing these various parameters.

15 In addition, I think it's very important that we
16 start standardizing--and I think the panel is going to be
17 working on that--a lot of definitions so that we can clearly
18 set the expectations for what the therapeutic agent is
19 doing. For example, what is mild disease, moderate disease,
20 severe disease? What is a mild expression of a specific
21 sign?

22 The degree of improvement also is something that
23 marketing people love to get hold of, and some people will
24 say a 50 percent improvement is marked, whereas others would
25 say it has to be 100 percent improvement to be marked. So I

1 think this is very important because it's important that we
2 are fairly setting the expectations of the consumer who is
3 both the patient and the physician.

4 The criteria of success Alice very aptly
5 described, and I, too, hold to the idea that it should be
6 something--a sliding variable dependent on the benefit/risk
7 so that more toxic drugs certainly should be reserved for
8 patients who need really a more effective therapy.
9 Conversely, when you have something of lesser efficacy, it
10 still has a place in the treatment of psoriasis as long as
11 it is a safe drug. So I think the criteria of success has
12 to be moving and has to be based on the assessment of
13 benefit/risk.

14 Again, the criteria and the definitions in the
15 benefit/risk need to be carefully defined so that the
16 patient's and the physician's expectations are correctly
17 set.

18 We propose the use of the much maligned PASI.
19 It's a composite variable that's been used a lot in the
20 evaluation of drugs in psoriasis in Europe and a little bit
21 it's coming in in the U.S., but not a lot. It is a
22 composite variable, and it is a single number that reflects
23 the overall disease status at a certain time point when
24 you're evaluating, and it's comprised of evaluations of the
25 key signs and the extent.

1 Looking at the PASI's change from baseline, you
2 can see, without having to recall what the patient looked
3 like at baseline, what kind of improvement the therapeutic
4 agent is causing in that patient. And, again, as a
5 composite variable, you're looking at a lot of different key
6 aspects of the disease with one number, and it is conserving
7 on the end.

8 Now, the nice thing about it is while you have it
9 as a single number, it can be broken down into its component
10 parts and looked at separately. So you can get a good
11 understanding of what exactly is changing as the patient
12 undergoes therapy. The extent can be looked at separately
13 from the signs, and the different body regions can be looked
14 at separately, secondarily.

15 And what it is, for those of you who aren't
16 familiar, you break the body up into four regions--the head,
17 upper limbs, trunk, lower limbs--and in each area you
18 measure the three key signs and the area of that specific
19 region of the body. That whole number then is multiplied by
20 a number based on the rule of nines. It represents the
21 contribution of that body part to the whole body so that,
22 for example, in an adult, the head is roughly 10 percent of
23 the body based on the rules of nines, and so you'd multiple
24 it by 0.1. The PASI then is comprised of these numbers
25 added up for the whole body. The lower limbs in our system

1 is a little bit higher because we include the buttocks.
2 Again, definition is critical. You have to tell the
3 investigator and train them what is actually included in
4 lower limbs, what is included in the head. Does it include
5 the neck? So it's important there to define what you're
6 doing.

7 Now, in the studies that we have conducted with
8 Neor--excuse me, this was Sandimmune and cyclosporine. You
9 can see that there was a lot of similarity in evaluations
10 that were done across a lot of different ways of measuring
11 disease response. There was an overall evaluation where the
12 physician gave a gut feeling, as he markedly improved or
13 whatever, and for the placebo, you see basically the number
14 reflected unchanged, pretty active, marked improvement.

15 There was an overall evaluation, which was the
16 investigator's gut feeling is this patient severe, mild,
17 moderate, and you can see here that there was, again,
18 significant improvement from baseline in that score. These
19 were categoric scores. PASI also improved dramatically.
20 this was the total improvement in PASI. Again, the placebo
21 is not doing anything.

22 And when they looked at the three target lesions
23 and took the average of scaling, erythema, and thickness,
24 they got basically between 70 and 80 percent improvement in
25 those key signs.

1 Now, if you look at the correlations between these
2 various types of assessments and PASI, if you look at the
3 global evaluation rating and the investigator's perception
4 of totally clear, almost clear, moderate, so this is what
5 does the patient look like, there was a very high degree of
6 correlation between the PASI score and these ratings. In
7 fact, Spearman(ph) rank coefficient, correlation coefficient
8 was 0.93, and it was highly significant, p less than 0.001.
9 Where you see a lot of overlap, I'm sure this reflects the
10 fact that in a PASI score you can have a patient come in
11 with very severe signs and lesser extent and get the same
12 PASI rating as a patient who has--I'll get this backwards--
13 has mild expression of signs but large body area surface
14 covered.

15 But even so, there is very little overlap, for
16 example, from the absolute categories of severe, for
17 example, to moderate to mild. It's when you get these
18 intermediate things you see the mild, moderate or--this is
19 moderate, severe. You see these overlaps. But they are
20 highly correlated.

21 If we look now at the other type of rating where
22 you're trying to look at overall improvement scores, this
23 again is the physician's gut feeling, is there marked
24 improvement, is there slight improvement, versus the percent
25 improvement by PASI scores. Again, these are highly

1 correlated. Again, the Spearman rank correlation
2 coefficient is minus 0.953 and highly significant, less than
3 0.001. And so you can see that the PASI actually does
4 correlate with these sort of gut-feel measures, so why not
5 use just the gut-feel measure? And the reason is that with
6 PASI you have discrete entities that are comprising that
7 score that can be looked at independently, so you can see
8 where that score is coming from. You can't get brain scans
9 into your physician to ask for what is your real reason for
10 saying the patient is marked, mild, moderate, whatever.
11 With PASI you can actually get in there and look, what is
12 the erythema score for the head and neck? Are we seeing
13 differential responses in the various body regions?

14 Of course, again, as a secondary variable, there's
15 nothing to preclude looking at indicator lesions in certain
16 areas--elbows, scalp, whatever you want to use specifically.
17 But with the PASI, again, it gives you this composite
18 variable, or you can break it into its components, look at
19 exactly what is happening and where your final number is
20 coming from.

21 PASI then is a one-shot view of the disease status
22 reflective of the overall activity of the drug as you look
23 at it changing from baseline and doesn't depend then on
24 looking--at having the physician remember what did the
25 patient look like at baseline, how much did he improve from

1 something I can't remember six months ago. So you can look
2 at both the picture, the static picture of the patient at
3 the time you're doing the PASI, and by relating it to
4 various visits from baseline, you can see how much effect
5 the drug has had from baseline.

6 And since it is a composite variable, it's
7 conserved on the sample size a little bit relative to having
8 multiple primary variables that have to show significance.
9 And by breaking it down, you can get detailed information on
10 individual components, the specific signs, the extent, the
11 body region improvement differentially. It does have fairly
12 good correlations with standard measures, and because of
13 that, I think you can translate it into something that the
14 physicians can understand.

15 Finally, you can measure the components to see
16 where you variability is coming from, and this lends itself
17 to training programs which increase the consistency across
18 the investigators in their assessments of the drug effects.

19 So that's our experience, and I think we've
20 looked, as I showed you, at a number of ways of evaluating
21 psoriasis with target lesions, with overall scores, with
22 global score. And I think PASI, because of its ability to
23 be broken up into discrete entities that you can really
24 visualize, so far has come out in my mind to be the most
25 useful of the measures.

1 Thank you.

2 CHAIRMAN MCGUIRE: Thank you, Dr. Abrams.

3 Dr. Krueger?

4 DR. J. KRUEGER: May I make a comment? Is that
5 permissible?

6 CHAIRMAN MCGUIRE: Yes. I was just checking with
7 counsel. Yes, you can.

8 [Laughter.]

9 DR. J. KRUEGER: Dr. Abrams and I have agreed to
10 disagree on a couple of points of the PASI, and I'm speaking
11 this afternoon about some objective measures of response,
12 and perhaps it should have been this morning following her
13 talk. But I'm just saying it will be this afternoon.

14 The one thing I would point out is that I think
15 the PASI is a fairly good tool for late-phase development,
16 and that is, you can accept the inter-rater variability
17 within that so that you're essentially considering what
18 happens within an individual physician's evaluation of
19 outcomes.

20 However, what is not clearly published is this
21 inter-rater variability with the PASI such that I've
22 actually been present at meetings which are not published
23 where patients were lined up among experienced psoriasis
24 investigators, and what is a 20 to one investigator may very
25 well be a 40 or a 50 to another. There is probably a two-

1 and-a-half-fold variation to the assignment of the number,
2 most of which is biased on a guesstimate of the surface
3 area, so that scale, erythema, and thickness are
4 fundamentally better measures in terms of achieving
5 consensus on what exactly the number is.

6 So I would agree with the breaking out, but it is
7 misleading, and I think the PASI is essentially worthless in
8 early-phase development where you're looking at groups of
9 six or ten patients at particular dose levels, and for
10 early-phase dose-ranging studies and for proof of concept, I
11 think objective measures that don't depend upon just looking
12 and making a guess, which is essentially what this is, are
13 more useful.

14 DR. ABRAMS: I agree--

15 CHAIRMAN McGUIRE: Thanks for your comments, Jim.
16 We'll have more to say about PASI later, and I think in the
17 interest of time we better--

18 DR. ABRAMS: If I could just make one comment to
19 that, though. I agree that for early-stage PASI is not
20 useful. I also would like to point out there are numbers of
21 techniques now that allow you to get consistency in the
22 evaluation of area and extent, so these can be controlled.
23 I think the earlier studies lacked that control, which is
24 now available.

25 CHAIRMAN McGUIRE: Sometime we will make a

1 determination as to whether PASI has been appropriately
2 maligned or unfairly maligned.

3 Mr. Barton? I've lost track of the laser pointer.

4 MR. BARTON: I don't have a laser pointer. I
5 don't have any slides. I was asked to come here as a
6 patient to represent the millions of people who have
7 psoriasis to talk to the panel. I take it as a kind of
8 awesome responsibility.

9 My name is Tom Barton. I'm Chairman of the Board
10 of Trustees of the National Psoriasis Foundation. I've had
11 psoriasis since I was 16. And I have to say, just reading
12 the materials here, because I was unaware of both the format
13 and the substance of the meeting, I find the subject matter
14 of the meeting a little scary.

15 People with psoriasis who have incurable, chronic,
16 life-controlling disease have only in recent times begun to
17 have some hope that their disease will ultimately be treated
18 and their lives given some peace and meaning. For the
19 people on the panel who are considering ways to treat us,
20 the millions of us, I think in the materials that I just
21 read while sitting here, there are some fundamental
22 assumptions that are either wrong or are misunderstood.

23 Imagine how it feels to have a disease that
24 multiplies--inflames your skin, multiplies the reproduction
25 of your skin cells by at least seven times so that it cakes

1 up and flakes off, distances you from all tactile feeling
2 with your skin, continually gives you the physical
3 sensation--and I know because I've been dramatically cleared
4 and dramatically uncleared--the physical sensation of being
5 enveloped in your own skin and separated from the world with
6 your own skin, and a disease that the rest of the world
7 finds repulsive and incomprehensible, a disease that I came
8 down with when I was 16 and shattered my life at that time,
9 terminated my athletic career because nobody wanted to be in
10 a locker room with me, nobody wanted to share towels, nobody
11 wanted to look at me, altered friendships beyond--people
12 talk about the sexual results of having a disfiguring
13 disease, and it's certainly true. But it also affects
14 regular friendships. Nobody likes to be associated with
15 somebody that has a disfiguring disease. And then go to the
16 medical profession and find out that at that time there was
17 nothing.

18 Now, that didn't mean that people didn't try
19 something. Honestly, you know, physicians are not in
20 business to say that they can't do anything about disease,
21 so people will try things. But it rapidly became apparent
22 to me that there was nothing that worked on psoriasis other
23 than constant, intense doses of sunlight had some kind of
24 quieting effect on the psoriasis. And I don't mean just a
25 day in the sun. I mean really intense sun. If any of you

1 read John Updike's autobiography where he talked about how
2 it controlled his life so that he spent a month on Martha's
3 Vineyard in the sand dunes, hiding in the sand dunes getting
4 sun, and then took at least two weeks--this is for his
5 entire life--in the Caribbean in the winter trying to smooth
6 the curves between the seasons, when I read that I laughed
7 out loud because my family used to go to Martha's Vineyard
8 when I was a kid, and I had this aerial visual image of
9 being in the same sand dune next to John Updike and the sand
10 dunes being covered with people with psoriasis trying to get
11 the only thing that had any effect on their disease at all
12 to work. That was all we had.

13 Recently, there have been some accidental and,
14 frankly, often foreign--in the sense that the discoveries
15 took place overseas--some advances that have given us some
16 hope. I flew to Paris because we couldn't get anything
17 through the FDA to get the retinoids, so I got the retinoids
18 and I got my prescription filled from Paris for years. I
19 flew to Europe to get Dovonex (ph). I was in the first
20 clinical trials for PUVA. I was in the first clinical
21 trials for cyclosporine. I joined many people who were
22 trying to assist the biomedical profession in coming up with
23 effective therapies for psoriasis.

24 This by no means has happened. There is nothing
25 that works for everybody. Everything that works seems to

1 work in direct proportion to its toxicity. These are not
2 trivial drugs, and we're not stupid people. We know that
3 when we take these drugs we're incurring a risk, and we,
4 forgive me, are presumptive enough to believe that we have
5 some right in this to make our own cost/benefit analysis,
6 our own risk/benefit analysis. And while we appreciate the
7 assistance and everything that you do at the FDA level,
8 there's a million people out there that are waiting for
9 advances in these drugs who don't like to make runs for the
10 border, who don't like to fly overseas, who don't like to
11 have their prescriptions filled overseas.

12 And what I find a little scary reading the
13 materials is kind of the assumptions behind what I read in
14 this risk/benefit analysis and the disempowerment of the
15 people who have the disease and their physicians from making
16 these very fundamental decisions. This is my life. This is
17 the life of millions and hundreds of thousands of people
18 with very severe disease. Part of the problem with
19 psoriasis is that it exists on a spectrum from mild to very
20 severe, so it can be trivialized. I can assure you, for
21 people who have it in severe form, it's not trivial. And we
22 pay attention. We work. The Internet is this great
23 communications media. We know what's going on out there in
24 the world. There is a lot of misinformation. There's a lot
25 of disinformation. We know there's misinformation and

1 disinformation.

2 But don't take away from us our right to work with
3 our physicians to treat our disease. We need that right.
4 And one way or another, we're going to get it. Now, it may
5 be easier for me to go overseas than it would be for other
6 people, but I'll do that. I'll go to other places if I have
7 to. We need it here, though, in this country. And I would
8 ask you, when you make these decisions, to recognize that
9 there are people out here who really feel very deeply about
10 this, that you are affecting, and we want to be part of
11 making these decisions.

12 I'm not stupid. I can sit down with my doctor,
13 and I can understand what the consequences are of
14 methotrexate, cyclosporine, PUVA, anything else that comes
15 down the road. And I want to continue to have that right.

16 Thank you very much for giving me the opportunity.

17 CHAIRMAN MCGUIRE: Tom, that was a wonderful thing
18 for the committee to hear and also for the agency to hear.

19 I wonder if anyone from the agency would like to
20 respond to Mr. Barton.

21 DR. SCHWIETERMAN: No, only to thank you for your
22 comments. I think that we share, actually, your concerns
23 about depriving patients like you of these new therapies
24 that come along. And I hope at the end of the day we have
25 some consensus as to how to go about the risk/benefit, and

1 thank you very much.

2 DR. WEISS: And also to share that and to say that
3 I think part of the purpose of having open forums like this
4 is to hear input, to invite people like you, other people
5 that represent other groups, to come to the podium at the
6 times that are appropriate when you have comments to make
7 with respect to, you know, even these questions and your
8 input to these questions. We really do want to hear that.
9 You provide a perspective that we don't oftentimes see. So
10 just to please encourage you to continue to do that.

11 DR. SCHWIETERMAN: Dr. McGuire, if I could add
12 just one last thing.

13 CHAIRMAN MCGUIRE: Yes.

14 DR. SCHWIETERMAN: One of the unfortunate things
15 about working at the agency is that there's a perception
16 that--or maybe it's a real one, I don't know--that there's
17 this wall between the bureaucracy of the government and the
18 rest of the world out there. And to the extent that you can
19 communicate these things to us through different
20 organizations or inform like this, I think it's very
21 helpful. The worst thing in the world is for there to be a
22 lack of communication between the patient groups and agency
23 reviewers like me and the rest of the panel up here.

24 So, you know, I think this is an important meeting
25 for a lot of reasons, not the least of which is that we're

1 establishing dialogues with the NPF and other organizations
2 about what's needed, and we'd encourage you to continue to
3 communicate these to us directly, if need be.

4 MR. BARTON: Thank you.

5 CHAIRMAN MCGUIRE: Tom, thanks.

6 We're going to hear--John? Dr. Wilkin?

7 DR. WILKIN: I would just like to add I think
8 these are--the points that you've raised we need to think
9 about when we're talking about labeling. The goal of
10 labeling is to inform, and to inform what possibilities
11 there are of improvement from the therapy and also to inform
12 what the risks are for therapy. I don't think the goal of
13 the agency is to usurp the right of the patient and the
14 physician to work out mutually the risk/benefit ratio for
15 that individual at that time. But what our goal is is to
16 craft into labeling the right kind of information that will
17 help the patient and physician be able to arrive at that
18 relationship in an informed manner. And I think that's a
19 large part of what we're trying to do today.

20 MR. BARTON: I think we wholeheartedly support
21 labeling and information as complete as it can possibly be
22 made. We wanted to be sure that that doesn't--there isn't a
23 subtext in that that ends up with labeling requirements so
24 chilling that companies don't endeavor to look at psoriasis
25 as a disease to be treated. It's already got kind of a bad

1 rep as kind of a black hole of research dollars for
2 biotechnology companies, and if the bars are set too high
3 for these companies to experiment with psoriasis and look at
4 psoriasis, since most of the advances that have taken place
5 have been kind of accidental, incidental observations on
6 therapies that were directed at other disease states, then
7 the advances that I'm talking about that have given us hope
8 may also slow down.

9 CHAIRMAN MCGUIRE: Tom, I truly appreciate your
10 frustration, but there is a dilemma, and that is, what
11 someone as sophisticated as you would see as
12 disenfranchisement would actually be dangerous for someone
13 who is uninformed. You are very well informed about this
14 disease, and you are very sophisticated. You know exactly
15 what risks you are taking, and you're willing to game the
16 situation. But the same rules that would be fair for you
17 might be dangerous for someone else, and that's a problem
18 that gets into the labeling issue.

19 You're rather unique. You're a rather unique
20 patient.

21 MR. BARTON: Well, I would like not to stand here
22 as somebody unique. I mean, I'm involved with the disease,
23 obviously. I do pay a lot of attention to it. But I think
24 that the thrust of what I'm expressing is not unique among
25 the psoriasis population.

1 CHAIRMAN MCGUIRE: Okay. Let's hear from the--

2 MR. BARTON: Thank you very much.

3 CHAIRMAN MCGUIRE: Thank you very much.

4 The National Psoriasis Foundation is represented
5 by Tara Rolstad.

6 For those of you who are looking at the schedule,
7 we're obviously running over, and we're going to run over.

8 MS. ROLSTAD: Keep the lights up for just a
9 moment.

10 Before I start, I am Tara Rolstad. I'm the
11 Director of Public Affairs for the National Psoriasis
12 Foundation. Most of you are familiar with the organization,
13 but in case you're not, we're a non-profit organization
14 dedicated to improving the lives of people with psoriasis,
15 and our mission is advocacy in situations such as this and
16 also education for people with the disease and supporting
17 research towards a cure, which is far off in the future,
18 which is why we're addressing the issues we are today.

19 Before I go into my comments, I would like to
20 address the last comment that you made, Dr. McGuire, which
21 is that I think Tom's comments were very valuable, and Tom
22 is a great guy. Tom is also the Chair of my Board of
23 Trustees, but I have to say Tom is not that unique. This
24 patient group is very educated. These people are not
25 dealing with a crisis health situation in their life. These

1 people are dealing with decades and decades and decades of
2 treatment. And I have to say that I have spoken with many,
3 many, many patients. The people that I work with and work
4 for have spoken with hundreds and hundreds and thousands of
5 them. This is not a group that is unsophisticated. They
6 are very sophisticated. They know what their treatment
7 options are. They've been through this routine. They're
8 very well informed. They ask good questions. They often
9 tell us that they feel, unfortunately, that they probably
10 know more about the disease and its treatment than some of
11 their physicians just because of how much they've had to
12 deal with it and how long they've had to deal with it. So
13 Tom's a great guy, but he's not that unique.

14 My purpose today is to share the experiences of
15 our membership, which currently stands at about 40,000
16 people, and we also represent the six and a half million
17 people in this country who have the disease, including, as
18 Tom said, over a million folks who have very, very severe
19 disease that really compromises their quality of life. This
20 disease does compromise quality of life, day-to-day
21 activities, sleep, work, sexual relationships, personal
22 relationships, friends, pretty much every aspect of life you
23 can think of. And I've got some recent survey data to share
24 with you that hopefully will illuminate this a little bit.

25 As has been said earlier, there are many treatment

1 choices available for this disease. Unfortunately, if you
2 are a person with moderate to severe psoriasis, none of
3 those treatment choices come without very serious risk. And
4 so that's why we're here today to encourage you to do
5 everything you can as you make these decisions to encourage
6 more development and more therapeutic options.

7 One recent survey, not of our membership but a
8 survey of the psoriatic population in general in the United
9 States, showed that as many as half of people with
10 symptomatic disease are not seeking treatment, and I have to
11 say, if we could clone Alice Gottlieb, perhaps that wouldn't
12 be the case. She says she can put 90 percent of her
13 patients into remission. I don't think that that's a
14 typical experience for the psoriasis patient. I think many
15 of them are very frustrated and very unhappy. And the
16 information that we have shows that there are some real
17 costs to them giving up on treatment like that.

18 This is a survey that we did of our membership.
19 There are two different surveys, actually, and I'm going to
20 try to be clear about which survey I'm talking about as I go
21 through, and I apologize for being confusing. We have a
22 survey that went out that was a mail survey to our 40,000
23 members. It was mailed this summer, and I think the most
24 important thing for you to recognize is that this is a group
25 of people who very much wants to be heard, and that's why

1 I'm giving you this information today.

2 We received--this says 17,000. Actually, the
3 final results were 18,000 surveys mailed back. That's
4 nearly a 50 percent response rate, when normally in mail
5 surveys you expect 2 to 4 percent, maybe in an organization
6 like ours maybe slightly higher. This group of people
7 really, really wants to be heard. And I think this speaks
8 to their dissatisfaction with treatments and the real unmet
9 need that still exists.

10 This survey indicated that the most common
11 symptoms that are experienced--many of you are familiar with
12 this--scaling, itching, red skin, tightness of skin, and
13 bleeding, even. Thirty percent of our membership--and this
14 is across all levels of severity--experienced bleeding on a
15 frequent basis. So this is really a very physically
16 unpleasant disease. It is not a mild thing. It is not a
17 cosmetic thing at all.

18 Now, we also surveyed by phone to get a little bit
19 more in-depth information. We surveyed 500 of our members
20 who have severe disease, and that was defined by our medical
21 advisers as how to choose who those folks were. And this
22 information is from that survey, which just really honed in
23 on how seriously these different symptoms affect them. And
24 this is how many days in the last 30 days they experienced
25 those different symptoms, and you can see that red skin,

1 scaling, and itching affects them over half of the time. I
2 mean, this is not, you know, a day here and there. This is
3 over half the time of their lives that they're experiencing
4 very, very unpleasant physical symptoms.

5 Again, the whole spectrum of membership, all
6 levels of severity. They experience really serious physical
7 limitations in their daily lives. One in five of them have
8 problems sleeping. One in five of them also have problems
9 in their sexual activities. I don't mean to be emphasizing
10 that area. It's just one that obviously really speaks to
11 the personal and deep way that this disease affects people.
12 Sixteen percent of them have difficulty using their hands.
13 Twelve percent of them have difficulty walking. This begins
14 to affect your ability, obviously, to hold a job, to take
15 care of your children, those kinds of things.

16 When you look at our membership, our entire
17 membership, those of them that have psoriatic arthritis,
18 those disability levels really go up. And I include this
19 for a couple of reasons. Psoriatic arthritis doesn't have a
20 lot of treatment options of its own. It kind of also speaks
21 to the fact that many of these folks tend to have more
22 serious skin disease. If you have psoriatic arthritis,
23 you're also likely to have more serious psoriasis, and you
24 can see that these quality-of-life measurements are very,
25 very severe.

1 Tom spoke a little bit about this, and I just want
2 to give you some numbers. This again is across all levels
3 of severity within our membership. It includes people with
4 mild disease. One in 20 of them have actually contemplated
5 suicide specifically because of their skin disease. One in
6 ten of them, nearly, have been excluded from a public
7 facility because of their skin disease. And you can imagine
8 the humiliation of being asked to leave the swimming pool
9 when you're with your friends as a kid or being asked to
10 leave a hair salon, being asked to not try on clothes in a
11 store. This is very, very difficult for people to
12 experience.

13 I don't have the slide with me, but our survey
14 also showed that a very high percentage, one in ten of them,
15 have been clinically diagnosed with depression. So this is
16 really affecting their emotional and psychological well-
17 being.

18 This overhead is a little bit difficult to read,
19 but I want you to see the fact that these people really have
20 a pretty positive outlook on life. Eighty-eight percent of
21 them think that they--they agree, strongly or somewhat, that
22 they generally cope pretty well with this disease
23 emotionally, which is good news for us. I mean, we're very
24 happy to hear that. What is more disturbing, though, is to
25 look down the list a little bit and see that they're

1 actually consumed a large part of the time worrying that
2 their disease is going to get worse. And they're
3 embarrassed by it and they're stuck with very serious
4 feelings of being unattractive. So even though they feel
5 that they're doing pretty well emotionally, they're still
6 dealing with some really difficult issues. And over half of
7 them often, as it shows here, are depressed just because of
8 their skin disease.

9 This is, again, within the severe psoriasis
10 patients, and just to really give you some numbers as to how
11 many of them have experienced this public discrimination.
12 Twenty-four percent of them have been asked to leave,
13 refused treatment, something like that, at a hair salon, and
14 20 percent have been asked to leave a pool. So I think that
15 those numbers kind of speak for themselves. Again, this is
16 the severe psoriasis patients, and they do experience that
17 more often.

18 Again, the severe psoriasis patients spend an
19 average of 25 minutes a day, 24 minutes a day, treating
20 their skin. I have a difficult time finding 25 minutes,
21 extra minutes in the day to do pretty much anything, and I
22 think that we're all like that. And they spend 25 minutes a
23 day just treating their skin--lotions, bathing, oils,
24 topical treatments.

25 The costs come in when it comes to physician

1 visits. It shows that these folks are in the doctor's
2 office just for their psoriasis an average of five times a
3 year, and 22 percent of them, three to five times a year, 12
4 percent of them between six and ten times a year. So,
5 obviously, the health care costs really add up.

6 We asked our entire membership what bothers you
7 the most about psoriasis treatment right now, and this is
8 where it really drives home the point that they are not all
9 being seen by Alice Gottlieb. Forty percent of them are
10 most bothered by the fact that the treatments don't work.
11 Plain and simple, they just don't work. The ones that are
12 using something that seems to be helping them, the treatment
13 is time-consuming, whether it's smearing some topical agent
14 over, you know, a large percentage of their body or bathing
15 or going to the doctor's office four times a week for a PUVA
16 treatment. These are the things that they're dealing with.

17 That's my last overhead.

18 The other thing that I want to share with you is
19 that we did have a meeting in August where we were glad to
20 have Dr. Schwieterman and Dr. Wilkin with us to give us kind
21 of--some overview of some of the issues that you're dealing
22 with right now, and they indicated that they did want to
23 hear more from patients and more what the patients were
24 going through. So we did a survey in our newsletter, and we
25 asked them some of these questions and got a very good

1 response back, and I have kind of a summary of that. I want
2 to share some of those with you.

3 One of the questions we asked them was: You want
4 a drug that clear your psoriasis, obviously, but how do you
5 balance that with the risk of side effects? And one answer
6 that we got kind of summed it up: I would like the
7 treatment to be available even if the side effects are
8 considerable, as long as they're well documented so my
9 doctor and I can make an educated decision for ourselves.
10 This was not a plant. This is a verbatim response, I
11 promise you. A drug should not be banned or prevented from
12 being on the market due to bad side effects as long as those
13 side effects are well known.

14 One interesting result we had was how would you
15 feel about a product that offered only 50 percent clearing
16 but had little or no side effects, because this is something
17 that many people experience anyhow, and it's also something
18 that was indicated was being considered. So we asked them
19 that, and 90 percent of the respondents--and we have some--
20 it depends on which question you're talking about, but we
21 had between 50 and 75 respondents here, so it's a small
22 sample, self-selected, subjective, I acknowledge that, but
23 we feel it's pretty representative, anyhow.

24 Ninety percent of them felt positively that a
25 product that offered them 50 percent clearing with little or

1 no side effects would be of value. They felt very
2 positively about that, and only 10 percent of them felt that
3 that wasn't worth their trouble. If I speculate, I'm
4 guessing that those 10 percent probably have very, very
5 severe disease.

6 Would you take a drug that almost guaranteed your
7 psoriasis would clear if there was even a very small risk of
8 potentially life-threatening side effects? How does the
9 patient evaluate that? How did they look at that?

10 Well, this one is a little more complicated.
11 Forty--adding in my head, not adding so good, 40 percent of
12 them said yeah, they'd consider it or they'd definitely do
13 it. Sixty percent of them said no. So I'm not giving you a
14 clear position here. What I'm saying is that it's very,
15 very split.

16 What about a product that stopped psoriasis from
17 itching but did not clear your lesions at all? Again, 50
18 percent think that would be great, and 50 percent of them
19 think that's not even worth their time.

20 Does it make sense for a person with moderate to
21 severe psoriasis covering at least 10 percent of their body
22 surface area to participate in an experimental drug trial
23 with a small but very real chance of potentially life-
24 threatening side effects? And, believe me, the answers I
25 got in these questions were very well thought out, very

1 lengthy, very passionate. Fifty-one percent thought it made
2 sense and such trials should be available; 49 percent felt
3 that it did not make sense for a person with that degree of
4 psoriasis.

5 Now, if it seems like I'm not being totally
6 helpful to you because these aren't going to one side or
7 another, what I'm trying to indicate is that the choice
8 needs to be available because the patients need to be making
9 this decision for themselves.

10 Just a couple of other verbatim comments from
11 folks on that particular question of would you take
12 something that had life-threatening side effects as a
13 potential:

14 I'm now taking methotrexate, and I didn't get any
15 guarantee with it, either. Again, it must be a risk-based
16 decision, but many of us are already opting for the more
17 dangerous regimens without assurance of results.

18 The other side of the coin: No. I also wouldn't
19 drive drunk on a dark and dirty night on an empty highway.

20 No, I would never do this.

21 Absolutely yes.

22 So I guess the point that I'm really trying to
23 make is that as you're considering these issues with
24 clinical trials and approving therapies for psoriasis and
25 how to label therapies for psoriasis, two things seem really

1 clear to us. The first is that there is a very clear and
2 tremendous need for more therapeutic options, both more
3 effective options and safer options. Someday we're going to
4 ask you for both, but right now we're going to look for one
5 or the other. We would hope that as you consider this you
6 will do everything you can to encourage and not discourage
7 more research and development in this area, and then that
8 you would allow patients and their physicians maximum access
9 to these new therapies and let the patients with full
10 information, well-documented information, make the decisions
11 for themselves.

12 CHAIRMAN McGUIRE: Thank you.

13 Are there questions from the committee? Yes, Dr.
14 Kilpatrick first?

15 DR. KILPATRICK: Thank you, John.

16 I really do feel compassion for patients with
17 psoriasis, but in the pursuit of scientific objectivity, I
18 have to point out that less than 50 percent of your members
19 responded to the survey. I'm speaking as a statistician
20 who's concerned about extrapolation from a sample to the
21 population, and I don't consider a response of less than 50
22 percent to be representative because of potential bias.

23 MS. ROLSTAD: I'm not a statistician, so I'm
24 certainly not going to argue that point. What I can say is
25 that we've done some initial comparison of the results of

1 this survey with other published and validated surveys and
2 studies, and they seem to be consistent.

3 CHAIRMAN McGUIRE: Dr. DiGiovanna?

4 DR. DiGIOVANNA: As a dermatologist and clinical
5 researcher who has taken care of and done psoriasis patients
6 for many--too many years, and done clinical studies also, I
7 can really empathize completely with just about everything
8 that you said.

9 One of the rarest things you'll ever find is me
10 arguing with a statistician or an epidemiologist. However,
11 I think that as a committee member I'm very pleased to see
12 data or numbers, and I think that in this environment where
13 individuals with a variety of conditions want various types
14 of access to the government and to the moving ahead of
15 various issues, I think it's very helpful to know the
16 numbers that you're talking about. And I think that it's
17 very important to me to know that 50 percent of almost
18 20,000 people with psoriasis do want to make a decision
19 where their life may be threatened if they are so severely
20 disturbed by this condition in an effort to move the field
21 ahead. And I know that because I deal with those people all
22 the time.

23 So I think this sort of information is helpful for
24 the committee.

25 CHAIRMAN McGUIRE: Other comments from the

1 Advisory Committee or from the agency?

2 [No response].

3 CHAIRMAN MCGUIRE: Dr. Plott?

4 MS. ROLSTAD: I have one final thing to say, which
5 is that I'm going to be handing out something later. The
6 copy machine is broken, and so I can't give it to you right
7 now. But it is a consensus statement from our Medical
8 Advisory Board, and I can't presume to speak for them, so I
9 wasn't able to present that. But it's a statement from our
10 Medical Advisory Board that addresses many of the issues
11 that you're addressing today, and more specifically in terms
12 of clinical trials. So I'll hand that out to you later.

13 Thank you.

14 DR. SCHWIETERMAN: Tara, could we get copies of
15 your overheads?

16 MS. ROLSTAD: Absolutely. I'll send those to you
17 when I get back. Absolutely.

18 CHAIRMAN MCGUIRE: Okay. I'd like to introduce
19 Dr. Plott, who is representing Schering-Plough.

20 DR. PLOTT: My name is Todd Plott. I'm the
21 Director of Clinical Research at Schering-Plough Research
22 Institute, and I represent Schering-Plough.

23 I would like to address the issues regarding how
24 we're going to make decisions regarding effectiveness in our
25 clinical trials. We're faced in the pharmaceutical industry

1 with demonstrating effectiveness, and we need to do that
2 today. As you've heard, there's a great need, and we have
3 to--or we should agree on some general measurements to use
4 in our clinical trials in order to do that..

5 I'd like to begin with introducing you to several
6 issues and responding possibly to the discussion that began
7 last spring at this Advisory Committee.

8 First, is there a justification for using multiple
9 target lesions? And with regard to global evaluations, what
10 kind of scale might be ideal and how should we use the
11 global evaluations in our clinical trials? Also, with
12 regard to clear or almost clear criteria, what should the
13 role of this criteria be in our clinical studies?

14 Looking at target lesions--and target lesions are
15 picking one spot, one psoriatic plaque and looking at that
16 plaque--this is probably the best clinical evaluation that
17 we have of the drug's effect today, the best evaluation that
18 we all agree on, using a representative area on a psoriatic
19 plaque, or maybe even the entire plaque, to get an idea of
20 the overall effect of the drug. And this evaluation, the
21 target evaluation, consists of looking at plaque thickness,
22 scale, and erythema.

23 Typically, we just this on a 0 to 3 scale for each
24 of these three signs, meaning none, mild, moderate, or
25 severe. We combine these three signs into a 0 to 9

1 composite score that we feel best characterizes this overall
2 effect of the particular drug in this target area.

3 But is there a justification for looking at more
4 than one target area? Should we be sampling from different
5 areas of the body? And why should we do that? If we decide
6 that there is justification for more than one target lesion,
7 we should provide data for why that's true. And I have
8 looked at a clinical study that was performed by Schering.
9 This is a multi-center, randomized, parallel group study
10 comparing active treatment A and active treatment B. This
11 is in moderate to severe psoriatic patients for three weeks.
12 And it's important to realize that each patient had one
13 target lesion evaluated, either in the knee-elbow region or
14 one other region. These represent the sum of the target
15 lesion score or the composite score, and this is the mean
16 percent improvement at endpoint.

17 It's important to point out that even though we
18 selected endpoint because we feel this is important, these
19 results were representative of this clinical trial. And
20 what's important to see on this slide is this particular
21 number, that there is a statistically significant difference
22 between the effectiveness of drug A at the knee and elbow
23 area compared to other sites, that other sites, like the
24 trunk, are much more responsive than knee and elbow lesions.
25 And we know that from our clinical experience, but that was

1 not true for treatment B.

2 So we believe that in using target lesion
3 evaluations in clinical studies that there is a
4 justification for doing two target lesion evaluations, one
5 either at the knee or elbow sites and then one at these
6 other body sites, either non-knee or -elbow or trunk areas.
7 We believe that these differences in responsiveness may
8 depend on the drug that's being studied, and that the--push
9 this up just a little bit--that the way we're going to
10 select how our drug is--if our drug is effective or not--
11 this is the primary endpoint--is to take an average of these
12 target--sum of the target lesion scores and to use that and
13 compare between, say, an active and the placebo or vehicle
14 in our clinical study.

15 It's important, after saying all this about the
16 target lesion, to emphasize that the target lesion
17 evaluations do not replace the global evaluation--the global
18 evaluation meaning that the physician stands back and looks
19 at the patient and says you're improved, you're not
20 improved, your psoriasis is mild today, it's moderate. And
21 the global evaluation that we use that is probably most
22 useful looks at a patient to say today you're mild, today
23 you're moderate, and then compare that retrospectively in a
24 statistical way to what the patient's disease status was at
25 baseline.

1 The problem with that is that there's no standard
2 tool that exists. You've already heard a discussion about
3 the PASI scoring, and that might be an example of that. And
4 there's no agreement on how to use this global evaluation.
5 But the retrospective or memory scales where a physician
6 says you're 50 percent improved from baseline, you're 70
7 percent improved, may not be reliable because we can't
8 expect that every physician for every patient is going to
9 remember 12 weeks ago what that patient looked like. So
10 that the ideal would be some type of evaluation that
11 utilized body surface area and severity. But we feel that
12 this is probably most useful as a secondary variable in our
13 clinical study, something that's supporting our primary
14 variable.

15 With regard to using the clear or almost clear
16 criteria, we believe that this can be done with a target
17 lesion score, but it may not necessarily provide additional
18 information over what we have found in our target lesion
19 score. That might be because we're basing it on the target
20 lesion.

21 It's certainly useful for labeling, but it should
22 be a secondary not a primary variable because therapies that
23 provide improvement but not clearing can still be useful to
24 patients, as you've heard, and that the clear or almost
25 clear criteria should not be based on the global evaluation,

1 because treatment to the point of clearing could expose the
2 patient to unnecessary toxicity and unnecessary risk in
3 pushing patients to that point in a clinical trial.

4 Let me offer another example based on data, and
5 this is looking at the same clinical trial I introduced
6 earlier. Again, at endpoint, if we looked at the sum of the
7 target lesion scores and defined that the sum of these
8 target lesions scores for all three of those evaluations
9 being 1 or less than 1 was the same as saying clear or
10 almost clear, we actually found that the results in this
11 trial would have been identical to what was seen with target
12 lesion scores. And, interestingly enough, knees and elbows
13 still responded differently.

14 Let me conclude with the fact that we have offered
15 evidence here to support our clinical experience that knees
16 and elbows respond differently than other body sites, and
17 that because of this fact, it may justify the use of two-
18 target lesions in clinical studies; that the sum of the
19 target lesions can be averaged and used as our primary
20 efficacy endpoint, the measurement that we use to determine
21 if our drug is effective.

22 And for our global evaluations, because there's no
23 accepted standard--you've heard some of the controversy and
24 probably will hear more later--there should be some sort of
25 overall evaluation included in the trial, but it should be

1 conducted as a secondary efficacy endpoint. And the use of
2 the clear or almost clear criteria should also be a
3 secondary endpoint, and we feel that it may be based on the
4 target lesion scores.

5 Thank you.

6 CHAIRMAN MCGUIRE: Are there questions for Dr.
7 Plott? Dr. Schwieterman?

8 DR. SCHWIETERMAN: I guess we're going to get into
9 this later this afternoon, but--and having discussed this
10 earlier, I think there's a lot of attraction of target
11 lesions for determining bioactivity or even efficacy,
12 particularly in early drug development. But I guess the
13 thing I'm struck by by this is that you're measuring the
14 global evaluations at the same time that you are measuring
15 the target lesions, and using the global evaluations as
16 supportive data to what is, in fact, a more limited
17 although, I think by your argument, perhaps, some more
18 sensitive and meaningful indicator.

19 But is that, in fact, the case? Wouldn't it make
20 equal sense to measure global lesions as a primary endpoint
21 using target lesions as supportive data, with the argument
22 being that the global evaluation is, in fact, a more
23 comprehensive view of the patient's overall status; and that
24 by use of these representative target lesions, you could
25 confirm and even amplify on what you thought you had

1 measured by a global score?

2 DR. PLOTT: I would agree that the use of a global
3 evaluation would be more helpful if in the clinical trial
4 all lesions are being treated. And I think that if we make
5 that assumption, a global evaluation could be more
6 interesting.

7 The problem is that there's not a global
8 evaluation that most people can agree on and recognize and
9 understand as this is a helpful evaluation for me in my
10 clinical practice or in my everyday work doing clinical
11 trials.

12 So I'm left today with what can I use right now in
13 my clinical studies in order to demonstrate efficacy for
14 this group, and today the best tool that I have in my box is
15 the target lesion evaluation, and then possibly coming up
16 with some sort of global that should support what I found in
17 my target lesions.

18 DR. SCHWIETERMAN: I'll just make one comment,
19 because I think we'll defer it to this afternoon. I think
20 this bears more discussion because I think that there is a
21 role for target lesions in there. The thing that troubles
22 me, though, is the uncertainty that you associate with the
23 global lesions is certainly obviated by use of a target
24 lesion, but then that introduces another uncertainty that is
25 equally troublesome to me and actually documented by your

1 presentation in that target lesions may not, in fact, all
2 behave the same and, therefore, be representative of how the
3 patient is doing. But we can discuss this later.

4 CHAIRMAN McGUIRE: Dr. Kilpatrick?

5 DR. KILPATRICK: Thank you. I am more or less on
6 the same track. I see this as an important issue. In my
7 terms, the presenter's conclusion is that there's the
8 possibility for heterogeneity among different sites. And I
9 don't see why that should not be taken into account together
10 with the evaluation of a PASI or composite score.

11 May I ask, Dr. Plott, I understood that you said
12 that there was one target site per patient.

13 DR. PLOTT: In the clinical study that we
14 presented.

15 DR. KILPATRICK: In the clinical study, yes.

16 DR. PLOTT: That's correct. And there were not
17 two sites on patients, and we looked to see. This was a
18 parallel study.

19 DR. KILPATRICK: But were the--these psoriasis
20 patients had the same severity, and were they randomized
21 into the two treatment arms?

22 DR. PLOTT: Yes, these--in order to be enrolled in
23 this clinical study, the sum of these target lesion scores
24 had to be at least a 6, with at least 2 for scaling. And,
25 of course, they were randomized into the clinical trial in a

1 parallel manner.

2 DR. KILPATRICK: Thank you.

3 CHAIRMAN MCGUIRE: Dr. Duvic?

4 DR. DUVIC: I just wanted to make the point, with
5 the topical therapy, if you are only treating certain
6 lesions, others can occur during the course of treatment
7 which will mess up your global evaluation. So I think it's
8 very difficult to use a global evaluation as a primary
9 indicator for topical treatment of a skin disease.

10 DR. PLOTT: If I could comment on that, I think
11 that it's important that topical treatments and systemic
12 treatments, at least in late-phase development, be treated
13 somewhat similarly because topical treatments can have
14 systemic effects, and we should be treating all lesions with
15 our topical agents.

16 DR. DUVIC: I think both are important variables,
17 but they give it different information, and I agree with
18 you.

19 CHAIRMAN MCGUIRE: Other questions? Dr. Weiss?

20 DR. WEISS: No. I think the point I was going to
21 make has already been said by Dr. Duvic, which is--you know,
22 I was listening to your presentation and becoming somewhat
23 confused about how you can use indicator lesions. But I
24 realize, I think, it was because of my frame of reference
25 that most of my experience has been with very systemic,

1 potent type of immunomodulatory agents where it wouldn't
2 make any sense to look--at least in my mind--at a single
3 target lesion because the material, this therapy, should be
4 broadly disseminated to all parts of the body; and,
5 therefore, you'd want to look at all lesions and to be able
6 to evaluate that in the context of the overall risk to the
7 patient, which isn't, you know, also very--you know, isn't
8 compartmentalized in a certain area.

9 So I think it speaks to the issue which we'll
10 hopefully get into when and if we start our actual questions
11 to the committee on whether or not it's even appropriate to
12 categorize therapies as topicals, topicals with systemic
13 absorption, and then it goes to, I guess, how much systemic
14 absorption, and then the systemic therapies, because there
15 seems to me in my mind, as I'm hearing all this, some very
16 pertinent maybe differences in the way those therapies
17 should be evaluated.

18 CHAIRMAN MCGUIRE: Dr. Weiss, you're really
19 pointing out a cultural difference. I mean, we're really
20 talking about two different things, and we'll be sensitive
21 to that.

22 DR. PLOTT: If I could comment, I think that
23 topical agents, particularly when they're applied to
24 diseased skin in the case of psoriasis, there's a compromise
25 in the barrier function. We can get systemic effects with

1 topical agents, even when we're not treating the entire
2 body, and certainly we run the risk of systemic effects when
3 we treat larger surface areas.

4 CHAIRMAN MCGUIRE: Dr. Wilkin?

5 DR. WILKIN: I would just like to add that, in
6 general, in Phase 3 trials, unless there is a compelling
7 reason not to, we like to see topical agents applied to all
8 involved areas of psoriasis.

9 CHAIRMAN MCGUIRE: Thank you.

10 All right. It's 9:42. I think it would be
11 appropriate to take a break until 10 o'clock, so let's
12 reconvene at 10:00.

13 [Recess.]

14 CHAIRMAN MCGUIRE: If the members of the Advisory
15 Committee could come to the table, I'd like to start the
16 session.

17 [Pause.]

18 CHAIRMAN MCGUIRE: Where is the committee?

19 DR. KILPATRICK: I'm here.

20 CHAIRMAN MCGUIRE: Many of you did not attend the
21 March 20, I think, meeting on psoriasis evaluation of
22 therapy and evaluation of severity of the disease. You can
23 access that, if you have not already found it. It's on the
24 Web. Go to the FDA home page. Go to dockets, go to
25 committees, go to dermatology, and there you'll find it.

1 There are 194 pages, and we had two expert advisors, Rob
2 Stern and Mark Lebwohl. And you'll be interested in reading
3 their testimony. Much of it was on PASI and inter- and
4 intra-observer variation.

5 What I'd like to do now is go to page 3 of the
6 agenda. Much of page 2 has to do with the history and the
7 OTC monograph, which I don't believe we have to deal with,
8 unless I'm coached otherwise.

9 The agency has outdone itself in generating
10 questions, and I may have had something to do with this
11 because often I will take one of their questions and
12 deconstruct it into two or three questions which are easier
13 to deal with. But I think they've beat me at that game.

14 Later this afternoon, I will have a brief summary
15 of the March meeting, which I will share with you, because
16 some of these points came up in March and were dealt with
17 then.

18 Item 1 is claims and qualifiers of claims. Now,
19 let me tell the committee that I will just ask people
20 arbitrarily to deal with these issues, so stay with me.

21 Recognizing that the objectives in therapy may be
22 varied in psoriasis, and that many treatments do not address
23 the fundamental process, what would you consider as
24 appropriate claims or qualifiers of claims related to
25 psoriasis therapies? a) Claim for the treatment of

1 psoriasis; b) Claim for the relief of specific signs and/or
2 symptoms of psoriasis (scaling/hyperkeratosis, redness,
3 plaque thickness, itching; c) Qualifiers relating to the
4 types of psoriasis (plaque, erythrodermic, pustular,
5 guttate).

6 Who'd like to step up? John? This is Dr.
7 DiGiovanna.

8 DR. DiGIOVANNA: Thank you. Yes to all of them.
9 I think that there are some agents that are less than
10 effective in--in fact, most agents probably are not as
11 effective in clearing as we'd like them to be but are useful
12 at various times. So those agents that might not be as
13 effective could conceivably be claimed for the treatment of
14 psoriasis.

15 On b), there are, for example, a number of
16 individuals who've raised the issue of pruritus, which is
17 frequently a concern. An antihistamine or another agent
18 that was an anti-pruritic could relieve that, and I could
19 see that being used as a claim while it might not have
20 effects on the other symptoms of psoriasis.

21 And certainly we all know that there are different
22 types of psoriasis that are differently responsive. If you
23 had a patient with erythrodermic psoriasis or pustular
24 psoriasis, you might not want to blast them really hard with
25 PUVA. And I'm sure there are a number of other variations

1 which would relate to having a utility to qualifying
2 specific types of psoriasis in association with a particular
3 treatment.

4 CHAIRMAN MCGUIRE: Now, as some of you will
5 recall, the committee in March considered scaling to be one
6 of the least reliable monitors of psoriatic activity, A,
7 because it's so easy to remove with--well, it's quite
8 variable and it's easy to remove, and it almost--it often
9 has an inverse relationship with redness because if the
10 patient has a chronic lesion, a chronic plaque with thick
11 scale, once the scale is removed, we now have a red lesion
12 where we had a white lesion before. And so there is that
13 inverse relationship which confuses the data in the PASI if
14 you weight all the elements equally.

15 Fred, I think you were one of the people who felt
16 that that plaque thickness, which is a criterion that is
17 probably most difficult to measure, is the best indicator of
18 psoriatic activity. And Dr. Krueger is going to speak to
19 that this afternoon.

20 Did you wish to comment, Dr. Miller?

21 DR. MILLER: Yes. I would just comment on the
22 scaling. It was interesting in the NPF presentation that
23 scaling, I think, was the highest percentage of people--that
24 was their complaint. And yet when we talk about scaling, we
25 say that that is the easiest aspect of the psoriatic plaque

1 to remove with therapy and it can be the vehicle alone. And
2 I'm wondering in the NPF study if the scaling is not the
3 amount of scale that people see on and about themselves as
4 opposed to on the plaque itself when they complain about
5 scaling being a problem. Is it the scaling that I see or
6 the scale that I see, or is it the scale that I leave about
7 that really is an affliction of the disease?

8 CHAIRMAN McGUIRE: Ms. Rolstad, do you have--

9 MS. ROLSTAD: I think it's probably both. But I
10 think--

11 MS. RILEY: Would you use the microphone please?

12 MS. ROLSTAD: This is fine. I was trying to avoid
13 that little visual picture.

14 I think the scaling that people leave behind or
15 about or around themselves is obviously of a bigger social
16 concern. I think there's probably something to be said,
17 though, for even if you can use a lotion to get rid of the
18 scaling, how quickly does it come back and how much does it
19 come back, how voluminously does it come back. So I think
20 it's probably both of those things, actually.

21 CHAIRMAN McGUIRE: Dr. DiGiovanna?

22 DR. DiGIOVANNA: I can dramatically recall a
23 particular patient who would complain bitterly when her
24 psoriasis was active about leaving what she called
25 "croutons" all over the house and trying to follow them

1 along with a vacuum cleaner. Patients get very, very
2 disturbed when the scale is in the environment on a
3 consistent basis.

4 CHAIRMAN MCGUIRE: So we're trying to make some
5 distinction between adherent scale and shed scale.

6 Dr. Duvic?

7 DR. DUVIC: Although scale is easy to get rid of
8 with moisturizing and vehicle, no psoriasis treatment would
9 be effective without reducing it. So it's a necessary thing
10 to clear, to improve psoriasis, but it is removable with
11 non-drug agents as well as medication. I think it usually
12 has to do with what vehicle you put your drug in. And it is
13 a manifestation of how fast the skin is growing, so it's an
14 indicator of hyperproliferative rate.

15 CHAIRMAN MCGUIRE: Okay. I'm satisfied with b).

16 Karen?

17 DR. WEISS: There wouldn't be agents, something
18 that just improves scaling, is there such--there are things
19 that do improve scaling--

20 DR. DUVIC: Moisturizers.

21 DR. WEISS: Okay. But that would not be a--that
22 would be something for a symptomatic thing, but it would not
23 be an appropriate claim, so to speak, for people with
24 psoriasis, just an ancillary therapy that they would be
25 using.

1 DR. DUVIC: No. I think patients with psoriasis
2 use moisturizers to improve scaling.

3 DR. WEISS: Okay. But I guess what I'm talking
4 about is if you're talking about specific agents that are
5 being evaluated in psoriasis, something that simply has an
6 improvement in scaling would be a useful thing to have and
7 to have labeled. But what does that say, though, about the
8 rest of the lesions and the rest of the disease?

9 CHAIRMAN McGUIRE: Karen, I think what you want us
10 to say is that there is a hierarchy of criteria and scale
11 is--the reduction of scale is important, but it is not as
12 important as reduction in area and reduction in plaque
13 thickness. Area and plaque thickness are probably going to
14 turn out to be our two most important criteria. But that is
15 not saying that we're ignoring modalities that reduce scale.
16 It's just that that is not a dependable criterion for the
17 treatment of psoriasis. It's easy to do. It's a necessary
18 part.

19 Dr. Duvic?

20 DR. DUVIC: Although it's easy to do, it is
21 necessary.

22 CHAIRMAN McGUIRE: It's necessary.

23 DR. WEISS: But it's something that to me doesn't
24 seem to be necessarily unique to psoriasis. I mean, there
25 are a lot of other types of conditions that produce scaling,

1 and moisturizers are used in lots of different settings.

2 CHAIRMAN MCGUIRE: Dr. Wilkin, did you have a
3 comment?

4 DR. WILKIN: Yes, actually, Dr. Weiss was going
5 down the pathway that I was thinking about, and that is,
6 let's say a drug is being developed for psoriasis, and it
7 turns out it really does very little for the plaque
8 thickness, for scaling, or for erythema, but does extremely
9 well for the scaling of psoriasis, really keeps the scaling
10 way down. Would the committee think of that, a scaling of
11 psoriasis, as a sufficient indication for that drug product?
12 Or would the urge be for the sponsor to evaluate other forms
13 of hyperkeratosis to see if it's more of a broad spectrum
14 anti-scaling agent?

15 CHAIRMAN MCGUIRE: Would anyone like to respond to
16 that? Dr. Miller?

17 DR. MILLER: I would just say that if the scale
18 alone is reduced, I think you can't necessarily attribute it
19 to the pharmacologic action of the medication, because as
20 Madeleine said, we see reduction of scale with bathing and
21 with various emollients and moisturizers. So you'd have to
22 have, I think, the other criteria affected to say, gee, this
23 is the pharmacologic action of the medication or the
24 preparation.

25 CHAIRMAN MCGUIRE: Dr. Rosenberg?

1 DR. ROSENBERG: Well, I think, Jonathan, the
2 answer would be yes, and I think that's one of the problems,
3 as I see it, with the PASI which lumps all these criteria--
4 the redness, the thickness, the scaling--and treats them the
5 same as the numbers. And I think--well, Dovonex for one. I
6 think the Vitamin D products are more effective at reducing
7 scale than they are redness and so forth. But I think, yes,
8 I think absolutely, I think it would clarify things and help
9 the physician making a decision, help the patient work with
10 the physician if it said right up this is what it's good for
11 and we've shown that. And I think that someone who has an
12 agent that's good for scaling should not be held to a
13 redness and so forth--if that person--if that company were
14 willing to accept a limited indication. But you can be sure
15 that that's not going to be an acceptable monotherapy
16 because patients will want more than that. I would want
17 more than that.

18 CHAIRMAN McGUIRE: John, did you have--Dr.
19 DiGiovanna?

20 DR. DiGIOVANNA: Yes, I think Dr. Rosenberg said
21 in essence what I was going to say. What I would like to
22 say is that I think that from my perspective psoriasis is an
23 extremely variable disease, not only variable over time and
24 in individual, but I think that the types--the way it is
25 amenable to treatment and the way that it is treated is by

1 using many different modalities, either at different times
2 or together at the same time. And I think having many
3 modalities allows the dermatologist at least some, if not
4 very good, ability to control the disease. And I think
5 that, for example, if there was an agent that was extremely
6 effective for either the pruritus or for the scaling and did
7 very little for the other manifestations, I think it would
8 be useful.

9 So I think that when we think about how to
10 evaluate psoriasis for the purpose of having a drug
11 approved, we may need to have different ways of evaluating
12 psoriasis for a topical and a systemic, certainly, but also
13 in the early phases and the late phases. And it very well
14 may be that if some particular lipid emollient or some sort
15 of agent was extremely effective for the scaling, I think
16 that would be useful. And I think that if we cast it in
17 stone now, every product that has a claim that does not
18 fulfill all of these criteria, I think it conceivably could
19 exclude some products.

20 DR. SCHWIETERMAN: Dr. McGuire, if I could just
21 elaborate on--

22 CHAIRMAN MCGUIRE: Identify yourself, please.

23 DR. SCHWIETERMAN: I'm sorry. Dr. Schwieterman
24 from CBER. The claim structure actually is something
25 relatively new to the agency, and I think there needs to be

1 a little bit of a perspective on this. We're writing a
2 guidance document here for the benefits of patients and
3 industry so that expectations can be clear and standards can
4 be high or set or standardized, whatever, so that everybody
5 knows what the rules are. But that's not to say that we
6 would reject things that aren't in these particular claims.
7 So perhaps something to keep in mind here is what would be a
8 reasonable hierarchy of claims to put into a guidance
9 document which would not imply that other claims lesser than
10 that, say a scaling agent that had no toxicity--I don't
11 think anybody on the FDA staff would object to a non-toxic
12 therapy that reduces scaling. That clearly would be a
13 benefit. But is that claim alone something that ought to be
14 put to the guidance document given that there are so many
15 other things in psoriasis that need to be addressed?

16 It's sort of a rhetorical question. We could put
17 it in there. But I think we just have to consider it in
18 that guise.

19 CHAIRMAN McGUIRE: Is the agency comfortable with
20 how we've handled 1 a) and b)?

21 DR. WEISS: Just to summarize, then, if we had an
22 agent that maybe only worked in scaling or best in scaling
23 and maybe next in pruritus but not in the other areas, one
24 could potentially have a label that says: Product X is
25 indicated for the treatment of psoriasis to reduce the

1 scaling and pruritus, and, you know, it's only been studied
2 in the context of other agents. We'd put that in, perhaps,
3 that it's not to be used as a--you know, it's not--it can be
4 used or it should be used in conjunction with, and whatever
5 was studied. Some type of working like that would probably
6 be in general terms acceptable?

7 CHAIRMAN MCGUIRE: Yes, I would turn that around
8 and say that I suspect if a sponsor had a product that only
9 dealt with scaling and didn't affect the thickness and area
10 of involvement, the sponsor would not be very pleased with
11 the product. I mean, but that's not for me to decide.

12 John? Dr. DiGiovanna?

13 DR. DIGIOVANNA: I think the way I was reading
14 these questions and the way I would interpret it would be I
15 think would think if I read a labeling claim for the
16 treatment of psoriasis, I would want to see the psoriasis
17 studies having been done to treat the psoriasis, as was
18 discussed at the prior meeting, with the hierarchy of
19 expectation that there would be improvement in the thickness
20 of plaque and all of the other parameters, however that
21 would be studied.

22 However, the way I read b) is a claim for a
23 specific sign. So I could see reading the label product
24 useful for the itching of psoriasis or for the scaling
25 whereby the expectation there would be that it was not an

1 agent that we would expect to treat the psoriasis but to
2 treat that specific sign. That was the way I was reading
3 it.

4 DR. WEISS: Thank you. That's, I think, more or
5 less what I was trying to get at. I just didn't phrase it
6 well, so thank you. That's very helpful.

7 DR. DiGIOVANNA: And you're right. It may or may
8 not be very effective. I know that. As far as for the
9 company.

10 CHAIRMAN McGUIRE: Qualifiers relating to the
11 types of psoriasis (plaque, erythrodermic, pustular,
12 guttate).

13 I think implied in question 1.a) is that we have
14 different modalities for treating these different clinical
15 expressions of psoriasis, and what is appropriate and
16 applicable for one may be contraindicated for another. And
17 does the agency want us to do anything more than indicate
18 that these types of psoriasis should be dealt with
19 specifically?

20 DR. SCHWIETERMAN: Yes, I guess we're looking for
21 general commentary on to what extent we need to delineate
22 claims with respect to the different types of psoriasis, or
23 is there less of a need to do that than we might think.

24 CHAIRMAN McGUIRE: Who would like to comment?

25 DR. DUVIC: You need to differentiate them.

1 They're different subsets of the disease.

2 DR. WEISS: And this will be addressed a little
3 bit more when we get to Section C, if we get to that today,
4 which is to talk about extrapolation between various types
5 of sub-populations of diseases. So we'll expand upon that a
6 little bit more in that part, but this is specifically for--
7 if we're talking about writing an indications statement on a
8 label, how descriptive to be.

9 CHAIRMAN MCGUIRE: Well, I think all of us who are
10 treating dermatologists deal with these clinical types quite
11 differently. And unless we specify otherwise, I think we're
12 talking about plaque disease today. And if you want to
13 expand that to other clinical forms, we can. The committee
14 is comfortable with that.

15 There may be three scenarios where sponsors may
16 request a claim of "maintenance of therapeutic effect": (i)
17 continuation of benefit after discontinuation of treatment,
18 (ii) improvement and then maintenance of beneficial effect
19 with prolonged treatment, and (iii) maintenance of relief
20 achieved by another therapy.

21 Maintenance of relief achieved by another therapy--
22 -I'm trying to imagine who wrote these questions, and I
23 haven't quite--

24 DR. WEISS: I think maybe the thought on that is
25 that there may be something that's quite a potent agent that

1 is not maybe useful for a maintenance type of therapy, but
2 can really quiet down--not really a flare, but, you know, a
3 very active part of the disease to the point then where it
4 may be more amenable to being treated with maintenance
5 therapies that are less toxic and are more useful in longer-
6 term type of therapies. So if that--

7 CHAIRMAN MCGUIRE: Yes, the first condition is
8 long-term--is remission of some duration in the absence of
9 treatment. Condition two is improvement and maintenance
10 that is sustained but requires prolonged treatment, that is,
11 there is no remission. And condition three is that the
12 benefit obtained by another therapy can be maintained by the
13 therapy at hand.

14 Please address whether these subsets are
15 substantially informative and specific.

16 b) It may be difficult to evaluate "continuation
17 of benefit after discontinuation of treatment" because of
18 the fluctuating nature of psoriasis and the lack of a
19 suitable comparator group (equivalent benefit usually not
20 attainable with placebo to provide a comparable baseline for
21 the posttreatment period). Is the "time to relapse"
22 adequately informative for the prescriber to be reported in
23 the Clinical Studies section of the label?

24 Please discuss the appropriate length of time to
25 be studied for establishing such a claim in each scenario.

1 Well, the committee has to help here. My view is
2 that these issues are easy to discuss and, practically,
3 extremely difficult to carry out in terms of evaluating
4 products.

5 Bill, do you want to take a swing at these?

6 DR. ROSENBERG: I think where we know something, I
7 think it should be said. I think where we know that
8 patients treated, X number of patients treated thus way,
9 that 50 percent of them were still clear after Y number of
10 months, or, conversely, if we know that relief of symptoms
11 lasts only while the medicine is being actively given, and
12 within a month of stopping, patients return to baseline. I
13 think when there is some knowledge, the approval process in
14 terms of what the package insert will say, you ought to say
15 that, I think without being in some sort of a straitjacket
16 where there's some things you say and don't say. These are
17 important things.

18 I think to the degree that they can come out in
19 clinical--in the pre-release clinical trial, it should be
20 said, and then I think the agency should be--I think it is
21 open enough so that if at Phase 4, once products are already
22 out, if companies will do comparative studies between one
23 treatment and another, and get them printed in journals
24 showing that the one treatment provided a longer benefit,
25 then I think they should be allowed to say that in their

1 advertising as well.

2 CHAIRMAN McGUIRE: You would respond affirmatively
3 to 2.a).

4 DR. ROSENBERG: Yes.

5 CHAIRMAN McGUIRE: And then b) It may be difficult
6 to evaluate "continuation of benefit after discontinuation
7 of treatment" because of the fluctuating nature of
8 psoriasis, it strikes me that's simply a population issue,
9 how many patients you're dealing with?

10 DR. ROSENBERG: These are things that can be
11 arrived at. With properly blinded studies and adequate
12 numbers, Jim, I mean, you'd get to know. You'd get to know
13 these things.

14 CHAIRMAN McGUIRE: So do you think that it would
15 be too difficult to evaluate continuation of benefit because
16 of fluctuation, or do you think it's achievable?

17 DR. ROSENBERG: It's achievable, and if it's being
18 done under blinded--if it's done under adequately blinded
19 conditions and with proper numbers, yes, I think so.

20 You know, I saw the data that Dr. Gottlieb
21 presented today. I had no problem understanding what she
22 was saying or believing what she was saying. I thought it
23 was important information, too. It would help doctors
24 trying to make therapeutic decisions.

25 CHAIRMAN McGUIRE: Please discuss the appropriate

1 length of time to be studied for establishing such a claim
2 in each scenario. And the scenario is the continuation of
3 benefit after discontinuation of treatment. How long would
4 you like to see clinical benefit maintained after the
5 treatment is discontinued?

6 Madeleine?

7 DR. DUVIC: Psoriasis patients want something that
8 they can put on their skin and the lesions will go away and
9 stay away forever. That's the gold standard.

10 What we don't know is how acceptable something is
11 if it's gone for three months or six months, and I think
12 three to six months being gone after treatment is
13 reasonable.

14 There are agents that we use regularly, that most
15 dermatologists use all the time for psoriasis that actually
16 make it worse. Steroids, for instance, which kill the T-
17 cells, make the psoriasis go away, but it comes back within
18 several weeks, and it's worse than it was when you started
19 in many cases.

20 You have no information on that in the literature,
21 but that's what happens in patients. They get tachyphylaxis
22 or they get worse.

23 So I believe that some information about the
24 remittive property of the medication would be helpful to
25 patients and doctors in choosing therapies once that kind of

1 treatment is developed.

2 DR. SCHWIETERMAN: So just so I have this
3 straight, if we were to have a short-term claim of X number
4 of months, a longer-term claim that we might call durable
5 benefit, say, in your eyes it would be appropriate for you
6 to pick a three- to six-month time beyond the short-term
7 benefit for that?

8 DR. DUVIC: I think with the systemic that has
9 risks, you want it to be probably three to six months, if
10 you could. Topicals people may tolerate a shorter time.

11 DR. SCHWIETERMAN: Because we recognize that
12 psoriasis is a chronic disease and patients have it for a
13 lifetime, and with some of the other chronic diseases we
14 study, we're looking for data in the one- to two-, even
15 five-year range on that. But perhaps that's unreasonable
16 for psoriasis. We're trying to come up with a standard that
17 we think is both reasonable and maximally informative to
18 patients. I just want to be clear that you're satisfied
19 with three to six months.

20 DR. DUVIC: I think you have to divide topical
21 versus systemic therapy for duration of remission here.

22 CHAIRMAN MCGUIRE: Implicit in Dr. Duvic's
23 comments was that not only do we have suppressive and
24 remittive therapy, we also have therapy that results in
25 relapse that's worse than the original disorder. And the

1 discontinuation arm will tell you about that.

2 DR. WEISS: In some of our chronic therapies, we
3 have--

4 CHAIRMAN MCGUIRE: This is Dr. Weiss.

5 DR. WEISS: --sorry--successfully managed to have
6 some of our sponsors, not necessarily on psoriasis, do
7 studies that are the randomized withdrawal type of study
8 design to look and see whether or not in different settings
9 where it would be--where it's unlikely that a single dose,
10 single course would make the disease go away and never come
11 back. But obviously those would be important things to
12 know, and so that's oftentimes a useful study design. I'm
13 just wondering if anybody's had experience with that in
14 psoriasis. Dr. Rosenberg said, well, if the studies are
15 proper--long enough and properly blinded, do you mean--and
16 to look at durability of effects, so do you mean something
17 such as like a randomized withdrawal type of study design?

18 CHAIRMAN MCGUIRE: Dr. DiGiovanna?

19 DR. DiGIOVANNA: I'm not quite certain about the
20 answer to your question, but the first point I wanted to
21 make is that if we had an agent in psoriasis that would give
22 us a five-year clearing rate, I think we don't have to be
23 here today, because there is no question about it that there
24 isn't anything available like that. And I think that
25 there's extraordinarily little, if anything, known, in my

1 opinion--and this is a very personal opinion, and many other
2 psoriasis--many psoriasis experts would disagree with me.
3 But in my opinion, there's precious little known about the
4 duration of remission after treatment with a variety of
5 different therapies.

6 In my own personal experience, I've had a lot of
7 experience in treating patients with retinoids for
8 psoriasis, and after following specific patients over more
9 than a decade, I have seen some patients consistently flare
10 very rapidly after stopping treatment and other patients
11 consistently have very prolonged, six- to 12-month
12 remissions after treatment. And I don't know if there is a
13 certain percentage where it's patient-specific and a certain
14 percentage where it is medication-specific. But I know of
15 very little in the literature that's really probed this in
16 any way.

17 So if that's the type of study you were talking
18 about, that would be useful. And the way I would envision a
19 study like this, in answer to point c) being done would be,
20 for example, at the termination of treatment, continuing the
21 patient without active medication, maybe on lubricants, and
22 then seeing the percentage of patients that relapse over
23 time to the point where they require other therapies, such
24 that by month two, 10 percent or 90 percent of patients had
25 to be put on a different therapy, or by month six, 10 or 90

1 percent has to be treated.

2 CHAIRMAN MCGUIRE: You're leading into Question 3,
3 definition of "remission."

4 DR. DiGIOVANNA: I didn't read that.

5 CHAIRMAN MCGUIRE: What?

6 DR. DiGIOVANNA: You're ahead of me. I didn't
7 read Question 3.

8 CHAIRMAN MCGUIRE: Well, I'm not far ahead. The
9 time to relapse in a given situation depends upon the
10 definition of "remission." Would "remission" be an
11 appropriate term for complete clearing or is it acceptable
12 for lesser degrees of improvement?

13 We discussed that at length in March, and most of
14 us felt that 100 percent clearing was too stringent a
15 criterion and that something like 75 percent, however we're
16 going to measure that, was closer to reality. Is that
17 everyone else's recollection of where we were?

18 DR. DiGIOVANNA: Yes.

19 DR. WEISS: Is it appropriate to speak about that,
20 whether it's 75 percent or 60 percent, whatever, as
21 remission? I mean, is the term "remission"--you know, it's
22 clear in certain diseases like oncology setting. Is such an
23 entity in existence in psoriasis, and would everybody know
24 what we're talking about if that terminology is used? Or is
25 it best to avoid those kinds of more subjective words?

1 CHAIRMAN MCGUIRE: Yes, well, we're not talking
2 about treating acute lymphocytic leukemia 75 percent. We're
3 talking about treating a chronic illness and returning it to
4 something that's 75 percent improved.

5 We have yet to define the criteria which will
6 measure the improvement, and that will take a while.

7 Dr. Wilkin?

8 DR. WILKIN: Perhaps there could be a dissociation
9 of the efficacy statement from the remission statement and
10 that when one is looking at efficacy, you could accept some
11 notion of almost clear, pretty much clear, in addition to
12 completely clear. But, again, when you're talking about
13 remission, I think implicit in that is the notion of how
14 long are you going to stay clear? I don't know of an
15 example of remission where how long do you stay, you know,
16 75 percent clear? Would it be possible to separate those?

17 CHAIRMAN MCGUIRE: Well, I think it would be
18 possible. I'm not sure that it does very much for us
19 because if we say that four months is the duration that we
20 would accept as remission, do you expect 100 percent
21 clearing for four months or 75 percent clearing for four
22 months? And so they're really integrated?

23 DR. WILKIN: Maybe Dr. Gottlieb could tell us
24 whether those folks were completely clear or whether they
25 had, you know, 50 percent or whatever.

1 DR. GOTTLIEB: I don't have--

2 CHAIRMAN McGUIRE: Take John's microphone or the
3 standing microphone.

4 DR. GOTTLIEB: These are published data. I just
5 don't know the exact details. But PUVA, they're published
6 actually in multiple sources, one of our papers that Jim and
7 I had, that's where that's from. Also, I remember the 50th,
8 the gold, JID edition where there was David Bicker's article
9 where he summarized experience with PUVA. But basically the
10 data are how to define when somebody is clear; basically
11 we're talking about 75 to 90 percent. It's not defined in
12 drops in PASI scores or whatever kind of scoring that one
13 uses. As people have pointed out, you don't go for 100
14 percent clearance because it generally doesn't exist.

15 And I'd like to point out in oncology, if
16 remission were 100 percent clearance, why are so many people
17 dying still of cancer after having been in remission? You
18 just can't find it. In the skin, you have the advantage
19 that you have a visible organ, and so you can see more. But
20 in oncology, you don't have that. So I would argue that
21 that doesn't exist either in oncology for most of the
22 oncologic--

23 DR. WEISS: It's just that there is an agreed-upon
24 definition. We all know that it doesn't mean you're cured,
25 but it just means that there's no evidence of disease. And

1 whether or not--I just think that if we can--we face this
2 with Crohn's disease, with rheumatoid arthritis, a lot of
3 other chronic diseases where people bandy around these
4 terminologies and use it in advertising and promotion. And
5 I just want to make--if we can be clear on what those terms
6 are--

7 DR. GOTTLIEB: Now, with these curves, the curves
8 that I showed you and the one in David Bicker's article--and
9 I'm happy to send--if you'd like, I'll send you the
10 articles. Basically you can pick whatever you want because
11 there are curves that show you proportion clear months after
12 treatment, and so if you want, rather than talking from our
13 not precise memories, basically one can actually--I'll give
14 you one. I'll send you the articles, and you can get how
15 it's defined there.

16 But in a practical sense, to be honest, since
17 we're talking about who's the ultimate consumer, it's the
18 patient, really. Basically when the patient wants some kind
19 of treatment is the time one can define relapse, and clear
20 is basically when the patient can--it's based on more
21 quality-of-life issues, I mean, where the patient could go
22 on the beach and they can wear their one-piece swimsuit or
23 their bikini. That's clear, whether there are 75 percent or
24 90 percent drops in whatever score one uses. But in
25 practice, how we defined it at Rockefeller, it would

1 basically be somewhere between a 75 and 90 percent drop in
2 PASI score.

3 CHAIRMAN McGUIRE: Dr. DiGiovanna?

4 DR. DiGIOVANNA: Dr. Gottlieb, I just want to
5 agree with your agreeing with me, and I'll make it a little
6 more specific, I think. I'd like to know what your
7 experience is. But in my experience, it's a more rare event
8 to take a patient with severe psoriasis and get them
9 absolutely, completely, totally clear. However, I look at
10 it more like asthma where it's a disorder that individuals
11 will have flares and will go from having maybe a little nail
12 pitting, a little scalp psoriasis, a little elbow or knee
13 psoriasis, to having an overwhelming debacle of psoriasis,
14 which then becomes under control and may stay in remission
15 for months.

16 So I think when they're talking clear here, and
17 they mean totally clear, isn't that a rare event in your
18 experience?

19 DR. GOTTLIEB: Yes. Totally clear, it's a rare
20 event. But clear to the point where they'll go wear a
21 bathing suit on the beach and wear skimpy shorts and a top,
22 not unusual. You can achieve that with cyclosporine,
23 methotrexate, acitretin, plus UVB. So I don't want to
24 belittle their ability--I also would like to point out that
25 in all of these, the implicit thing is that psoriasis is

1 fluctuating and vague and how are you going to get a handle
2 on it. The fact of the matter is if you look at patients
3 after cyclosporine cream and you stop in cold turkey--we're
4 talking about the severe psoriatic--there's nothing subtle
5 about how it comes back. I think that's an easy study to
6 look at. Within a month, maybe two months, they're all
7 going to go back to what they started as.

8 Basically there is nothing subtle about it. I
9 think that's easy to look at maintenance of remission when
10 you're dealing with cyclosporine. It is harder with PUVA
11 where the length of remission is so much longer. But when
12 you have the suppressive treatment, it's not hard to do
13 that. And, in fact, some of us are actually in the process
14 of designing studies to do exactly that because that's
15 really where the need is in moderate to severe psoriasis, in
16 how to maintain remission safely.

17 CHAIRMAN McGUIRE: I think everyone has made that
18 observation. It was in the original observation that came
19 out of Ann Arbor, and it hasn't changed since.

20 Dr. DiGiovanna, did you want to agree with
21 yourself again?

22 [Laughter.]

23 DR. DiGIOVANNA: Thank you, no. All I wanted to
24 say is maybe remission isn't the exact proper word, or if it
25 is, maybe we're talking about remission of the flare of

1 psoriasis and then coming back to the baseline.

2 DR. SCHWIETERMAN: Schwieterman from CBER. I'll
3 pick up. Is there usefulness, in your opinion,
4 distinguishing remission from complete clinical response,
5 given that what I'm hearing is that while remission may be
6 rare--100 percent clearing, that is--it may, in fact, exist.
7 And if we're establishing a hierarchy here of claims, even
8 though we don't have the agents now that do that, is it
9 possible or likely that there would be some agents that do
10 induce remission, in fact, while others might induce the 75
11 percent, the 90 percent clearing?

12 CHAIRMAN MCGUIRE: Dr. Krueger?

13 DR. J. KRUEGER: I would also like to split hairs
14 a little bit here and say for the photo-based therapies that
15 we have, very often the case when we're talking about 75 to
16 90 percent clear, is, in fact, that the regions of skin that
17 we can shine light on and get access with our therapy clear
18 completely; whereas, there are some difficult areas that you
19 can't get photons to, and they don't clear. So you're left
20 with 90 percent of the body surface clear and a few
21 resistant plaques.

22 There are also instances where there may be
23 virtually complete clearing of the skin; there's still some
24 trace of disease activity. And we may also call that 90
25 percent clear. But functionally, the skin is basically

1 normally. And there are instances of therapy which, in
2 fact, do give you 100 percent complete clearing. They're
3 not usual, but there certainly are examples of that.

4 CHAIRMAN McGUIRE: Yes, I would like to add that
5 the reason that we picked 75 percent, which sounds like sort
6 of an arbitrary number--and it was picked arbitrarily--is
7 that we didn't want to set the bar so high that we would be
8 excluding drugs that were clinical effective and acceptable
9 to the patient.

10 DR. SCHWIETERMAN: If I can amplify on that, I
11 think that I agree with that position. I don't think we
12 want to set it too high. But by the same token, I don't
13 want to set the ceiling too low, either, if there are drugs
14 that come down the line that actually do induce remission,
15 100 percent clearing, would that be a useful thing to put
16 into a claim structure and perhaps distinguish those from
17 those drugs that would be obviously approvable but,
18 nevertheless, not reach that standard?

19 CHAIRMAN McGUIRE: There was no intention that the
20 75 percent would be the ceiling.

21 DR. SCHWIETERMAN: Okay. I'm just picking up on
22 what Dr. Weiss said. Normally, when we think of these
23 diseases, remission doesn't, in fact, imply--and I'm not
24 sure it's the case with psoriasis--the absence of observable
25 disease, whether that be in rheumatoid arthritis or cancer.

1 Maybe a better category for the 75 percent response would be
2 something like--and it's all semantics, I suppose, but
3 complete clinical response or something like that. Major
4 response, rather, yes.

5 CHAIRMAN McGUIRE: I think that's still too
6 stringent.

7 Dr. Wilkin?

8 DR. WILKIN: Yes. Well, we're going to come up in
9 Section B and actually talk about efficacy, and I think
10 that's part of what is entering into this discussion. And
11 there, you know, we've thought, at least at the March
12 meeting, about a hierarchy where there would be a minimal
13 but clinically meaningful efficacy that could be
14 demonstrated, and that would be sufficient for further
15 consideration. But then in the labeling, one could craft in
16 statements of higher achievement in efficacy, such as, you
17 know, almost complete clearing or complete clearing.

18 But that is apart, then, from the idea of
19 remission. I think we heard from several members of the
20 committee and the guests in the audience that it's important
21 to look at the people who are almost clear in addition to
22 complete clearing as the group that one follows to see how
23 long remission actually lasts.

24 It's been my clinical experience that the folks
25 that actually end up with absolute, complete clearance, that

1 you really cannot find any evidence--and it's a very small
2 number of folks--that those people end up with much longer
3 periods of remission than the folks that are--you know, they
4 still have 20, 25 percent involvement. And I see some nods
5 on that. And so how one defines the subset that you're
6 going to follow to determine remission is going to
7 materially affect the percentages and the times that we'll
8 craft into labeling to inform folks.

9 I think we can do it either way, but it
10 nonetheless is going to affect the numbers.

11 CHAIRMAN MCGUIRE: Dr. Wilkin, I think it depends
12 upon how you got from here to there. If you got from here
13 to there with cyclosporine, you're going to have a relapse,
14 even though the patient while being treated is 90 percent,
15 98 percent clear. And if you get from here to there with
16 PUVA, then that will be remitted. I mean, that's what Dr.
17 Gottlieb showed this morning.

18 DR. WILKIN: It's more than just how clear the
19 subject is. It's how he or she got there. But I would
20 think that if one just looked at a population that received
21 a single treatment modality, say PUVA, that if you looked at
22 that group and you looked at the people who had complete
23 clearance, truly 100 percent, that those folks would tend to
24 have a longer remission than the folks that, you know, still
25 had 10 percent remaining at the actual cessation of therapy.

1 That's just--

2 CHAIRMAN McGUIRE: Why don't you state that to Dr.
3 Gottlieb and see if she agrees?

4 DR. WILKIN: Well, I think she heard it.

5 DR. GOTTLIEB: I feel passionately about this.
6 That's why--with PUVA, if you're talking about 100 percent
7 clearance, first of all, many psoriatics have scalp and
8 genital lesions. As Jim pointed out, they are not going to
9 be 100 percent clear. If you're talking about the arm which
10 got the PUVA, that will be 100 percent clear, but, again, it
11 depends how you define it. Total body, they're not going to
12 be because you're not going to irradiate the genitals and
13 you're not going to--the scalp is useless. For that matter,
14 the axilla is going to be difficult, but that you can deal
15 with. But you know what I'm talking about, or the soles of
16 the feet. They're standing in the light. I mean, soles you
17 can even deal with. So how you define that I think will
18 make a difference.

19 I want to emphasize, I think it was Dr. McGuire,
20 that it does make a difference how you get there. I mean,
21 that was the point that I was making with the use of these
22 pharmacodynamic markers early in drug development, is that--
23 take a PUVA patient, take a cyclosporine patient. Except
24 for the tan that the PUVA patient gets, the degree of
25 improvement is dramatic, whether it's 95 percent, 90

1 percent. To me it doesn't make so much difference because
2 the patient had a new life. I mean, you just have to talk
3 to these patients.

4 But clinically, the clinical response parameters
5 look the same except for the tan. But the histology looks
6 different, and the difference counts. I mean, so that it
7 does make a difference how you get there.

8 I would strongly agree with that statement.

9 DR. WILKIN: If I--because I think that was--there
10 was a slightly different question. Maybe you could--

11 DR. J. KRUEGER: May I--

12 CHAIRMAN MCGUIRE: Let's see. We have a traffic
13 jam here. John, make your statement, and then Dr. Krueger.

14 DR. WILKIN: Yes, I think the question was that if
15 you had someone that had complete clearance--and let's not
16 use PUVA because there are places the light doesn't shine.
17 We recognize that. Let's say a systemic drug. And you have
18 a group of folks that have absolutely 100 percent complete
19 clearance. You cannot find any evidence of psoriasis, you
20 know, after a course of treatment--what's that?

21 DR. GOTTLIEB: Even the nail?

22 DR. WILKIN: Well, you might find something, but,
23 see, in the nail, you're looking--that's like a chest X-ray
24 after treating pneumonia. I mean, you don't want to look
25 for two weeks, because even though you've successfully

1 treated the pneumonia, it's still going to have unpleasant
2 looks to it.

3 But I'm talking about active disease. If you can
4 get someone 100 percent clear of active disease, is that
5 person likely in your mind to have a longer period of
6 remission than someone who still has active plaques at the
7 conclusion of therapy?

8 DR. GOTTLIEB: It depends on the treatment. With
9 cyclosporine, I think the answer is no. You can get them--
10 to be frank, cyclosporine, if cyclosporine was safe long
11 term, we wouldn't be having any more drug development in
12 psoriasis. It is a drug that is probably the single most--
13 of a single agent, the most effective in terms of clearing
14 that one sees. The ones who I would say are, let's say for
15 the sake of argument, 100 percent clear, take away the
16 nails, those patients will still relapse within a month or
17 two. I mean, it's like Cinderella at midnight. It turns
18 back to a pumpkin. It just does. You know what I mean?

19 CHAIRMAN McGUIRE: That's going to be on all the
20 wire services tomorrow. I can see it now.

21 [Laughter.]

22 CHAIRMAN McGUIRE: Dr. DiGiovanna? Oh, I'm sorry.
23 Dr. Krueger, you were waiting.

24 DR. J. KRUEGER: I think to some extent this
25 discussion that we're having is very difficult without

1 talking about mechanism of disease. And so to some extent,
2 the way this discussion has been structured over the next
3 two days is difficult because the discussion by Gerry
4 Krueger on pathogenesis occurs tomorrow. So let me just
5 start that discussion a little bit early and say I think
6 there is reasonable consensus in the dermatology community
7 that psoriasis is an immune-mediated disease, that
8 fundamentally there is a T-cell reacting to some antigen in
9 skin.

10 DR. DUVIC: In a host that can respond to
11 psoriasis.

12 DR. J. KRUEGER: In a host that can respond to
13 psoriasis. But if you get rid of the activated immune
14 component, you get rid of the disease.

15 Now, with that said, I think there are
16 mechanistically two kinds of therapies. There are therapies
17 that suppress T-cell activation such as cyclosporine but for
18 which there is no evidence that they are fundamentally
19 cytotoxic for T-cells, that is, T-cells enter a resting
20 state, shut off cytokine synthesis, and the disease improves
21 clinically. But when you stop cyclosporine therapy, those
22 T-cells are still there. They're still there in the body,
23 and a lot of them are still there in skin. And that's some
24 of what Alice has been talking about. So the disease
25 relapses when you withdraw the drug because they're there to

1 reactivate.

2 In contrast, we think treatments like PUVA,
3 cyclosporine, thioguanine, and some of the other toxins
4 actually kill the activated T-cells in skin and, therefore,
5 the issue is reamplification of disease in clones, which
6 takes longer to achieve than simply reactivating a cell
7 that's already there.

8 So if we can't move this discussion towards
9 mechanism--and this becomes particularly critical tomorrow
10 when we start talking about biologics--and all we talk about
11 is scaling, erythema, thickness for the rest of this next
12 two days, I'm going to be very dissatisfied, and I think
13 ultimately the panel will be dissatisfied with the
14 discussion that ensues.

15 DR. DUVIC: And there is one curative treatment
16 for psoriasis. It's bone marrow transplant. For the
17 oncologist.

18 CHAIRMAN MCGUIRE: Dr. DiGiovanna and then Dr.
19 Rosenberg.

20 DR. DIGIOVANNA: What an act to follow. I wanted
21 to make a comment on Dr. Schwieterman's point about cure or
22 about complete clearing as a higher standard. And I think
23 the point I wanted to make is that the answer to the
24 specific questions that Jonathan Wilkin asked and that
25 relate to that are not really known, in part because of the

1 way that we treat psoriasis. We don't treat psoriasis as a
2 malignancy to eradicate the last cell. Usually we treat it,
3 and as we get closer to clearing, the therapies that we use
4 are so toxic, we back off.

5 So many people who treat a lot of psoriasis will
6 have the sense that treating the last 5 percent is much
7 harder than going down from the worst psoriasis to getting a
8 50 percent improvement. So if you're going to treat a
9 patient with methotrexate or some other potent agent, very
10 often you'll back off before you get to the complete
11 clearing. And the same thing often will happen with
12 retinoids and with many topical therapies. So I think
13 that's part of the reason we don't have that information.

14 On the other hand, I think if an agent was
15 developed that did give a prolonged remission of many years,
16 I think that would be obvious.

17 CHAIRMAN MCGUIRE: Thanks, John. I think we all
18 agree with that position.

19 Dr. Rosenberg?

20 DR. ROSENBERG: I will, I hope, not take too much
21 time to expand on what Dr. Krueger just said, and I would
22 start off agreeing with what he said. And I've made some
23 notes, so I won't go beyond them.

24 I think we have to distinguish between clinical
25 assessment, what the physician who is looking at a patient

1 thinks as looks at it and finds versus what we're really at
2 the heart of the matter here, which is regulatory decision-
3 making. And I think--they don't, but I think we ought to
4 make it explicit and clear that the agency is not bound to
5 act in a mindless kind of a way and react to just what stops
6 being red and what stops scaling and approve and disapprove.
7 I think at least it should think about the biologic
8 plausibility of what's going on.

9 If I could back up into my own experience in
10 psoriasis, which began with dandruff and seborrheic
11 dermatitis at the other end of the spectrum, but just as
12 involved in it, the question of this redness and scaling and
13 so forth and the histopathology that looks like psoriasis,
14 and the role of the perhaps causative yeast that had been
15 suggested in 1873 by Ravolta (ph), and we, of course,
16 pursued that, and you can treat seborrheic dermatitis with
17 Ketoconazole, with selenium disulfide, with zinc parathion,
18 all agents that kill yeast, and you can achieve clearing.

19 You can also get an equivalent suppression of the
20 symptoms of redness and scaling and itching with
21 corticosteroids, but you can get an equal score if you're
22 looking at the two patients. But I would submit that
23 there's a far lesser benefit from the symptomatic
24 suppression of inflammation than there is from treatment
25 directed at the cause of seborrheic dermatitis, unless

1 someone wants to discuss that further.

2 I think as a general principle a drug which is
3 anti-inflammatory which interferes with immune function
4 should be held to a much higher standard of safety and
5 efficacy than agents that might be more likely to be aimed
6 at the cause of inflammation, which brings us to psoriasis
7 and what is the cause of psoriasis. And I think it's
8 unfortunate that Dr. Krueger's talk tomorrow will not be for
9 everybody to hear.

10 The word that shows up in the National Psoriasis
11 Foundation handout we got this morning is that psoriasis is
12 an immunologically mediated disease, and then in the second
13 paragraph, the fact that psoriasis is a T-cell-mediated
14 immune response. And Dr. Krueger mentioned that it's an
15 immunologically mediated disease, but so is seborrheic
16 dermatitis and so, for that matter, is the fever of
17 pneumococcal pneumonia. And the question is: What is the
18 immune system doing there, and why is it acting? Is it, in
19 fact, as it's been suggested--Dr. Krueger in the New England
20 Journal Review two years ago--that it's an autoimmune
21 disease, that, in fact, the immune system is acting because
22 of a mistake and the things which suppress immune activity
23 are, therefore, permissible and actually appropriate?

24 It's my position that anybody who makes that
25 statement should have very heavily the burden of proof upon

1 them to show that, in fact, the immune system is not acting
2 appropriately and reacting to what it's designed to be there
3 for, which is microbial antigen. For if, in fact, there is
4 microbial antigen involved, then things which suppress
5 immune function are not only less desirable, but they could
6 predictably lead to a poor long-term effect. In other
7 words, the patient getting worse and worse and sicker and
8 sicker and perhaps dying more rapidly than he otherwise
9 would, and I'll talk about that a little later when we talk
10 about safety.

11 I think there should be--I think people who want
12 to say that this is an autoimmune disease rather than
13 begging the question by saying it's T-cell-mediated, which
14 really comes down--doesn't say anything, ought to be held to
15 a high standard. And to leave seborrheic dermatitis, which
16 I think is easy, and go to the other end of the spectrum,
17 which is the mix of reactive arthritis, spondylo-
18 arthropathies, Crohn's disease, Reiter's disease, psoriatic
19 arthritis, anterior uveitis, et cetera, I think one has to
20 be aware of the immense amount of information now becoming
21 available which bring microbial material into the forefront
22 in discussions of those diseases. Taurog's (ph)
23 demonstration at the human B27 gene transvected into rats is
24 not operative if the rats are delivered and raised in a
25 germ-free environment. These are crucial studies, and

1 Arnette at Dallas Southwestern is making that point.

2 And I would suggest to anybody, before they want
3 to think about this further, to take advantage of the
4 October 1998--right literally off the press--issue, which I
5 saw for the first time yesterday, of the American Journal of
6 Medical Science, it has a symposium organized by Professor
7 Espinoza, the rheumatologist at LSU, on seronegative
8 spondylo-arthropathy symposium. I'll just read the titles
9 of the six papers or seven papers, and I'll stop: "The
10 Histopathology of Ankylosing Spondylitis: Are There
11 Unifying Hypotheses?" "The Clinical Aspects of Spondylo-
12 Arthropathies." "HLA-B27 in Seronegative Spondylo-
13 Arthropathies." "Arthritis and HLA-B27 Transgenic Animals."
14 "The Pathogenesis of HLA-B27 Arthritis, Role of B27 in
15 Bacterial Defense." People with B27 do better if they catch
16 the HIV virus. It seems to be protective in terms of their
17 long-term outlook. I didn't know that. "Infectious Agents,
18 Triggers of Reactive Arthritis, Insights into the
19 Pathogenesis."

20 And just the first paragraph of one of these
21 papers from Finland, Wurilla(ph) and Granfors(ph), the
22 original--this is the first paragraph of their article in
23 this issue:

24 The original definition of reactive arthritis as a
25 sterile joint inflammation following infection elsewhere in

1 the body was challenged ten years ago when Chlamydia
2 antigens in lipopolysaccharide of Yersinia 03 were
3 demonstrated in synovial fluid of patients with
4 Chlamydia/Yersinia-triggered reactive arthritis
5 respectively. Thereafter, different antigens, as well as
6 DNA and RNA of various triggering microbes, have been shown
7 to exist at the site of inflammation in the joints.
8 Microbial antigens or intact pathogens have been suggested
9 to be important for the pathogenesis of reactive arthritis,
10 at least in the early phase of the disease. And so forth
11 this article reviews.

12 I'm not here to say that I'm going to be able to
13 convince all of you or any single one of you at this time
14 that microbial material is in a lesion, that it is not
15 autoimmune, and that we mess around with immune system at
16 our risk, but I would plead with everybody not to accept--
17 not to settle for immune-mediated as a kind of a weasel word
18 that allows one to leap immediately into heavy
19 immunosuppressive therapy and to insist on looking
20 critically at whether it's autoimmune or not, and to do
21 that, one would want to hear all the autoimmune arguments
22 but also look at numbers of papers cited in this journal.

23 Thank you.

24 CHAIRMAN MCGUIRE: Thank you. The point is well
25 made, and I think it's important to keep our line open. I

1 wasn't smiling at you. I was smiling at the fracas in the
2 first row there.

3 Dr. Krueger, let's have a brief response. I
4 really would like to cover a few more points before we break
5 for lunch.

6 DR. J. KRUEGER: I'll try to restrict my response
7 to about 45 seconds. I'd say first of all I acknowledge
8 that we don't know whether psoriasis is autoimmune or
9 immune-appropriate. However, I think we do know that T-
10 cells are critical in the pathogenic role.

11 Secondly, I would say that most of the therapies
12 that we now used which were discovered by chance and for
13 which mechanism was not understood initially have been
14 investigated relatively recently. I believe a case can be
15 made that everything that we now use for psoriasis is
16 essentially immunomodulating one way or the other.

17 The third point I would like to make is we've
18 already accepted the idea that there's a reasonable benefit-
19 to-risk ratio with use of immunosuppressant agents in this
20 disease with the approval of cyclosporine. I don't think
21 there's anyone in this room that would want to argue that
22 cyclosporine doesn't have at least action in part through
23 immunosuppression. So I think that there is--we need to
24 keep our eyes open and consider the risk-to-benefit ratio.
25 I think we also want to try to develop immune-modulating

1 agents that are as selective as possible in the effect or
2 mechanisms that they interrupt, and to try to titrate this
3 risk-to-benefit ratio in the future, and hopefully not
4 clobber the immune system by doing bone marrow
5 transplantation, which probably is too risky to consider in
6 most people.

7 DR. DUVIC: I agree.

8 DR. ROSENBERG: I would go along with part of what
9 Dr. Krueger said if he'll accept tonsillectomy as an immune-
10 mediating mechanism.

11 CHAIRMAN MCGUIRE: I'm ready to go on to
12 anatomical regions.

13 DR. MILLER: Joe, may I make--

14 CHAIRMAN MCGUIRE: Yes, you've been very quiet.
15 Dr. Miller?

16 DR. MILLER: May I make just a final comment on
17 the issue of remission and crafting? I think that for most
18 patients or for many patients, you know, if you talk about
19 remission that means total clearing, and the person will
20 come in and say, you know, this isn't totally clear, whether
21 it's erythema or a small bit of plaque or scale, whatever
22 remains. So I think it's not a good word. I think that
23 labeling has to be so honest so there's no obfuscation, and
24 I think it has to be crafted by saying, you know, it cleared
25 and then with an adverb or with a percentage so that there's

1 real honest when we read this. And then it has to be
2 crafted for each individual pharmacologic agent, you know,
3 depending upon the time out and how much it has been looked
4 at and, you know, how far did they follow it before they saw
5 exacerbation of what was done in that time period. Was it
6 no therapy or was it other therapy?

7 I think each one has to be individualized, but to
8 use a noun like remission, it means different things to
9 different people, and to many it means complete clearing.
10 So I think you have to use a word description or a
11 percentage.

12 CHAIRMAN McGUIRE: For many patients, it means
13 what I'm willing to put up with.

14 DR. MILLER: Exactly.

15 CHAIRMAN McGUIRE: It's when the treatment is more
16 of a nuisance than the disease, and that's where they stop.

17 Dr. Duvic?

18 DR. DUVIC: I just wanted to say that I think the
19 oncologists have a clearer way of doing this. It's partial
20 remission, greater than 50 percent improvement, complete
21 remission, complete clinical remission, no disease is
22 evident, and then complete remission, no pathology present.
23 And I don't think that psoriasis is any different or should
24 be held to higher standards than cancer of the breast.

25 DR. SCHWIETERMAN: Let me just respond to that--

1 DR. DUVIC: You need to define your terms, and
2 then you have to define what progressive disease is. Is it
3 greater than 25 percent return or 50 or whatever.

4 CHAIRMAN MCGUIRE: Dr. Schwieterman?

5 DR. SCHWIETERMAN: Dr. Schwieterman, CBER. I
6 fully agree with that, actually, Dr. Duvic. We certainly
7 don't want to hold this disease to any higher standards.
8 Quite the contrary, we want to hold it to the very same
9 standards that we approve other drugs. I was merely
10 suggesting that there might be a different--that there may
11 be a difference between something that allows for a 75
12 percent response and calling it whatever you want to call
13 it, and then 100 percent response which might be reasonably
14 called remission. If there is a clinical--if there's a
15 difference in those, a clinical difference in what the
16 patients feel, it might be useful to define those in some
17 sort of claim structure. That's all.

18 CHAIRMAN MCGUIRE: Dr. DiGiovanna, I'm going to
19 give you the--I'm going to give you number four, anatomical
20 regions. Please address whether (and if yes, when) it is
21 appropriate to make a claim regarding the treatment of
22 psoriasis in a specific anatomic location (scalp, knees,
23 elbows), and the "et cetera" must mean intertriginous.

24 DR. DiGIOVANNA: I think that there are certain
25 preparations that are particularly tailored for certain body

1 locations such as for the scalp treatment of psoriasis with
2 foams or mousses or shampoos, and in those cases, I think
3 it's obvious that the anatomic locations are important.

4 I think that from my perspective--and I certainly
5 have an opinion that is changeable on this--if the studies
6 are being done, they need to be consistently. But,
7 generally, if a particular topical product is effective in
8 one location, it's usually effective in other locations,
9 albeit possibly more or less effective. So the areas of
10 psoriasis that tend to be most resistant, tend to be most
11 resistant. But if you're going to compare a knee to a knee
12 or a lower leg to a lower leg, then you can, for the purpose
13 of demonstrating efficacy, do that. So I think consistency
14 across those body locations for clinical testing purposes is
15 what's important. Certainly those areas where treatments
16 may have increased toxicity like body folds need to be also-
17 -that needs to be noted.

18 CHAIRMAN McGUIRE: Yes. I think implicit in
19 Question 4 is the relative resistance of psoriasis in
20 certain areas, or the slower response that there be in
21 certain areas. And clinically, there seems to be a
22 consensus that knees, elbows, and shins are slow;
23 intertriginous areas are generally more responsive. The
24 scalp is slow.

25 Does the agency want more than you got?

1 DR. SCHWIETERMAN: That's fine.

2 CHAIRMAN MCGUIRE: Number 5, additional
3 considerations. Are there additional appropriate claims
4 that may be considered?

5 What were you looking for there?

6 DR. SCHWIETERMAN: Well, again, we're open to
7 ideas from the committee and from investigators in the field
8 on how to best structure a document that provides for
9 clinically meaningful outcomes, thereby standardizing and
10 setting expectations. But we don't--we're not sure we
11 covered everything that might actually be clinically useful
12 and wondered if others had ideas.

13 DR. DUVIC: In this day and age, I think cost-
14 effectiveness is really important, something that, you know,
15 is--

16 DR. SCHWIETERMAN: Yes, we agree, Unfortunately,
17 or fortunately, that's not our purview, but I agree with
18 you, .

19 CHAIRMAN MCGUIRE: Dr. DiGiovanna?

20 DR. DIGIOVANNA: In some clinical circumstances,
21 dermatologists will use multiple therapies, multiple topical
22 approaches together. So one of the things that
23 occasionally, for example, might be done is to use a topical
24 tretinoin preparation with a topical steroid or another
25 preparation, and the idea there is to enhance the

1 penetration of the efficacy. The mechanism is not exactly
2 quite clear, but often resistant areas will respond with
3 that approach.

4 So, conceivably, there may be other products that
5 are brought to you as adjunctive therapies, and that's one
6 of the areas that I would think is a possible. But I don't
7 know that anyone has been marketed.

8 CHAIRMAN McGUIRE: And then many dermatologists
9 are using sequential therapy, using a drug or drugs with a
10 certain repertoire of unwanted effects, and then going to a
11 second drug, discontinuing the first drug, hoping that there
12 is some period of biological forgiveness for the toxicity
13 from the first drug while the second drug is being
14 administered or applied.

15 Dr. Gottlieb, you had a comment.

16 DR. GOTTLIEB: Yes, two. One, in terms of
17 assessing, I know that in the beginning people have talked
18 about that quality-of-life measures are not so good. But
19 I've actually been quite impressed with some of the
20 psoriasis-specific ones, how they can actually be in a way
21 more useful than some of the parameters you spoke about
22 here.

23 I'll give you an example. There was recently a
24 trial which looks at cyclosporine relapse, and it has been
25 publicly presented and where the relapse was defined in a

1 certain way that I personally feel was not clinically
2 useful. And if you define it that way, cyclosporine looks
3 very good in terms of length of remission off treatment.
4 However, if you looked at the quality-of-life data, they
5 were what reality was, and you notice the deterioration in
6 terms of quality-of-life data was very pronounced within a
7 month or two, even though the clinical parameters based on
8 their definition of relapse were not.

9 So I personally think that that is worth pursuing,
10 the quality-of-life data, because I've actually been
11 impressed with them, and I think that they are quite useful.

12 I also wanted to--I was glad Dr. McGuire mentioned
13 it, is that certainly in moderate to severe psoriasis where
14 we have treatments that may induce remission but may be
15 toxic to use long term, I think it would be very helpful to
16 the practitioner if the sponsors were asked to do studies
17 that would help the sponsor switch people off onto something
18 else, and I'll give the example of cyclosporine where you
19 don't have much time to get them off the cyclosporine, and
20 you know you have to get them off the cyclosporine to switch
21 on to something else. And there are no data that help us.
22 We really don't know how to use acitretin, UVB based on
23 fact. We don't know how to overlap methotrexate, and you
24 know you're going to have to overlap a little; otherwise,
25 that patient will flare again.

1 So I think that was my understanding of what Dr.
2 McGuire was saying. Is that right, what you were saying?
3 We could use help in the community on how to do that, and
4 right now there are no data.

5 DR. SCHWIETERMAN: That's very helpful, actually.
6 Typically when we write guidance documents, we include a
7 study section where we point out some of the particular or
8 peculiar things about the disease through the indication
9 that need to be addressed during product development, and
10 that sounds like one of them.

11 CHAIRMAN MCGUIRE: My ambition is to deal with
12 part of Section B before we break for lunch. I will read a
13 paragraph, and eventually we're going to revisit much of
14 what we dealt with on March 20.

15 Response variables for evaluation: Efficacy for
16 drugs used to treat stable plaque psoriasis has been
17 demonstrated by reduction in each of the three clinical
18 signs--plaque elevation, scaling, and erythema--plus an
19 overall global evaluation by investigators that shows
20 superiority over placebo. Other response variables are
21 commonly used outside the U.S. Some issues concerning these
22 outcome measures have been discussed at the DODAC meeting on
23 March 20, 1998. Since there may be a hierarchical structure
24 in the reporting of responses to treatment in the Clinical
25 Studies section of labeling, the evaluation parameters need

1 to provide adequate support for the several levels of
2 therapeutic achievement. Please consider the following
3 outcome variables in light of the claims discussed above in
4 Section A. Please also address the effect on sample size
5 and power calculation when considering the use of these
6 variables.

7 Item 1, clinical signs of psoriasis: plaque
8 thickness, scaling, and redness.

9 Should reduction in each of the three clinical
10 signs be necessary for a claim of "the treatment of
11 psoriasis"?

12 Well, let me proffer yes, although they differ in
13 importance.

14 Dr. Miller, how would you deal with that? Should
15 reduction in each of the three clinical signs be necessary
16 for a claim of "the treatment of psoriasis"?

17 DR. MILLER: These are certainly the three
18 criteria that we've used traditionally, and they're the ones
19 that we see. We've talked about scaling and the problems
20 that might be associated with scaling. Certainly plaque
21 thickness is measurable and erythema is very visible. So I
22 think these are very necessary.

23 CHAIRMAN MCGUIRE: Area is not included at this
24 point, but will be picked up later. So area has not been
25 excluded.

1 Should these clinical signs be evaluated on
2 selected "target" lesions in different anatomic regions in
3 order to support claims for efficacy in those anatomic
4 regions, or should each sign be scored according to the
5 overall (whole body) response for that sign?

6 John? Dr. DiGiovanna?

7 DR. DiGIOVANNA: I have a question. Wouldn't that
8 be different for systemic and topical therapies?

9 CHAIRMAN McGUIRE: That's a good point.
10 I assume that whoever framed this question was
11 thinking about topical therapy, but I don't know.

12 DR. WEISS: I think it would be helpful to assume
13 that and to respond as if we're talking about topicals. Is
14 that correct? But the same caveat would apply since some
15 people--I think Dr. Duvic said earlier that the topicals
16 with systemic absorption may also affect other lesions as
17 well. But certainly think about it as topical when you're
18 addressing it.

19 DR. WILKIN: Actually, it could be topical or
20 systemic. I mean, it's open for the committee's
21 interpretation on that. In either case, if it's a topical
22 drug that is in Phase 3, it should be applied to all active
23 lesions of psoriasis. So it won't just be applied to one
24 small lesion that has been predesignated, easy for the
25 patient to get to, that sort of thing. It would be all

1 lesions that we would want to see treated in Phase 3, in
2 part because we want some idea also of a safety signal.

3 CHAIRMAN MCGUIRE: But in Phase 2, you could be
4 treating symmetric lesions.

5 DR. WILKIN: Well, in Phase 2, when one is doing
6 one of these proof-of-concept kinds of studies, we clearly
7 would be interested in a surrogate that would be somewhat
8 less than maybe the efficacy endpoint required in Phase 3.
9 I mean, someone could look at plaque thickness and just show
10 that it's, you know, going in the right direction by, you
11 know, maybe two out of six steps, something like that. That
12 might be sufficient to encourage industry to develop that
13 particular product.

14 But moving on to Phase 3, you know, it would be a
15 different kind of endpoint.

16 CHAIRMAN MCGUIRE: Okay. The question is: Should
17 these clinical signs be evaluated on selected "target"
18 lesions in different anatomic regions in order to support
19 claims for efficacy in those anatomic regions, or should
20 each sign be scored or evaluated according to the overall
21 (whole body) response for that sign?

22 John had his hand up first, and then we'll--

23 DR. DiGIOVANNA: I would like to expand on what
24 Jonathan said and then, if you'll allow me, ask another
25 question.

1 I think that the way this question is framed, it's
2 a little too focused. I think that besides being different
3 with respect to whether one's dealing with a topical or a
4 systemic approach, one is also looking at variation whether
5 one is dealing with early studies or late studies. In a
6 Phase 1 study, you wouldn't want to apply a topical to every
7 lesion; whereas, in a Phase 3 or 4, you might want to do
8 that.

9 In addition, I'm not certain--my question here is
10 I'm not certain with respect to the words anatomic regions
11 whether we are talking about asking someone to do a study in
12 particularly difficult areas so that the claim could say
13 that specific anatomic lesion and a resistant plaque, or
14 that's referring to the fact that in an early study you
15 might want to choose symmetrical anatomic--or the same
16 anatomic area in many of the study patients.

17 CHAIRMAN MCGUIRE: Dr. Wilkin, what's your reading
18 of that question?

19 DR. WILKIN: Someday, if we get really good, we'll
20 actually craft the questions sort of right at the time of
21 the meeting so it kind of builds on, you know, all the
22 previous discussion.

23 I think the idea here is, in part, target. Do we
24 really want information coming from a preselected target?
25 And then there's another part to this. If we're interested

1 in target, are we interested in targets from, say, one on
2 the trunk and one on one of the more difficult areas, like
3 the knee or the elbow? I think in a previous presentation
4 by Dr. Plott, that was one of the considerations, that there
5 would actually be two varieties of target lesions.

6 CHAIRMAN MCGUIRE: John, does that help you?

7 DR. DIGIOVANNA: I think it does, but I think what
8 it then seems that you're trying to do is to, in addition to
9 an easily responsive lesion, potentially choose also a
10 lesion which may be a little more difficult to respond.

11 DR. WILKIN: Well, that would be--I mean, we tried
12 to make this open enough that, you know, the committee would
13 work with it and Dr. McGuire would deconstruct it and that
14 sort of thing.

15 Basically, you know, we're thinking of sort of a
16 range of possibilities. One could be that you would say,
17 well, what we're really interested, what the patient is
18 interested, is not really on how well that one lesion that's
19 easy to reach responds, but instead how they respond
20 overall. So maybe at the end of this, the committee would
21 say something like it's really important to look at how
22 these lesions respond over the whole body. And the second
23 part is if you're going to take the other point of view that
24 you can use a lesion to represent, do you want one lesion to
25 represent how the patient is doing, or would you want to use

1 a lesion from an easier treated site along with a lesion
2 from, say, the knees or the elbows, a relatively more
3 difficult to treat site? Does that make sense?

4 DR. DiGIOVANNA: Sure.

5 CHAIRMAN McGUIRE: Dr. Duvic and then Dr. Ko.

6 DR. DUVIC: I'm going to limit my comments to
7 topical therapy.

8 When you have a psoriasis patient, you have
9 lesions on that body that are two or three years old, on a
10 knee, they're very thick. You have a lesion on the trunk
11 that might be two months old; it's thin; there's not a lot
12 of hypertrophy. Those lesions are going to respond
13 differently. And it's got to do with how thick they are,
14 probably how long they've been there. The knee may respond
15 ultimately as well as the trunk, but it may take three
16 months longer. There may be more time to clear it.

17 And I think it's important if you're going to have
18 a general claim for the product, that it can be used for
19 plaque psoriasis anywhere, that you do have selection of
20 different kinds of lesions, and not just two lesions but
21 four or six lesions in different body areas, and that there
22 be probably a grouping of those lesions for statistical
23 comparison in the efficacy.

24 I think that this thought of generalizing over the
25 body the amount of redness or scale or plaque elevation will

1 end up with garbage resulting from just summing up stuff.
2 And I don't think it's a very objective way of measuring a
3 topical therapy.

4 CHAIRMAN MCGUIRE: That was pretty much our
5 consensus seven months ago, or whenever it was.

6 Dr. Ko?

7 DR. KO: Hon-Sum Ko. I was just going to clarify
8 the question. This question was raised because we have
9 applications in which studies use specific target lesions,
10 clinical signs, evaluation, and also there are studies in
11 other applications where they don't use target lesions and
12 evaluation of the overall plaque elevation, erythema, and
13 scaling. And the question is to get your opinion on which
14 is more preferable.

15 DR. DUVIC: I have done a lot of psoriasis studies
16 with topical agents. In my opinion, you have to look at how
17 a lesion responds or several lesions respond. The global
18 response is also important, but it gives you different
19 information, somewhat related to how active the patient is,
20 whether they're getting a lot of new lesions, whether
21 there's a systemic effect of the topical product. I think
22 it's a different kind of information.

23 DR. WILKIN: If I could ask Dr. Duvic, to follow
24 up on that, then for a systemic agent, though, the similar
25 logic would apply, that rather than trying to really

1 calculate an erythema score for the whole body or a plaque
2 score for the whole body, one would also want to look at
3 four to six target lesions? Is that--

4 DR. DUVIC: The way I would do it, if I were
5 designing it, in a topical I'd look at index as the primary,
6 and body surface area, some sort of global, as the
7 secondary. In systemic, I'd reverse it. I'd look at body
8 surface area or global as the primary and look at index
9 lesions as a secondary. That's the way I would do it. Does
10 that make sense?

11 CHAIRMAN MCGUIRE: Is there general agreement of
12 the Advisory Committee? Fred?

13 DR. MILLER: I agree.

14 DR. DiGIOVANNA: I agree.

15 CHAIRMAN MCGUIRE: Bill? Gosh, we got 100
16 percent.

17 Okay. 1.c) Should there be special provisions
18 for a claim on scalp psoriasis, or should an
19 indication/claim for stable plaque psoriasis cover scalp
20 psoriasis?

21 The agents are often different, and many of us use
22 different modalities for scalp psoriasis than we do for body
23 psoriasis. So I would--my bias would be to keep them
24 separate.

25 What would you do, John? Again, I'm talking about

1 topical medication at this point.

2 DR. DiGIOVANNA: I think that, as you say, there
3 are some preparations that are specifically made for the
4 scalp. There are some preparations, some gels, which are
5 specifically made for the skin but are cosmetically
6 acceptable to many people in the scalp and that work quite
7 well.

8 My general sense of psoriasis, which may be
9 slightly at odds with the approach of the FDA--at the
10 moment, at any rate--is that I think to some extent plaque-
11 type psoriasis is psoriasis, and that while agents that are
12 weakly effective on the knee may be very effective in other
13 places. They tend to over time have utility and usefulness,
14 in part because we constantly have to rotate out of
15 tachyphylaxis into some other treatment.

16 So I wouldn't try to deny something a roll if it
17 was weaker by necessarily adding a difficulty or raising the
18 pole by saying, well, you have to use knee lesions or
19 something like that. I wouldn't have a problem with someone
20 just using easy to treat lesions. Maybe you'd have to label
21 it differently.

22 So I tend to not see a problem with allowing--or
23 with labeling a preparation that's effective as being
24 effective and including that for the scalp, unless there is
25 some reason why it has--

1 CHAIRMAN MCGUIRE: Well, but you run the risk of
2 excluding something that is not--you run the risk that--the
3 way I read the question, if the modality has to work in both
4 locations, then to be approvable, the modality that works on
5 the trunk has to be acceptable to use on the scalp, and I
6 don't think we want to say that because there are a number
7 of things that you would use on plaque psoriasis elsewhere
8 that you wouldn't use on the scalp, wouldn't be acceptable,
9 not elegant, cosmetically unacceptable, whatever.

10 DR. DIGIOVANNA: I think that was what I was
11 saying. If it is acceptable--

12 CHAIRMAN MCGUIRE: Okay, well, I misunderstood
13 you.

14 DR. DIGIOVANNA: I may have not said it exactly--
15 is the question that in order to be labeled as such, it must
16 be tested in the scalp or not? Or it's approved--

17 DR. WILKIN: Yes, that is actually what the
18 direction of the question is, and I thought actually, John,
19 it related to an extent back at the beginning when we were
20 talking about anatomic at the very beginning, Question 1,
21 and you were talking about scalp and you were saying I think
22 some vehicles might work much better on the scalp. So if
23 one had an ointment that was clearly efficacious in plaque
24 psoriasis on the body and it was approved for "the treatment
25 of psoriasis," to obtain an additional claim of scalp

1 psoriasis, should they actually need to do this study?

2 CHAIRMAN McGUIRE: But there are two ways to read
3 this question, Dr. Wilkin. One is, if you have a
4 preparation that is effective on the trunk, on plaque
5 psoriasis on the trunk, do you have to show efficacy in the
6 scalp before it's approvable on the trunk?

7 DR. WILKIN: Well, but that wasn't the intent.
8 The intent is--

9 CHAIRMAN McGUIRE: Oh, well, I'm just--

10 DR. WILKIN: --if one is actually seeking to say
11 something about the scalp in labeling, in marketing--

12 CHAIRMAN McGUIRE: Then you have to test it on the
13 scalp.

14 Okay. I think this question had several
15 interpretations, and I think we have it straight now.

16 1.d) Should these clinical signs be analyzed as
17 reductions from baseline or in terms of successes and
18 failures for individual patients (dichotomous outcome) at
19 endpoint (see example below on page 9)? Please discuss.

20 Most of page 9 is a table showing example data on
21 clinical signs in psoriasis, drug versus placebo.

22 Jim, are you comfortable dealing with that?

23 DR. KILPATRICK: Thank you. Kilpatrick.

24 First of all, I take it that this is spurious
25 data, this is made-up data, it's not real data. Secondly,

1 as such, it shows a placebo effect. If you look at the
2 placebo, the second part of the table, the interpretation
3 that I make of this is that there is a slight placebo
4 effect. Whether or not it's statistically significant is
5 another question. But if there's placebo effect, then it
6 would be clear that, yes, there should be a comparative
7 study done, to answer--reduction in baseline, so, again, we
8 go back to what I think I was saying in March, the
9 difference of differences, a difference from baseline to
10 endpoint and a difference between two arms.

11 DR. WEISS: First of all, going back to the issue
12 of the placebo in many, many, many diseases, there is quite
13 a strong placebo effect, and maybe the committee can correct
14 me if I'm wrong, but I would venture a guess that in
15 psoriasis that is also the case and that it would be quite
16 appropriate, and has been done, that trials are done with a
17 comparator groups, whether it's you know, add-on therapy, on
18 arm gets the standard therapy plus placebo, one gets the
19 standard therapy plus the new agent, but that that's not--
20 it's not unexpected that you might have a placebo effect.
21 Is that a correct assumption?

22 CHAIRMAN MCGUIRE: Well, this begs the question of
23 whether the vehicle is a placebo.

24 DR. WEISS: Right.

25 CHAIRMAN MCGUIRE: And vehicle actually has--the

1 vehicles are emollients, lubricants.

2 DR. WEISS: Yes. You know, I'm thinking from my
3 bias also of systemic therapies, but obviously with the
4 experience we've had with topical agents, there have always
5 been questions about whether the vehicle itself has
6 activity.

7 CHAIRMAN McGUIRE: Dr. DiGiovanna?

8 DR. DiGIOVANNA: I think that's--the vehicle
9 certainly does in a topical, and I think also--and if Dr.
10 Kilpatrick can help me out with this, often in doing
11 studies, patients that have severe psoriasis diseases that
12 wax and wane and flare, there is--I think it's called
13 reduction to the mean where you tend to get--

14 DR. WEISS: Regression.

15 DR. DiGIOVANNA: Regression to the mean, thank
16 you. Those patients who are worse, many of those patients
17 at the time are willing to go into study, and it's not
18 uncommon to see patients improving on placebo.

19 DR. WEISS: But to go back to--I guess I would
20 like Dr. Kilpatrick just to clarify the questions about--can
21 you just restate? You said there's two comparisons. You
22 can compare somebody to the baseline, but the more relevant
23 is to compare cross the randomized treatment arms?

24 DR. KILPATRICK: I did not say that, as I
25 remember, but first of all, there are two parts of this, and

1 the question as has been stated says a choice between
2 dichotomous outcome, success or failure, or a difference
3 from baseline to end effect. That, again, is a matter of
4 sensitivity of the response variable. But then I was going
5 on to talk, since we were referred to page 9, to point out
6 that according to this hypothetical example, there was a
7 placebo effect. And if we are, as we would probably be
8 doing, evaluating in terms of randomized clinical trials, it
9 will have a second arm. And, also, as John has said, this
10 condition certainly waxes and wanes, and so there would be a
11 need for--what I said was in the analysis of a difference of
12 a difference. Let me explain that.

13 By difference, I mean a difference between the two
14 arms in the differences between baseline and end, and that's
15 what I was trying to get to.

16 Did I answer your question, Dr. Weiss?

17 DR. WEISS: Yes. Thank you.

18 CHAIRMAN MCGUIRE: Dr. Wilkin?

19 DR. WILKIN: In many ways, this is one of the most
20 critical questions that the committee is going to be working
21 with and that we want to hear all kinds of thinking on,
22 because, you know, what are the statutory bases for the
23 approval of drugs. One can infer from that that what is
24 ultimately needed is a clinically meaningful degree of
25 efficacy that can be demonstrated. And so the question is:

1 How can one find that minimal clinically meaningful efficacy
2 in these kinds of data? I mean, should it be searched for
3 in a dichotomization? Should it be searched for in an all
4 category comparison where there can be edging up and
5 multiple categories? For example, I think with PASI, one
6 can have a score anywhere from 0 to 72. So at the end of
7 the day, you know, if treatment A, which may be active, you
8 know, ended up with one unit of change in the positive
9 direction higher than treatment B, which is the vehicle or
10 placebo, you know, would that--would the committee think of
11 that as a clinically meaningful endpoint? Or, you know,
12 should it be some other way of looking at these signs?

13 Should in the end there be a minimum amount of
14 plaque improvement or at the end--which implies change from
15 the beginning to end of treatment, or should there be at the
16 end of treatment no more than X amount of plaque involved?

17 It's a very complicated type of issue, but in the
18 end, you know, that's what we're seeking. And it's not
19 just--you know, it needs to be statistical, but it probably
20 is going to be more than statistical. It needs to have this
21 clinically meaningful component to it because, arguably--and
22 Dr. Kilpatrick will probably make the point that if one
23 dichotomizes, one is losing some evidence of drug effect,
24 but it would be below the threshold of clinically meaningful
25 effect.

1 CHAIRMAN McGUIRE: Let me make a brief comment,
2 and you wanted to comment, right, John?

3 DR. DiGIOVANNA: Well, I think Jonathan made in a
4 fashion what I was about to say, which is the time we
5 discussed this several months ago, this question was a lot
6 clearer to me. It didn't have the "dichotomous" in it. And
7 what it was was whether or not you wanted the criteria to be
8 efficacy at a minimal level, a detectable level, or clinical
9 efficacy that the patients were happy with, that the
10 dermatologist was happy with, that wasn't, well, it got a
11 little better and then came back again. And I think that
12 really is a difficult issue. Where do you want to set the
13 bar and call it efficacious? Does the lesion have to go
14 away? Does it have to improve 50 percent? Or does it have
15 to improve over placebo?

16 DR. WILKIN: If I could speak to that, I think
17 that the actual bar, the minimal clinically meaningful
18 efficacy bar--I mean, I hate to say low, but let's say that
19 it shouldn't be any higher than what some patients are going
20 to derive some satisfaction from. And I think we heard from
21 the National Psoriasis Foundation that, you know, some
22 people might be surprised that patients would actually
23 appreciate something that offers something less than, you
24 know, complete clearing or even abundant clearing.

25 But the other part of this is a hierarchy of once

1 a product has achieved minimal clinically meaningful
2 efficacy, if the product goes on and can achieve something
3 at a higher level, let's say we do finally end up with that
4 magic mediation that really does clear 75 percent of patient
5 who are on the drug, that would be helpful to craft into the
6 Clinical Studies section of the labeling. So you might
7 consider higher levels of achievement in addition to this
8 low level, lower level that would be sufficient for
9 approval.

10 Does that help?

11 DR. DiGIOVANNA: If that's the case, then it would
12 seem to me for your lower level, which would seem
13 appropriate to me, some sort of quality-of-life measurement-
14 -in other words, asking the patients how they felt about it-
15 -would be appropriate to determine if they really did find
16 it a benefit, in addition to some of the other measurements.

17 CHAIRMAN McGUIRE: Seven months ago, we concluded
18 that quality of life was extremely difficult to measure and
19 that we would have difficulty using it as a meaningful
20 measurement of efficacy.

21 We also concurred with the two experts who helped
22 us that certain types of lesions were overread, and close
23 your eyes and try to remember the slide. I can't remember
24 if Dr. Stern showed it, or Lebwohl. It was a large
25 psoriatic plaque that was rated 4-plus in terms of erythema.

1 And, in fact, it wasn't red at all. It was white. And the
2 question was: Why do you call that red? And the answer
3 was: Well, I know it's red underneath the scale.

4 And so if we use PASI, we run the risk of
5 degrading the data by adding in material that we intuit or
6 we infer, and I think that's why we went to plaque thickness
7 and area and, to a lesser degree, scale and redness.

8 DR. DiGIOVANNA: But since that time, Jonathan has
9 now, I think, clarified that the patient's satisfaction in
10 addition to--that a minimal amount of improvement with the
11 patient satisfaction would be an acceptable amount of
12 improvement; whereas, many patients would--many
13 dermatologists would not be happy having an expensive
14 preparation that had that minimal amount of improvement. Or
15 am I--

16 DR. WILKIN: I didn't mean to imply that quality
17 of life would be the direct way of answering that. If my
18 statement suggested that, I certainly didn't intend that.

19 There's a nice British Journal of Dermatology
20 paper on how quality of life has a lot more to do with the
21 patient's perceptions than it does really to the objective
22 findings. And so one might actually be able to place
23 objective findings into the labeling, and the physician
24 could, you know, describe what chances the patient might
25 have of achieving a certain objective kind of endpoint. And

1 then the patient could get to the second derivative on their
2 own. They could add their own feelings and values to that
3 and draw back, you know, their value out of that kind of
4 discussion.

5 Then Mark Lebwohl had in Lancet a nice review
6 article--or, actually, an editorial that also commented on
7 that British Journal of Dermatology article, and I think
8 came to the same conclusion that quality of life adds things
9 other than these objective findings, and that when the
10 patients think about objective findings, again, they come up
11 with different answers for the same kind of changes in
12 erythema, just as an example.

13 So I think right now, you know, a sponsor could
14 persuade us later about quality of life, I mean, if we saw
15 the data and saw that, you know, there was some major merit
16 to it. But looking at the literature, it's not exciting at
17 the moment. I think we'd be more keen on hearing something
18 about, you know, either a global scale or evaluating the
19 different signs and coming up with some kind of difference
20 in number or some kind of morphological description. But,
21 you know, we want to hear from the committee to hear what
22 you think would be the best way of crafting clinically
23 meaningful--

24 CHAIRMAN McGUIRE: Okay. John? If you'll be
25 patient, you're going to hear some of that after lunch from

1 Dr. Krueger. But he also has a comment to make.

2 DR. J. KRUEGER: Yes, I would like to address the
3 issue of whether we should really consider the dichotomous
4 outcomes as separate from--in an analysis as separate from
5 sort of lumping everything together.

6 I think it's about 10 percent noise, or maybe a
7 little bit more, in terms of outcome measurements for
8 psoriasis, and that is, if you're not dealing with topicals,
9 with systemic treatments there's fairly low placebo rate.
10 However, I think it makes a tremendous difference if, let's
11 say, we had a patient group that we were looking at and
12 there was a reduction in PASI of, let's say, 10 percent in
13 the placebo group and 20 percent in an active treatment
14 group. And if every patient across the board had sort of a
15 10 percent reduction over placebo, I think that wouldn't be
16 very meaningful clinically.

17 If, however, let's say, 20 percent of the patients
18 in that study actually cleared and the other 80 percent had
19 absolutely no change in their psoriasis, that might actually
20 be a meaningful result for those people, and we might
21 consider whether, in fact, it would be worth a trial of an
22 agent like that in a bigger population to say for those 20
23 percent it's certainly very important. And we actually have
24 examples of drugs on the market which are somewhat akin to
25 that, although they're often intermediate responses. So I

1 think the dichotomous analysis is important, and somewhere
2 we're going to have to derive some idea of what really is
3 clinically meaningful.

4 CHAIRMAN MCGUIRE: Dr. Schwieterman?

5 DR. SCHWIETERMAN: Schwieterman, CBER. Actually,
6 Dr. Krueger said much of what I was going to say, that there
7 really is no right or wrong answer here. There's
8 disadvantages and advantages of each one. But before this
9 group adopts either a by-patient or dichotomous outcome
10 measure, one has to consider the disadvantages of that, and
11 that is perhaps obvious to everyone, but I'll state it
12 anyway. It's losing information. And what you gain by a
13 continuous outcome variable is more information at the
14 expense, perhaps, of clinical meaning. But oftentimes you
15 can use those continuous variables for a lot of different
16 things, including differentiating doses and so forth along
17 the way.

18 So, in some respects, we've tried to use both, and
19 we've had quite a bit of experience with this. But I just
20 want the agency--want to give my perspective from other
21 agency indications that we have that, you know, there is a
22 price to pay for using dichotomous outcomes.

23 CHAIRMAN MCGUIRE: Dr. Kilpatrick?

24 DR. KILPATRICK: I'd like to come back to page 9
25 again, and as far as I understand, this is unrealistic

1 because surely in a Phase 3 trial, the sponsor would be
2 using a comparison of a new therapy with the best therapy,
3 whatever that is, even though it may not be that successful.
4 And so, therefore, it would be a two-arm. In that sense, it
5 would not need to be a goal that it be reached as long as it
6 was shown to be markedly better than the current treatment.

7 However, since we are also required to talk about
8 the effect of sample size on par, it's also important to
9 indicate that the trial be designed to show that difference
10 with a high probability, if it exists.

11 On the other hand, going back to what Dr. Wilkin
12 was saying, if you are attempting to set up what I would
13 call a clinical significance, then, again, that can be
14 figured into a study and, again, properly designed to show
15 that a certain--a study can be designed to show that a
16 certain advantage is detected, is there.

17 CHAIRMAN McGUIRE: Dr. Rosenberg?

18 DR. ROSENBERG: The question of statistically
19 significant or visible versus medically significant
20 improvement, of course, is what we're talking about, and the
21 quality of life things--the quality-of-life people, of
22 course, have got techniques and hard data and tricks that
23 they know, for instance, the question: Would you be willing
24 to pay \$10 a week to be rid of this or to have this
25 treatment? Or some such thing as that. Although it sounds

1 bizarre, it's one of the ways in which those scientists, the
2 quality-of-life ones, get some hard data. And, of course,
3 that very question illuminates, I think, just as an aside,
4 the more pure nature of the over-the-counter market than
5 that written by--prescriptions written by physicians. The
6 consumers really make this decision very quickly for
7 themselves what's worth it and what's not. It's a much
8 cleaner marketplace.

9 CHAIRMAN MCGUIRE: Dr. Gottlieb?

10 DR. GOTTLIEB: I want to address Dr. Gil Martin's
11 and other statements, and one thing that has not been
12 discussed, we are blithely assuming that the placebo is a
13 good idea. And I'd like to first of all say that I think
14 that to have one particular discussion and one set of
15 rulings that fits the mild to moderate patient versus the
16 moderate to severe, i.e., topical versus systemic, I don't
17 think is--for some of the reasons that have been stated
18 here, I don't think is a good idea. For instance, I'll take
19 the placebo effect. The placebo effect with topicals with a
20 vehicle is large. Okay? For the systemic, it's not that
21 large, and in addition, as you'll see from Dr. Krueger's
22 data, if you use early in drug development pharmacodynamic
23 markers, the placebo effect is very small.

24 And so, again, it depends what you're studying and
25 what population you're studying. And then that gets back to

1 the placebo.

2 In the real life, if you have somebody who has
3 moderate to severe psoriasis, the kind of people who are
4 going to be on the biologics, to put in a placebo is even
5 worse than putting in the piddling doses that we talked
6 about this morning. Now you're asking patients to be off
7 their treatments for a month or two, to be on--let's say
8 they have a 1 to 4 or 1 to 6, 1 to 3 chance of being on
9 zero. Then those guys are also going to be excluded from
10 future studies with that. I think that's something that
11 although scientifically I understand, but I think ethically--
12 -is unethical. And, in fact, in the rest of the world, it
13 is not done that way necessarily. In Europe, at least for
14 Phase 3, the paradigm is not versus placebo. The paradigm
15 is versus an active drug. It doesn't necessarily have to be
16 the maximally active.

17 So I would argue that at least for some of these,
18 at least put some kind of a topical--you can have a double
19 dummy study, but don't give them nothing. And if you use
20 the pharmacodynamic markers, you'll see your placebo effect
21 is a lot lower.

22 DR. WEISS: I just want to clarify--

23 CHAIRMAN MCGUIRE: This is Dr. Weiss.

24 DR. WEISS: I'm sorry. I should put this over
25 here so people can see it better.

1 I just want to clarify that when--we're not
2 talking about--in early safety studies often there usually
3 is not a placebo, dose escalation trials. Early on, though,
4 in certain studies, it is oftentimes helpful to have a
5 placebo arm in there, in particular because of potential
6 side effects and determination of, you know, whether or not
7 this is background. It depends on the disease you're
8 talking about.

9 But what I meant placebo--and I'm talking about,
10 you know, the larger efficacy trials--I didn't mean placebo
11 being nothing. Oftentimes what I'm thinking about is the
12 context where a newer immunomodulatory agent is maybe
13 considered as an add-on to existing therapies, and so one
14 arm would have the standard therapy that they're on plus
15 placebo, and the other arm would have the standard therapy
16 plus the new agent. Alternatively, the active control type
17 of studies that you just mentioned are used very commonly in
18 many, many different areas, and that's another area--it's
19 fraught with another set of issues in terms of determining
20 what kinds of claims can come out of it, what kind of
21 comparative claims can be made. That has a lot to do with
22 the study size and the width of the confidence intervals and
23 what amount of benefit you want to be confident that you
24 preserve with the new agent relative to the existing agent.
25 But those are very important types of studies that are used

1 in the regulatory process.

2 DR. GOTTLIEB: So if I understand right, it is not
3 an absolute that even for first study in psoriasis patients
4 that there has to be a placebo, meaning not even a topical
5 active ingredient? Because I'm telling you, there are a lot
6 of companies that are saying that they're required to do it,
7 and actively--

8 DR. WEISS: I don't actually want to get off the
9 topic. That's some of tomorrow's discussion in terms of a
10 particular focus on the biological--the systemic
11 immunomodulatory therapies. So maybe we should just try to
12 bring that up again tomorrow.

13 CHAIRMAN MCGUIRE: I would like to invite the
14 committee to deal with Question 1.d), and then we could take
15 a break after that. We've had a good general discussion
16 over the question that was raised by the agency, and we need
17 to decide whether a minimum reduction should be required if
18 the former is preferred, and (ii), what the cutoff should be
19 if the latter is preferred.

20 Dr. Duvic?

21 DR. DUVIC: I was going to agree with Dr.
22 Schwieterman that you need both and that you would lose
23 information if you limit it to one.

24 CHAIRMAN MCGUIRE: Okay. In other words, both of
25 the above.

1 Dr. Wilkin?

2 DR. WILKIN: If I could just add, I don't think
3 the idea of the dichotomization is to exclude the categories
4 that one might think were--that had improvement that wasn't
5 clinically meaningful. I mean, all of those categories
6 would be collected, and it would be reviewed. It's whether
7 you think, you know, you could cut the line between above
8 this is acceptable and below this isn't.

9 CHAIRMAN MCGUIRE: Dr. Kilpatrick?

10 DR. WILKIN: The data would not be lost to
11 consideration.

12 CHAIRMAN MCGUIRE: Would you like to have the last
13 word on this?

14 DR. KILPATRICK: Certainly. I thought I answered
15 this question because I went back to what I considered and
16 has been discussed by others that the comparison would be
17 not between a placebo and an active drug, but between a new
18 drug put forward by the sponsor and by the existing
19 treatment, which Dr. Weiss was saying.

20 If that's the case, then I defer to the
21 clinicians, but my view is that the sponsor would be pleased
22 if they could show a statistically significant improvement
23 over the standard treatment as judged by whatever modality
24 we decide in terms of efficacy.

25 And so I really do not see that in either (i) or

1 (ii), given that it's a comparison between a new drug and a
2 standard treatment, that we need cutoffs.

3 DR. WILKIN: Yes. Actually, you know, this is
4 both for biologics and for drugs, and in general, for drugs,
5 unless there is an ethical reason why one would not have a
6 placebo arm, a vehicle arm, say, in the topical study, we
7 would like to see active versus vehicle control. So it's
8 not always the active versus active.

9 CHAIRMAN MCGUIRE: But it could be.

10 DR. WILKIN: But it could be, and in that setting,
11 you know, one can set it as a non-inferiority trial where
12 one is looking for at least equivalence of possibly
13 superiority, or one could say, well, here's a new drug that
14 is fairly toxic and here is another treatment modality
15 that's already been approved that's not so toxic, and make a
16 comparison and the agreement might be that superiority would
17 be--

18 CHAIRMAN MCGUIRE: Have you and Dr. Schwieterman
19 heard enough from the committee about this?

20 DR. SCHWIETERMAN: Yes, I think so. We're
21 obviously going to come back with guidance and for comments
22 later, but I think this is good.

23 CHAIRMAN MCGUIRE: Before we go to lunch, let's
24 look at e). Should different weights be given to different
25 signs to support different claims?

1 I think we have discussed that.

2 DR. KILPATRICK: At length in March.

3 CHAIRMAN McGUIRE: Yes, we talked about it in
4 March. My recollection is that the most important sign was
5 plaque thickness. The second sign was area involved, and
6 then redness and scale were below those two.

7 DR. ROSENBERG: I always think redness is the most
8 important. If they're not red, if they stop being red, the
9 rest of it gets better.

10 CHAIRMAN McGUIRE: Well, many of us felt that the
11 color was so variable from hour to hour and day to day that
12 it was not a reliable marker. But that's why there's a
13 committee. Let's hear from the committee.

14 Dr. DiGiovanna?

15 DR. DiGIOVANNA: I don't know that it's absolutely
16 necessary for us to grade them 1 to 4. I think that I have
17 seen patients where you look at them and the redness is so
18 intense, you know that the lesion is very angry. And then
19 there's a sort of redness that waxes and wanes. So I think
20 that most of the time, the thickness of the plaque is the
21 most stable indicator, the most, probably, valuable
22 indicator. I think there are times when redness could be
23 confounding or important.

24 CHAIRMAN McGUIRE: Well, the other issue--

25 DR. DiGIOVANNA: Can we leave scaling at the

1 bottom and put maybe redness closer?

2 CHAIRMAN MCGUIRE: If you will give me this--and
3 that is the paradoxical increase in skin color, in the
4 redness when the scale comes off. And patients say, you
5 know, what are you doing to me, I wasn't this red three days
6 ago.

7 DR. DiGIOVANNA: So you're saying that most of the
8 time plaque thickness is the most stable and, therefore,
9 it's probably the more important indicator. I'd agree.

10 CHAIRMAN MCGUIRE: I'm saying that there are a lot
11 of things that affect the degree of redness, and you thought
12 I was going to say they're red herrings, but I wasn't going
13 to say that.

14 Madeleine, did you have a comment?

15 DR. DUVIC: No--well, some drugs, like retinoids,
16 make the redness worse, but ultimately will clear lesions.
17 So on the way, the redness may even increase, but ultimately
18 you've got no plaque at the end of the day. So along the
19 way it's not a good variable. Maybe at the end of the
20 study, when you stop the drug and wait two weeks, you don't
21 have redness. So if you're going to consider redness and
22 the drug can cause redness, then you have to stop and judge
23 redness later.

24 DR. KILPATRICK: Joe?

25 CHAIRMAN MCGUIRE: Dr. Kilpatrick?

1 DR. KILPATRICK: Again, in March, I made a point
2 that there were various techniques in which you could get an
3 optimal weighting in order to discriminate between different
4 types, and some mention has been made this morning about the
5 precision or lack of accuracy about measuring these
6 different signs and symptoms. And that can be taken into
7 account, but it requires a considerable amount of work and a
8 very highly paid statistician.

9 [Laughter.]

10 CHAIRMAN McGUIRE: Let's break, and Dr. James
11 Krueger will speak to us at 1 o'clock.

12 [Luncheon recess.]

AFTERNOON SESSION

[1:08 p.m.]

CHAIRMAN MCGUIRE: Good afternoon. I'd like to call the afternoon session of Meeting 50 to order and invite Dr. James Krueger to address us.

DR. J. KRUEGER: Dr. McGuire, I'd like to thank you for allowing me to invite myself to this meeting and to give you some comments. Needless to say, I have no conflict of interest in that I'm representing my own views here and that of my patients.

Now, although I have opinions on many areas of psoriasis, I want to try to confine my talks in the next ten minutes to objective measures of outcome by something other than measuring scale, erythema, thickness, and body surface.

In the background of this--and we'll get into this more tomorrow--is the belief of many of us that psoriasis is either an autoimmune or an immune-appropriate disease in which there is an initiating of a resting T-cell into an activated cell that proliferates, and eventually the entry of these cells into skin tissues sets up the disease process that we call psoriasis. And if one is going to think about this disease in mechanistic terms and in terms of the pathobiology, I think it's very helpful to introduce the concept to you that the skin is plastic and it can undergo a change in its growth and differentiation pattern in response to

1 injury, such that the existence of an alternate growth in
2 differentiation program of the epidermis that we retentative
3 (?) growth is essentially a wound-healing response. And
4 what I'm going to try to argue for today is that psoriasis
5 is essentially a manifestation of this in terms of the
6 clinical symptomatology that we recognize, and that like a
7 skin injury which briefly grows and then reverses itself so
8 it goes back to a normal pattern when the skin wound is
9 healed, psoriasis too can be put back into a normal growth
10 pathway by the appropriate kinds of therapy.

11 Now, I don't know if it's possible to turn the
12 lights down at all. These clinical pictures are going to be
13 hard to appreciate without a little bit of reduced light.

14 Okay. Can you see this? This is a patient of
15 ours with typical psoriatic plaques, and I want to show you
16 what the response to therapy is, in this case PUVA, because
17 it shows you some of the problems with the PASI grading
18 scale.

19 So here we have plaques that are defined,
20 discrete. They have lots of scale on the surface, but you
21 can see underneath them that they're really quite red. So
22 if you're going to use a 3-point scale to describe
23 psoriasis, you might say this is a 2 for scale and maybe a 3
24 for redness, and you can't really appreciate the thickness
25 from a photograph, but suffice it to say that you might

1 assign a 3 to plaque.

2 Now, over the course of being treated with PUVA--
3 and this is response to 16 treatments--what you see is here
4 at an early phase in therapy, this plaque scales up, and all
5 the scale becomes white. If you're being perfectly honest
6 in the grading, you would say that this is now perhaps a 3-
7 plus of scale, and there isn't any erythema. You have to
8 assume that underneath it there is, and then finally, the
9 disease melts, and there's clearly less erythema here,
10 there's less scale, and, trust me, it's less thick.
11 Finally, you get to this, where it's continuing to fade.

12 Is there any appreciable change in surface area
13 over the course of this? No. In fact, what's happening is
14 the individual plaque is resolving, and only at the very end
15 of treatment do you get this, which is essentially an area
16 of hyperpigmentation that defines complete clearance of the
17 disease clinically. And that's why you can't use scale,
18 erythema, and thickness to gauge a therapy response with
19 full accuracy. Furthermore, if you've got a black patient
20 or somebody with very dark skin pigmentation, you can't even
21 measure the erythema as a starting point for any degree,
22 and, again, lots of scale precludes erythema. So this
23 system is fundamentally flawed, in my view, and the surface
24 area measurements are much more of a guess than they are a
25 science in terms of making the measurement.

1 Can I still be heard? Because I lost some of the
2 volume on the microphone? Okay.

3 All right. So, instead, what I want to argue is
4 that there are two ways of going about getting objective
5 measures of disease response, and they depend upon
6 understanding some of the patho-biology of this disease.
7 One is to just take routine H&E pathology and compare the
8 background skin on a patient with the diseased skin. And
9 what you see very clearly here is that this normal epidermis
10 thickens considerably, and there's also some inflammatory
11 cells down here in the dermis. But this thickened epidermis
12 becomes the primary thing, along with the inflammation, that
13 indicates the plaque thickness that's being measured
14 clinically. There's also scales heading out here which is
15 hard to quantify on histology, but it certainly is present.
16 You can say it's present or absent.

17 Now, this thickness response is based in turn on a
18 proliferative increase in keratinocytes, and I want to now
19 show you a series of markers that define the difference
20 between unaffected skin on a patient and the diseased skin,
21 and I want to show them to you because they not only define
22 the pathology of the disease, but actually each one of these
23 is reversible back to this stage by the appropriate therapy.

24 So this is keratinocyte proliferation as seen with
25 an antibody reacting with a DNA polymerase sub-unit, Ki-67,

1 and what you can do here is actually count up the number of
2 proliferating cells per area of skin, and you'll see that
3 there are perhaps ten times more proliferating cells. Here
4 there's also positional change in that there are more cells
5 above the basal layer.

6 Now, with this growth activation, there's a change
7 in the differentiation into this wound-healing program. I
8 think this differentiation switch is most clearly marked by
9 expression of new keratins. This is expression of keratin
10 16, which is co-expressed with keratin 6. You can see that
11 the plaque has abundant expression of this keratin; whereas,
12 in the background skin, there isn't any expressed by super-
13 basal keratinocytes.

14 So in some ways, this is the most useful
15 qualitative measure of psoriasis because it defines the
16 turn-on of alternate differentiation, and I'm going to show
17 you that this can also be turned off by the appropriate
18 therapy and, therefore, define a remittive response, at
19 least in pathological terms.

20 Now, the other thing this disease is associated
21 with is the infiltration of skin by T-cells, and you can
22 stain for T-cells in sections with a specific antibody, in
23 this case the CD3, and lo and behold, you can actually go
24 through and count up each one of these and derive a
25 quantitative analysis of how many T-cells are in the

1 disease; and when you are looking at therapeutic responses,
2 you can count what is the percentage reduction in these T-
3 cells; and with very potent therapies, it goes back to this
4 pre-treatment state.

5 Finally, the actions of T-cells in the lesion are
6 at least in part to spew out inflammatory cytokines, such as
7 TNF-alpha and gamma interferon. The keratinocyte in a
8 psoriatic lesion begins to synthesize ICAM and HLADR. It's
9 not present at all in keratinocytes of unaffected skin. So
10 that one can look at the expression of inflammatory
11 molecules like this as a gauge of inflammation. This, too,
12 is a reversible phenomenon with certain kinds of therapeutic
13 manipulation.

14 Finally, as it was suggested this morning,
15 psoriasis can be segregated into what is essentially called
16 thick plaque and thin plaque disease. This here is an
17 example of two patients where this is a biopsy of unaffected
18 skin here and psoriatic lesions here. I think you can
19 appreciate this is typical thick plaque psoriasis. You've
20 got a big difference between this and this.

21 For this patient, that difference is much less.
22 You can see that the epidermis is perhaps only half as thick
23 as it is here, and this is not the most extreme example of
24 thin plaque psoriasis in that it might be only a marginal
25 increase in thickness over the background state.

1 Now, while you can measure plaque thickness
2 clinically pretty well here, here it becomes much more
3 difficult because of this differential to measure plaque
4 thickness, and you might essentially have the ability to
5 describe this as a 1 in thickness and this is a 0, and that
6 doesn't give you very much room for saying that there is
7 improvement.

8 However, if you use some of the protein expression
9 markers such as keratin 16, you can see very clearly one can
10 distinguish psoriatic skin here in this patient from the
11 background skin the same as here. So this is an objective
12 measure of psoriasis, and, in fact, when keratin 16 is
13 turned on, I would say psoriasis as a disease is present,
14 and when it's turned off, psoriasis is absent.

15 Now, what about response to therapy? We define
16 two different scenarios for outcome, and while I can talk
17 about a lot of different markers of epidermal
18 differentiation, essentially what I'd like to focus on is
19 keratin 16. This is response of a patient to ultraviolet B,
20 and this is at the end point of four weeks of treatment on a
21 daily basis as an inpatient. You can psoriatic plaque
22 becomes thick, and it goes back to something that looks like
23 normal skin with a granular area if it's present and more
24 normal stratum corneum. However, the thing I want to really
25 point out is that while this is keratin 16 positive at the

1 beginning, the endpoint here is keratin 16 negative. So
2 this is remission of disease based upon an objective marker.

3 Now, this is useful to stratify responses. You
4 can look at the response of an individual plaque over time
5 using thickness and keratin 16 measures. And this, for
6 example, is a typical plaque in a psoriatic patient which is
7 being treated with two forms of ultraviolet B. I've elected
8 to show you only approved therapies for the disease.

9 So what you have here with one week of treatment,
10 I think you can appreciate, is about a 50 percent reduction
11 in the thickness of the plaque which, after another two
12 weeks of treatment, gets progressively thinner. And,
13 finally, you get to the point of four weeks of treatment
14 where the plaque is perhaps only about a third as thick as
15 where we started, and the keratinocytes are mostly keratin
16 16 negative. In fact, in this study, 88 percent of patients
17 achieve keratin 16 negativity with this particular form of
18 UV. With another form of UV treatment, what you can see
19 here is there is a slower response, and the endpoint that is
20 achieved is different, keratin 16 positive with somewhat
21 more of what's called psoriasiform patterning of the
22 epidermis. So in this case, psoriasis is off. In this
23 case, you would say psoriasis is still on. But there's a
24 substantial improvement in the overall thickness of the
25 plaque. I think thickness is a very useful measure.

1 I'd just go back and say the way we quantify this
2 is we put this image into a computer and measure in an image
3 analysis program the number of square microns and convert
4 that to an average across the sections. So there is a good
5 objective way of making a measurement with thickness.

6 Now, just as there is response over time of
7 plaques that you can see differences, there are therapies
8 that give you an end result which is less than complete
9 clearing. And perhaps the clearest example of this is
10 response to etretinate. So here is a psoriatic plaque
11 before and after treatment with etretinate for two months,
12 and I think what you can see here is that this plaque is, in
13 fact, somewhat thinner and that the scale up here is
14 virtually absent. But there's still psoriasiform pattering.
15 That's the case here in this plaque also. What you see is
16 this tremendously thick plaque with a lot of scale is now
17 thinner, the scale is absent, but there's still psoriasiform
18 pattering. And while I don't have the keratin 16 picture
19 to show you, trust me that all of these are keratin 16
20 positive. So this defines an average result that we call
21 remittive, which means the disease is still present but it's
22 substantially improved over the baseline. We might also
23 have an outcome of no significant improvement when the pre-
24 and post-treatment biopsy might look a lot like this, and I
25 promise you this happens quite a bit with new therapies.

1 Now, of course, this depends on doing a skin
2 biopsy, and that introduces the potential for some bias that
3 exists with using an index plaque score like we talked about
4 this morning.

5 The next thing I want to do is try to translate
6 for you this very good biopsy-based information into
7 something that is more clinically practical, and that is, to
8 use high resolution ultrasound to derive a thickness measure
9 in an objective fashion. And so what we did in a large
10 number of patients was to do an ultrasound of individual
11 areas of skin, and then to biopsy the area of skin that we
12 ultrasounded, and then to take measures of epidermal
13 thickness here by the computer-assisted program and then to
14 use the ultrasound program where thickness could be
15 quantified.

16 Now, what you see on an ultrasound image is that
17 there's a highly reflective zone here that corresponds to
18 the epidermis, and then this area that is less reflective
19 down here is the dermis. When we measure this highly
20 reflective zone, you can see that it has an average
21 thickness of 98 microns, which correlates with a measurement
22 in histology of 107. So these are fairly close in this
23 example. And if we measure a psoriatic plaque, what we see
24 is that there are, in fact, two zones that are superficial.
25 There's this highly reflective zone that comes from highly

1 keratinized cells, and then there is a dark zone here which
2 has to do with inflammation. And so if you sum up these
3 two, you derive an area of thickness that corresponds to
4 what is essentially the top of the epidermis to the
5 beginning of the reticular dermis. So this defines the
6 epidermis plus inflammation in skin.

7 Now, so you can see micron for micron this is 400-
8 -894 microns from the top of the epidermis to the beginning
9 of the reticular dermis. This is 811 microns on the
10 histological section, realizing that there is a shrinkage
11 artifact here by processing such that the tissue is
12 dehydrated, and there you would expect a little bit of
13 reduction here on the basis of the dehydration. Okay.

14 This is the normal. That's the psoriatic.

15 Now, if we ask about response to therapy, I showed
16 you a PUVA response before where the skin was clinically
17 normal. Histologically, it was also normal. So here is a
18 patient getting a PUVA treatment. You can see this
19 reflective zone plus the dark zone that defines the
20 psoriatic lesion. After treatment, you're back to the case
21 of normal skin where there's only a relatively thin
22 epidermis. So this can be quantified and measured. This
23 would, in fact, represent about a four-fold change in
24 overall plaque thickness.

25 For something that we call a suppressive

1 treatment, etretinate, where I showed you the thickness is
2 more, what we have before treatment is a thick plaque, and
3 after treatment you have a reflective zone and then a dark
4 zone. But you can see that if you measure from here to
5 here, it would only be about a third the distance as here in
6 the pre-treatment lesion. So, again, this is what gives you
7 direct way of measuring plaque thickness.

8 Now, does this correlate with histological
9 measures and tissue? I think the answer is yes. Since we
10 biopsied these lesions and ultrasounded them, we plotted out
11 the ultrasound measure of thickness versus the histology
12 measure and drew a line. And you can see the correlation
13 coefficient is 0.94, and these two things relate very, very
14 securely.

15 So I think this technique is amenable to
16 measurement of multiple plaques within a patient with a
17 downside that it depends upon a machine that isn't real
18 cheap to buy, but certainly could be rented for these kinds
19 of studies and represents a compromise position in terms of
20 assembling a data set that is absolutely uniform between one
21 site and the next in terms of ability to secure a picture of
22 the disease. I favor the biopsy because it also has the
23 potential to give you mechanistic information about
24 inflammation and number of T-cells and the number of other
25 inflammatory circuits that are going on. But as a surrogate

1 of that, as you will, I think the ultrasound is actually a
2 reasonable tool for measurement. And I think both of these
3 have major advantages over measuring scale, erythema, and
4 thickness, and certainly allows you to derive the plaque
5 thickness measure more accurately than you could by eye.

6 I think with that I'm going to stop. Questions?

7 CHAIRMAN MCGUIRE: Dr. DiGiovanna?

8 DR. DiGIOVANNA: I'm somewhat disappointed that we
9 didn't get to see the clinical correlate of your post-
10 treatment. I'm really astounded that in two months of
11 tegasone (ph), you're able to get a clearing of the clinical
12 lesion because usually it takes longer than that. And the
13 other thing I'm surprised at is that you can actually
14 demonstrate acanthosis or thickening both histologically and
15 by ultrasound and not feel it or see it in the skin.

16 So my question is: Is that two months really as
17 clear as the PUVA ones? Because--

18 DR. J. KRUEGER: No, no, no. It's not, and my
19 histology was, in fact, showing an intermediate state. That
20 is, you still had epidermal hyperplasia. It was reduced
21 over the background. The biopsy was still keratin 16
22 positive, and clinically--I'm sorry. I didn't think I was
23 going to have as much time as I did. I thought I had five
24 minutes.

25 DR. GOTTLIEB: You said remittive. That was the

1 problem.

2 DR. J. KRUEGER: Oh, I'm sorry. That's--

3 DR. GOTTLIEB: Instead of suppressive, you said
4 remittive.

5 DR. J. KRUEGER: I misspoke. I think etretinate
6 is the best example we have of a suppressive therapy. It
7 gives you a partial disease improvement. It does not remit
8 the disease clinically, pathologically, or on the basis of
9 discrete markers.

10 DR. DiGIOVANNA: I respectfully disagree with you.
11 I think in some patients that's true, and in other patients,
12 in my experience, that's not necessarily true.

13 DR. J. KRUEGER: These are published--

14 DR. DiGIOVANNA: I understand, and I've read them.
15 However, if your issue is that the ultrasound mirrors the
16 histology, I can agree with that. If your issue is that
17 this presentation demonstrates that etretinate is
18 mechanistically different because it hasn't gotten a
19 clearing by two months, I think that's something we
20 wouldn't--I wouldn't necessarily expect to happen by two
21 months.

22 DR. J. KRUEGER: Okay. That's a point we can talk
23 about further.

24 CHAIRMAN McGUIRE: McGuire here. I was really
25 pleased to see these data. I may have seen them some time

1 in the past and forgot it, but the correlation between the
2 ultrasound and histology I think is very reassuring.

3 When I was going over the material when I was
4 preparing my notes for the next couple of days, I had
5 written down under measures, ultrasound, Doppler blood flow,
6 and colorimetry. And at least you--

7 DR. J. KRUEGER: We've also done Doppler
8 measurements also for blood flow. They're much harder to do
9 and to get a firm baseline because of the way the machines
10 are set up. Colorimetry I have never tried.

11 CHAIRMAN MCGUIRE: But this for the first time
12 gets us a non-invasive way of looking at something
13 meaningful in terms of thickness of the plaque.

14 Dr. Duvic?

15 DR. DUVIC: This is really a gold standard for
16 measuring psoriasis, and I applaud the work. It's
17 beautiful.

18 Is there any variation from one part of the lesion
19 to the outer rim in terms of--are you really able to take
20 four consecutive biopsies from the same lesion and not have
21 a sampling error and still treat the lesion clinically, like
22 with a topical agent? Because I think that's been a problem
23 in designing these studies in the past, is how do you treat
24 and biopsy the same lesion.

25 DR. J. KRUEGER: Well, I think you'd have to have

1 a relatively larger lesion to do this with.

2 DR. DUVIC: Right.

3 DR. J. KRUEGER: Therefore, for mild patients with
4 small plaques, this may not be ideal. The ultrasound is not
5 an issue.

6 DR. DUVIC: I understand that.

7 DR. J. KRUEGER: And for most of what I'm dealing
8 with, it's the analysis of moderate to severe patients, not
9 on topicals. It does work for topicals, but you need larger
10 plaques to be able to do it so you don't interfere with the
11 psoriasis.

12 DR. DUVIC: So you would do it like in the center
13 of a lesion?

14 DR. J. KRUEGER: Yes, I would--often the response,
15 even with PUVA, the response of the very edge of the lesion
16 is the last to go. So we try to stay a centimeter or two
17 inside the lesion and biopsy essentially like a clock, to go
18 around the lesion and biopsy the same distance from the edge
19 so that we have something--and from the ultrasound that
20 we've done, we know that the plaques are uniform in
21 thickness across the plaques, so that's not really an issue.

22 DR. DUVIC: And I think that, whenever possible,
23 at least in small studies, this work should be done. But if
24 you're doing 350 patients at 20 centers, it might be a
25 little bit of a problem.

1 DR. J. KRUEGER: It's harder. I would say, you
2 know, if possible, in the larger studies it would be useful
3 either to have ultrasound or even a four millimeter punch
4 that's put into formalin for H&E because the thickness
5 measures and differentiation can be looked at there and
6 quantified by a central laboratory, so you take away the
7 inter-site variation in terms of measurements. And that's
8 not really a very big deal.

9 DR. DUVIC: I agree.

10 CHAIRMAN MCGUIRE: Dr. Rosenberg?

11 DR. ROSENBERG: To back up to the biological
12 markers of activity, including the one with the keratin 16,
13 the other with lymphocyte markers. I'm sorry I didn't bring
14 it, but there was an article in British Journal in the last
15 three or four months from, I think, France or Spain where
16 they used some--I think it was an IL-2 modifying agent and
17 found that the number of CD--is it CD11 cells, markers,
18 diminished greatly but that the psoriasis didn't get any
19 better. Then they speculated on that for a while, why that
20 could have happened. Do you recall that paper, and could
21 you comment on it?

22 DR. J. KRUEGER: No, actually, I haven't seen the
23 paper so it's hard to comment.

24 DR. ROSENBERG: Sorry.

25 DR. J. KRUEGER: The CD11 marker could be either

1 T-cells for CD11A or macrophages for CD11B.

2 DR. ROSENBERG: I think it was the macrophages.

3 DR. J. KRUEGER: It may have been macrophages, in
4 which case I wouldn't necessarily expect that rate of
5 change.

6 CHAIRMAN MCGUIRE: Gerald?

7 DR. G. KRUEGER: Mr. Chairman, can I get
8 unconflicted?

9 CHAIRMAN MCGUIRE: Yes. This is Dr. Gerald
10 Krueger speaking.

11 That's Dr. James Krueger.

12 DR. G. KRUEGER: I think that the paper you're
13 referring to was on tecrolamus(ph) and atopic dermatitis and
14 psoriasis where they showed the changes. I'm not sure on
15 that, Bill, but I think that is the paper. And I don't
16 understand a lot of things in life, but I don't understand
17 that one either.

18 There are two things that I think perhaps would--
19 in rushing through this, the remittive therapies, as I
20 recall, you have said in the past that you think you can
21 predict which ones are going to be remittive with your
22 biologic markers. So comment on that, if you would.

23 Then I fall down and scrape myself. I injure the
24 skin. Do I see the same kind of markers there relative to
25 keratins and the other?

1 Thank you.

2 DR. J. KRUEGER: Okay. The first question--well,
3 let me answer the second question, then the first question.
4 You fall down and scrape your skin. Actually, you do
5 activate exactly the same set of keratinocyte markers. You
6 may see less infiltration by T-cells, but fundamentally, the
7 keratinocyte response is the same whether it is psoriasis, a
8 wound, or another inflammatory disease. So that much is
9 pretty much the same.

10 Your first question was?

11 DR. G. KRUEGER: With the remittive therapy, can
12 you predict it?

13 DR. J. KRUEGER: By the way I'm using suppressive
14 and remittive here, I'm using them a little bit different
15 than Alice did in the morning session. I think you can say
16 with certainty on the basis of something like keratin 16 and
17 the other assembly of markers that you have remitted the
18 disease pathology at the time you do the biopsy. I think
19 that has implications for duration of remission, if you
20 will, in that you haven't turned off keratin 16 and you
21 still have inflammation, you will have a short period of
22 benefit. If you've turned it off all the way--and I think
23 it depends on the mechanism of anti-inflammatory, if you
24 will, and that is, a T-cell toxic agent that gives you no T-
25 cells in skin may very well then produce months of

1 remission; whereas, something like, let's just say,
2 cyclosporine or something like that, that left the T-cells
3 in skin and didn't kill them but may have turned off most of
4 the markers would still have a relatively short relapse
5 period. So I think you need to think about both mechanism
6 and the endpoint that you achieve in therapy. I think
7 probably there is some predictive value in terms of ability
8 to say what's going to happen in the long run with it.

9 CHAIRMAN McGUIRE: Dr. DiGiovanna?

10 DR. DiGIOVANNA: You showed one slide of the
11 ultrasound of psoriasis that differentiated two areas. The
12 top area was the hyperkeratosis and stratum corneum and the
13 upper part of the epidermis, and the lower area was, I
14 believe, down to the lower level of inflammation. And my
15 question is: If there is a change in the amount of
16 hyperkeratosis--

17 DR. J. KRUEGER: Yes.

18 DR. DiGIOVANNA: Can you distinguish that?

19 DR. J. KRUEGER: I think so. I think the
20 hyperkeratosis, particularly the scale out on top, would be
21 reflected by a decrease in this highly reflective zone,
22 because what's showing here is the highly keratinized
23 portion of the plaque. I've shown you the measure here to
24 the super-papillary area, but if you do electromicroscopy of
25 a psoriatic lesion, you see a lot of keratin filaments

1 packed in up here, and here they're relatively sparse. So I
2 think you could evaluation the hyperkeratosis component by
3 looking at that. We haven't really done it in a way that I
4 would feel comfortable telling you about here.

5 DR. DiGIOVANNA: So if you were going to use this,
6 let's say, if a pharmaceutical company was going to use this
7 as part of a trial to evaluate thickness, that thickness
8 might be confound--the thickness of the live epidermis might
9 be confounded by the amount of hyperkeratosis that was on
10 top?

11 DR. J. KRUEGER: No, I don't think so. I think
12 the measurement that I would urge one to make is this
13 measurement from here to here, which is the top of the
14 stratum corneum to the beginning of the reticular dermis,
15 and that, therefore, is relatively independent of the amount
16 of scale or very highly keratinized tissue on top. So this
17 is a pretty good measure of how much, how thick a plaque--
18 this is what is measured clinically with plaque induration.
19 It's some combination of scale buildup and inflammation and
20 induration in tissue. And that inflammation/induration
21 happens here in the papillary dermis with the component of
22 epidermal expansion. So I think it's valid clinically.

23 CHAIRMAN McGUIRE: Dr. Kilpatrick?

24 DR. KILPATRICK: Thank you. Could we go back,
25 sir, to the slide showing the correlation of 0.94?

1 DR. J. KRUEGER: Sure. I'm not sure I should show
2 it to a live statistician.

3 DR. KILPATRICK: Thank you, or apologies, or
4 whatever. I'm commenting about the--0.94 is very
5 impressive, explanatory of about 88 percent. I'm more
6 struck by the fact that the line doesn't go through the
7 double zero. Does that imply that there should be an
8 adjustment in the conversion from one to the other? Is this
9 a function of your shrinkage?

10 DR. J. KRUEGER: Well, the fact that it doesn't go
11 through zero means that normal skin has a definable
12 thickness. It's about 100 microns of thickness of normal
13 skin, so that's, in fact, why it doesn't go to zero.

14 DR. KILPATRICK: Well, good. I learned something.

15 CHAIRMAN McGUIRE: Dr. Rosenberg?

16 DR. ROSENBERG: Going back to the markers, what's
17 your experience with pustular psoriasis?

18 DR. J. KRUEGER: Pustular psoriasis is just like
19 plaque psoriasis in terms of the background keratinocyte
20 changes that I showed you. The difference is that it has
21 many, many more neutrophils in it compared to psoriasis
22 vulgaris. So you may see lakes of pus up in the stratum
23 corneum, but that's essentially it.

24 CHAIRMAN McGUIRE: Dr. Krueger, thank you very
25 much.

1 DR. WILKIN: Dr. McGuire, could I ask just one--

2 CHAIRMAN MCGUIRE: Sure. Dr. Wilkin?

3 DR. WILKIN: I would have kind of guessed at the
4 beginning that the histology and the ultrasound went in the
5 same direction, so correlation I think one would have
6 predicted. But how about something like concordance? Can
7 you actually use, you know, a certain ultrasound
8 measurement? How well does that predict a specific
9 histologic thickness?

10 DR. J. KRUEGER: I think we did the reverse
11 analysis, but from this it would be pretty close. The
12 individual data points are plotted here.

13 DR. KILPATRICK: May I ask Dr. Wilkin to define
14 "concordance"?

15 DR. WILKIN: I absolutely refuse to do that in the
16 presence of a statistician.

17 [Laughter.]

18 DR. WILKIN: I was thinking of the one that had
19 the cappa(?). You may want to--

20 CHAIRMAN MCGUIRE: Well, I think--

21 DR. KILPATRICK: This is--sorry. Let's leave it,
22 Joe?

23 CHAIRMAN MCGUIRE: I think so. I think we have to
24 do this work now. We've had a very pleasant lecture, and
25 we've all learned something and--

1 DR. J. KRUEGER: I'd better get out of here
2 before...

3 CHAIRMAN MCGUIRE: So take your slides and go,
4 Jim.

5 [Laughter.]

xx 6 CHAIRMAN MCGUIRE: Well, I think we have to face
7 the task that the agency has set up for us here.

8 By the way, I'd like to tell the committee, we got
9 a lot of work done this morning and thanks for sticking to
10 the issues.

11 The next topic to be discussed is global
12 evaluation by the investigator, and there are three items
13 under global evaluation. Should the evaluation be based on
14 changes from baseline (from memory or from photography) or
15 be static? b) What should be considered as a minimally
16 successful outcome for approval? What additional higher
17 levels of successful outcome may be crafted into the label
18 for information to the prescriber? c) Should there be a
19 minimal acceptable difference between the product and
20 placebo? If so, what would be acceptable?

21 If there is someone on the committee who doesn't
22 have any particular bias about global evaluation, you could
23 help me with this question. John? John took the bait
24 first.

25 DR. DiGIOVANNA: I think the global evaluation is

1 essential in evaluating a systemic therapy and useful in
2 evaluating a topical therapy. I think it requires some sort
3 of documentation such as photograph, or it's useless.

4 CHAIRMAN McGUIRE: Madeleine?

5 DR. DUVIC: I agree. An investigator cannot
6 remember baseline well, and I think either a static at the
7 time you see the patient or referral back to some sort of
8 diagram or photography is necessary. I agree with John.

9 CHAIRMAN McGUIRE: And the point that was made in
10 the March meeting is that the photography needs to be
11 comparative photography, because the interpretation by the
12 viewer was based upon the previous photographs of whichever
13 patient he had seen. If the previous photographs were
14 extensive psoriasis, then he tended to minimize the current
15 photo, or the photographs on the current patient. So it
16 needs to be serial photography.

17 DR. DUVIC: I will add, though, the technology is
18 available to take digital images with a small digital
19 camera, if you could standardize that and have a computer
20 measure body surface area if you wanted to us that as one of
21 your indicators of response.

22 CHAIRMAN McGUIRE: Okay. So global evaluation is
23 valuable, and it should be from photography.

24 What should be considered as minimally successful
25 outcome for approval? What additional higher levels of

1 successful outcome may be crafted into the label for
2 information to the prescriber? John? Dr. DiGiovanna?

3 DR. DiGIOVANNA: I don't know what exactly would
4 make the FDA--what sort of answer would make the FDA happy,
5 but I think once again that there are many partially
6 effective or most effective therapies that are useful in
7 some clinical situations in combination with other
8 therapies, and I think if someone wanted to develop such a
9 therapy, there would be potentially a use for it. And that
10 therapy probably could be documented as efficacious with a
11 very low level of rigor.

12 However, I think there's also a concern on the
13 part of dermatologists, patients, and people who pay for
14 medications that if a therapy is going to work very poorly,
15 they may want to know that fact and reserve that for
16 selected clinical situations. So those therapies that pass
17 a higher bar, that give a larger degree of improvement, 75
18 percent or higher, or whatever number one would craft, it
19 would be very valuable to know that. It might also be
20 valuable to have information for certain therapies about the
21 post-treatment remission.

22 CHAIRMAN McGUIRE: John, I'm quite sure that this
23 is your question. Dr. Wilkin?

24 DR. WILKIN: It's Dr. Ko's but--

25 CHAIRMAN McGUIRE: No, I was going to ask you if

1 we are responding to your question.

2 DR. WILKIN: Absolutely.

3 DR. DUVIC: Can I say something?

4 CHAIRMAN MCGUIRE: Okay. Dr. Duvic? Then Dr. Ko.

5 DR. DUVIC: Psoriasis isn't one disease, and there
6 may be 30 or 40 percent of patients who have 100 percent
7 response on one treatment. And then there may be other
8 treatments where more people respond. So I think if you
9 have to--whatever guideline you adapt has to take that into
10 consideration. For the 20 percent of people who get a
11 complete response on a drug, that's a very meaningful drug,
12 and that's important.

13 I think generally, if it's going to work in all
14 patients, it has to at least improve by 50 percent, but
15 that's just a cutoff, or 40 percent, something. That's kind
16 of arbitrary. All of these things are arbitrary.

17 CHAIRMAN MCGUIRE: Dr. Ko, you had a question or a
18 comment?

19 DR. KO: It's not really a question. It's about
20 this question itself. As you heard earlier today, the
21 agency is looking for some minimally clinically meaningful
22 outcome, and that's why this is the first part of the
23 question. But then in addition to that, there may be
24 additionally useful information if a drug has passed that
25 bar. And so that's the second part of the question.

1 CHAIRMAN McGUIRE: Well, Dr. Duvic, you spoke to
2 that. Who down here had--Dr. Rosenberg?

3 DR. ROSENBERG: I want to say that I am
4 sympathetic to the concerns of the FDA, of staff here, and
5 how are you going to be sure that something is good enough
6 to really say that it's good enough to be used. Without
7 going into details, there are agents that have been
8 approved, and, you know, they come out and we get samples,
9 and we write a couple prescriptions and come to the
10 conclusion this stuff really is hardly worthwhile at all, at
11 best. Then the sales rep comes around, and she says, well,
12 how do you like it? And we say, well, it really doesn't
13 seem to work at all. And she says, oh, well, the real way
14 to use it is to have him use the ultra-potent topical
15 steroid in the morning, and then use some of this at night,
16 and you do that for four weeks, or you use the potent
17 topical steroid twice a day for two weeks, and then you
18 start to ease in with this one, and then after a while they
19 really get the full benefit of it.

20 I'm not making this up, as the man says in the
21 newspaper. That is the way things are--in the outside
22 world, this is the way major products are promoted for
23 people with psoriasis.

24 CHAIRMAN McGUIRE: Okay. Did you want to comment
25 on Question 2.b), Bill? What additional higher levels of

1 successful outcome may be crafted into the label for
2 information to the prescriber?

3 Okay, Dr. DiGiovanna?

4 DR. DiGIOVANNA: In relationship to this question
5 and in support and reiteration of an extremely valuable
6 point that Madeleine Duvic made, I also very firmly believe
7 that psoriasis is more than one condition and acts
8 differently. And I've had several patients who have their
9 own drug and say this drug works for me and for other
10 patients it doesn't work as well. So there are really two
11 issues here, one of which is: Would a product be effective
12 for a small percentage of psoriatic patients? And the other
13 issue is: Would a product be marginally effective for a
14 larger percentage of psoriatic patients? And I think
15 they're both involved in this question.

16 CHAIRMAN McGUIRE: And I think the agency is
17 sensitive to that issue.

18 DR. WEISS: Dr. McGuire, I just want to say that a
19 corollary to that, it depends to some extent, too, on the
20 type of toxicities of that agent because if there's
21 something that works great in a small proportion but has
22 quite a bit of toxicities, then the difficulty is trying to
23 figure out, if possible, how to define that population for
24 whom the risk/benefit is acceptable, and it's not always an
25 easy thing when you try to tease out who--if you want to

1 indicate the agent, you know, who to indicate it for.

2 CHAIRMAN McGUIRE: Dr. Schwieterman, did you have
3 a comment?

4 DR. SCHWIETERMAN: Dr. Weiss just covered it.

5 DR. DiGIOVANNA: I think there's a new science
6 called pharmacogenomics that's looking at various
7 polymorphisms that relate to how people respond to drugs,
8 and I think when we learn more about psoriasis, we may be
9 able to do that.

10 DR. DUVIC: And that's why the molecular marker
11 studies are so helpful in subdividing subsets of the disease
12 pattern.

13 CHAIRMAN McGUIRE: I'm ready for c). Should there
14 be a minimal acceptable difference between the product and
15 placebo? If so, what would be acceptable?

16 We've already discussed the fact that a true
17 placebo is probably not going to be found, that most of the
18 vehicles have some therapeutic effect, and so what would be
19 the minimal acceptable? I think the question is stated in a
20 very helpful way. What would be a minimal acceptable
21 difference between the product and placebo?

22 DR. SCHWIETERMAN: Actually, Dr. McGuire, just to
23 clarify, it's not what would be necessary, but should there
24 be. In other words, if you saw a clinical delta between the
25 placebo arm and the investigational arm that was

1 statistically significant, that would be a difference.

2 Should there be a minimum in addition to that applied to
3 that before you'd approve it?

4 CHAIRMAN McGUIRE: And then if so, what--

5 DR. SCHWIETERMAN: If so, what would that be?

6 DR. DUVIC: Doesn't that depend on how good the
7 placebo is itself? I mean, maybe if you got a placebo
8 that's 40 percent effective just because it's a good
9 vehicle, and then you get 10 more with the drug, that's up
10 to 50 percent. That should be pretty acceptable. Whereas,
11 if you've got a placebo effect of 5 percent, then you're not
12 that impressed with the 15 percent response with the drug.

13 DR. SCHWIETERMAN: You're absolutely right. If
14 the placebo rate is high, then--well, it does make a big
15 difference on that, but I guess what this question is
16 getting at is not really so much the point estimate. But
17 when you detect clinical differences from placebo, wherever
18 that is, is that good enough or should there be some minimal
19 threshold? We've had a lot of discussion about how
20 different patients have different thresholds and so forth.
21 So I think there's room for debate on this.

22 DR. DUVIC: I think it's really hard with topicals
23 because there is such a big placebo effect. Systemic it's
24 probably a different issue.

25 DR. ROSENBERG: Isn't the placebo its own vehicle?

1 I mean, isn't that the way everybody's always done
2 everything? What's happened here? I mean, the placebo has
3 got to be the same vehicle that the so-called active is in.

4 DR. DUVIC: It is, and sometimes that works very
5 well.

6 DR. ROSENBERG: Well, then the active isn't worth
7 it. It's real clear.

8 CHAIRMAN McGUIRE: That's not the point.

9 DR. DUVIC: It does if it remits the disease after
10 you stop it but the vehicle, it comes right back. For
11 instance, that's another way to look at this effect.

12 CHAIRMAN McGUIRE: You could turn the question on
13 its head. Can you improve the placebo by adding the active
14 material?

15 DR. DUVIC: Exactly.

16 CHAIRMAN McGUIRE: And how much improvement--

17 DR. ROSENBERG: As they say in the business, they
18 can lower their cost of goods by leaving home the active and
19 selling it, getting approved for the placebo. That would
20 cheer up the business office.

21 CHAIRMAN McGUIRE: Go ahead, Dr. Schwieterman.

22 DR. SCHWIETERMAN: Still, the question really has
23 less to do with the placebo than you've demonstrated a
24 difference between the investigational agent and whatever
25 control arm used in this case. We're talking about placebo.

1 Ought that difference to be of some minimal clinical delta
2 or not?

3 CHAIRMAN MCGUIRE: Dr. Wilkin?

4 DR. WILKIN: Yes, I Dr. Schwieterman just nailed
5 it exactly. Basically, if one defines what a successful
6 endpoint is, at whatever level needs to be achieved, then at
7 the end of the day it's the proportion of patients assigned
8 the active versus the proportion of patients assigned the
9 placebo. It's proportion that we would be looking at.

10 DR. SCHWIETERMAN: I mean, just to--I'm sorry.
11 This is Dr. Schwieterman. One could easily say that no,
12 there isn't a need for minimal threshold. After all, you've
13 detected a difference, and if your clinical endpoint is
14 measuring some direct measure of clinical benefit, although
15 you have it, you have something that's more clinically
16 beneficial than the other, why would there need to be a
17 minimum?

18 On the other hand, if you would argue that what
19 you're measuring may be clinically meaningful but so
20 insignificant to patient benefit that there would need to be
21 some minimal threshold to rule out--I mean, if there were no
22 toxic events, then it wouldn't matter. But hardly any agent
23 we approve, if any, has no toxic events, you would want some
24 minimal threshold with that. In some sense, this is sort of
25 an arbitrary question because it would depend on the case,

1 obviously, and the toxicities. But in principle, ought
2 there to be a minimum or not? And I guess that's what we're
3 looking for.

4 CHAIRMAN McGUIRE: Dr. DiGiovanna?

5 DR. DiGIOVANNA: I don't mean to cloud the issue
6 more, but I think one issue that phrasing the question in
7 that way raises is if this is the sort of study that is
8 going to find a minimal overall improvement, but that's
9 going to represent a few of the patients having a
10 substantial improvement diluted by many patients not have a
11 substantial improvement, then you're going to miss a drug
12 that's potentially very efficacious for a small number of
13 patients, and even with a significant amount of toxicity, it
14 might prove to be an acceptable drug.

15 On the other hand, if it is a minimally
16 efficacious preparation that's very benign, that has no
17 toxicities, then if you're willing to adjust in labeling the
18 fact that this has a minimal amount of activity, it still
19 conceivably could be useful for some patients in certain
20 clinical circumstances.

21 However, I think what the public and the
22 physicians would like, and certainly all the people who pay
23 for the medications, is knowing if this is going to be an
24 expensive drug that does very little and separating that out
25 from a drug that really does have efficacy. So I think that

1 there is usefulness to look at all of those parameters in
2 certain situations.

3 CHAIRMAN McGUIRE: And the point that has been
4 made repeatedly is that we don't want to miss an agent that
5 is very effective for a small number of patients. We want
6 to capture those.

7 DR. DiGIOVANNA: And if I may, there are agents in
8 psoriasis that are like that. For example, etretinate and
9 Soriatane for pustular psoriasis and even acutane can be
10 extraordinarily effective in a life-threatening disorder and
11 can turn it off within a period of hours to a few days. So
12 there is a precedent for that with this disease.

13 CHAIRMAN McGUIRE: Okay. I'm through with c).

14 DR. SCHWIETERMAN: So are we?

15 CHAIRMAN McGUIRE: Pulling the committee, Question
16 3, body surface area of involvement. It is well known that
17 percent body surface area evaluations are difficult and
18 often inaccurate. It is also age dependent.

19 Question a) Should body surface area be used as
20 one of the major outcome variables? b) How can the
21 measurement of this parameter be improved? c) How should a
22 cluster of discrete lesions be measured, individually or in
23 combination, such that normal-looking skin between them is
24 included?

25 We covered 3.c) in some detail in March. Does the

1 committee feel that body surface area should be included?
2 John?

3 DR. DiGIOVANNA: I believe, and I believe I will
4 be at odds with Dr. Krueger, but I believe that body surface
5 area is a useful measurement in some clinical situations,
6 and in other clinical situations it may not be useful. In
7 patients or with treatments where the lesions, quote-
8 unquote, melt down, I don't think it's very helpful because
9 it doesn't change very much until it's no longer very
10 useful.

11 There are other therapies that occasionally
12 patients will flare intermittently and lesions will enlarge,
13 and in those situations, it conceivably could be useful or
14 would be useful. And there are some therapies where the
15 lesions will clear from the center and leave rings, and in
16 that situation also it can be a useful parameter. So I
17 think there are situations where it helps and there are
18 situations where it doesn't. I don't think there are
19 situations where it hurts.

20 CHAIRMAN McGUIRE: In other words, if you don't
21 collect the data, you can't do anything with it.

22 DR. DiGIOVANNA: Right.

23 CHAIRMAN McGUIRE: Dr. Duvic?

24 DR. DUVIC: I just wanted to make the point that
25 psoriasis, usually, it's like going, going, going, gone. So

1 body surface area is most useful at baseline and then at end
2 of study, but not very useful in the interim period unless
3 you have kevnarization(ph) where the disease actually
4 worsens, like John said.

5 Also, it's extraordinarily difficult to measure
6 objectively in a clinical setting. You're up there putting
7 palms on patients, and you've got little lesions and big
8 lesions. So if you're going to use body surface area as an
9 objective measurement, you've got to have some sort of a way
10 to measure it that's more objective, like digitization or
11 like a weighted burden score where you actually draw the
12 lesions on a grid or a little man and then measure them with
13 a grid or something. And that's very time-consuming. It's
14 very difficult for the investigator to do that kind of
15 measurement, and I'm not sure it's that accurate.

16 So I think it's a hard--I think when the data
17 works, it goes from 80 percent to 0, it's great, but it's
18 always not that clean-cut, is what I'm trying to say.

19 CHAIRMAN McGUIRE: I guess the committee is
20 telling the agency that we appreciate the fact that you put
21 this question on our card, and it's an important issue, and
22 measurement--you know, even if you're doing wound-healing
23 studies with a single ulcer, that's not easy. And if you're
24 dealing with a disorder in which there may be two to several
25 hundred lesions, it's very difficult. And that leads into

1 Question 3.c), which we discussed in March. And if you're
2 dealing with a disease such a varicella, you may have 95
3 percent of body surface involved, but actually only 3
4 percent of the skin is involved. But that 3 percent is
5 scattered everywhere. The same applies, obviously, to
6 guttate psoriasis. And I don't have a clever idea of how to
7 deal with that other than describe what is being seen.

8 Did you have a comment, Dr. Rosenberg?

9 DR. ROSENBERG: I was waiting for it to come up,
10 but it doesn't seem to be in this list of things. I think
11 subjective global evaluation by the subject on a linear
12 scale, on a 0 to 10 scale, unless that's on here, would be
13 very useful, because it will allow the patient who's upset--
14 does that come next? Okay. Well, then we'll get to that.
15 Sorry.

16 CHAIRMAN McGUIRE: Okay.

17 DR. KILPATRICK: May I ask--Dr. Kilpatrick. I'm
18 here to learn as well as criticize. Why is body surface
19 area evaluation age dependent?

20 DR. KO: Pediatric patients, the surface area may
21 vary in proportion to the actual size of the patient, or
22 weight. So that's the reason for saying that.

23 CHAIRMAN McGUIRE: Jim, I don't know what that's
24 about. The ratio of weight to area changes.

25 DR. KILPATRICK: For some people.

1 CHAIRMAN MCGUIRE: Well, as you go from a sphere
2 to something else. But I don't know what that--

3 [Laughter.]

4 CHAIRMAN MCGUIRE: I don't know how that relates--

5 DR. KILPATRICK: Thank you very much.

6 CHAIRMAN MCGUIRE: John, is there something in
7 that question that I'm missing?

8 DR. WILKIN: I think actually it emerged from some
9 internal discussions where if one uses the rule of nine
10 scale, that that really is for adults, and that if you're
11 going to look at children with psoriasis, it might be a
12 somewhat different scale. That was the question. We really
13 didn't see something in the literature that--you know, sort
14 of the allometry of development.

15 DR. KILPATRICK: But to follow up and be serious,
16 if this is--I understand that these measures may be taken
17 over a long period of time. Therefore, the patient will be
18 aging. But that's not a consideration. Is that right?
19 You're not thinking about--

20 DR. WILKIN: No, we were thinking that the
21 medication would probably work before they got too much
22 larger.

23 [Laughter.]

24 DR. WILKIN: We were thinking that the scale might
25 be--the manner of estimating body surface area, the rule

1 that would be used, the calculus, would be different between
2 adults and children. And we were just interested if someone
3 at the table knew of some particular methodology.

4 DR. DUVIC: May I speak?

5 CHAIRMAN McGUIRE: Yes, Dr. Duvic?

6 DR. DUVIC: The thing that changes body surface
7 area is obesity where you have a large, you know, frontal
8 protuberance, and that takes up more than it's supposed to
9 in terms of body surface area, I think.

10 CHAIRMAN McGUIRE: I'm through with 3 unless the
11 agency wants--okay. Subjective measures, pruritus.
12 Pruritus can be an important symptom in some patients with
13 psoriasis. a) Should the symptom be analyzed in those who
14 experience it from baseline, or should the entire study
15 population be included in the analysis?

16 Dr. Miller?

17 DR. MILLER: I think it should be included at both
18 times. You certainly would want to know if someone started
19 off with pruritus as he or she was treated, if there was an
20 improvement. And you also want to know if the drug causes
21 any problem. So I think it's something that you would
22 evaluate from start to finish.

23 CHAIRMAN McGUIRE: I agree. The committee agrees?

24 DR. DUVIC: Yes.

25 CHAIRMAN McGUIRE: Yes. Global evaluation by

1 patient. For some patients, psoriasis may be a cosmetic
2 problem. Should a patient's global be evaluated? If so,
3 should the data be stratified according to the patient's
4 baseline perception? What weight should be given to this
5 variable?

6 Comments?

7 DR. DUVIC: The patient's perception of
8 improvement is important, and I think a VAS (?) scale is a
9 good way of evaluating this that can be quantitated
10 somewhat.

11 CHAIRMAN McGUIRE: Okay. Patient populations.
12 Patient population for early, Phase 1, safety studies. One
13 of the issues that needs to be considered in clinical
14 development is the selection of the appropriate patient
15 population for Phase 1 studies. In many settings, Phase 1
16 studies are conducted in normal volunteers so that safety
17 and tolerability can be assessed in the absence of
18 confounding patient/disease-related factors. In cases where
19 the experimental therapy may have significant toxicities,
20 normal volunteer studies may not be appropriate; Phase 1
21 studies are then conducted in patients with this disease.

22 In the absence of prior human experience, it may
23 not be desirable or appropriate to expose patients with
24 stable disease and/or those who are doing well on existing
25 treatments to an investigational treatment with no known

1 benefit, but with potential/theoretical risks. Such new
2 agents for psoriasis, particularly systemically administered
3 agents or topicals with high systemic absorption, are
4 usually first administered to patients with more severe
5 disease.

6 Please discuss the criteria (e.g. total body
7 surface area involvement, grade of plaque thickness) that
8 are useful measures of severity for plaque psoriasis.
9 Please discuss the criteria that best define mild, moderate,
10 moderate to severe, and severe plaque psoriasis.

11 Any help over here? Dr. DiGiovanna?

12 DR. DiGIOVANNA: My recollection is that we had an
13 extensive discussion of this at the prior meeting, and I
14 believe it was Dr. Lebwohl who showed a very interesting
15 study you alluded to before where he had people grade
16 patients after seeing a very severe patient and then after
17 seeing a milder patient. And I think that these criteria
18 are difficult to define, and I don't know--certainly we
19 don't like the PASI score, but I don't know what the answer
20 is.

21 CHAIRMAN McGUIRE: One suggestion has been to have
22 standardized photographs and simply have one group of
23 photographs define that category, another group of
24 photographs define this category, another group of
25 photographs, and use those as standards. I think with this

1 kind of assessment that may be as precise as you can get.

2 DR. DiGIOVANNA: There's at least one, and maybe
3 more than one, published grading scale for photo aging that
4 does that, and in that condition it seems to do fairly well.
5 Bill Kunliff(?) has published an acne grading scale that
6 I've seen and used, and in that situation, it seems to work
7 fairly well.

8 I'm a little less confident with psoriasis because
9 it's so variable, but that might be an approach.

10 CHAIRMAN McGUIRE: Dr. Duvic?

11 DR. DUVIC: I'd just like to call your attention
12 to the NPF's Medical Advisory Board document where the
13 definitions of severity of psoriasis have been written out.
14 And this, possibly with some pictures, would be a start for
15 this complicated question.

16 CHAIRMAN McGUIRE: It may be. It may be very
17 good. I haven't studied it.

18 Dr. Gottlieb?

19 DR. GOTTLIEB: I wanted to allude to that
20 particular statement because notice that, at least the draft
21 one I saw, it doesn't just say purely BSA, body surface
22 area, but it acknowledges the fact that moderate to severe
23 can depend on whether you can go to work, whether you can do
24 your daily tasks of living, whether it costs more money to
25 treat with a topical than with systemic. So that at least

1 the original one did have that statement. I'm looking at
2 that not so much for early studies, but in terms of
3 labeling, you don't want to limit your moderate to severe as
4 defined by just a body surface area.

5 CHAIRMAN McGUIRE: This copy does have body
6 surface area, and they're surprisingly small. Mild is less
7 than 2 percent; moderate, 2 to 10 percent; severe, greater
8 than 10 percent.

9 I would suggest to the agency that we start with
10 this and see if it's acceptable. I'm not prepared to say
11 that right now, but at least we have something to start
12 from.

13 DR. DUVIC: There was discussion on the Medical
14 Advisory Board about whether severity should go up to 5
15 percent and whether moderate should go up to 20, so there's
16 some discussion. But I think that the consensus was as it
17 is written.

18 CHAIRMAN McGUIRE: You're talking about the
19 National Psoriasis Foundation Medical Advisory Board?

20 DR. DUVIC: Yes, 2 and then 2 to 10, and greater
21 than 10 being severe.

22 DR. WILKIN: Dr. McGuire, that actually might be
23 worthwhile for the committee to give us advice on that part
24 of it, those particular percentages, you know, of area of
25 involvement. What was it? Was it over 5 percent is--

1 DR. DUVIC: Less than 2 is mild on this, 2 to 20
2 is moderate, and greater than 10 is severe. I think it's
3 the moderate where people have problems. Where does mild
4 start and stop versus moderate? I think it depends on the
5 symptoms a patient is having and whether it's right on the
6 face or a covered area. I think it's somewhat subjective.

7 DR. WILKIN: Yes, I guess that's where I would
8 like to hear more about this. It seems to reduce it down to
9 just simple surface area, and not, you know, degree of
10 involvement of the individual lesions and, of course, where
11 they are. Anatomic regionality can have a lot to do with
12 how much it really interferes. As Dr. Duvic pointed out, it
13 can be in a visible area or an area that's not readily seen.
14 It can be on the hands where, you know, it interferes with
15 holding tools or writing. So it's a major reduction.

16 CHAIRMAN MCGUIRE: I agree. I think a patient who
17 has moderate plaque psoriasis and then develops psoriasis of
18 the palms graduates to severe because of the impairment.

19 DR. DUVIC: And I think this takes that into
20 consideration if you read it.

21 CHAIRMAN MCGUIRE: Yes.

22 Fred, did you have a comment?

23 DR. MILLER: I was just going to say the criteria
24 are qualified here by "generally." They don't just say this
25 is the only criterion. It's modified.

1 CHAIRMAN MCGUIRE: Okay. Dr. Gerry Krueger?

2 DR. G. KRUEGER: I guess I'd just like to offer a
3 little editorial on that because it came out of a committee
4 that I chair. You know, it's easy to focus on percent by
5 surface involvement because that's a quantifiable number.
6 But the fact of the matter is that mild, moderate, and
7 severe disease is a quality-of-life issue. I have a slide I
8 made up that says, Which one of the following is severe
9 disease? And it has 20 percent, 10 percent, 5 percent, 0
10 percent. The next slide says the answer is all. Okay? The
11 patient who has nothing, no psoriasis, and has crippling
12 arthritis has severe disease. The person who has 20 percent
13 disease and comes by and says hello once in a while, he can
14 trivialize his disease. It's not severe.

15 So it's a quality-of-life issue, and I know that's
16 a challenge for you. But it is for the patient with
17 psoriasis as well.

18 CHAIRMAN MCGUIRE: Gerry, I can underscore that.
19 Sometime in the early days of the National Psoriasis
20 Foundation, we were looking desperately for support, for
21 research support, and for federal support, and we finally
22 found a Congressman who had psoriasis. He had a fair amount
23 of psoriasis. And it didn't bother him at all.

24 Dr. DiGiovanna?

25 DR. DIGIOVANNA: I don't want to play the devil's

1 advocate on this issue, but I did want to make one point,
2 and that is that it should be considered that the goals of
3 the NPF in setting out fair criteria for mild, moderate, and
4 severe may not exactly mirror the goals for the purposes of
5 a clinical trial, and that while very debilitating,
6 psoriasis which is limited in extent may very severely
7 affect quality of life, but that particular individual may
8 or may not be an appropriate candidate for a very toxic
9 systemic therapy because of the nature of the disease that
10 they have and the limited nature. So it may require
11 thinking exactly what the purpose of the classification is
12 for including the various criteria.

13 CHAIRMAN McGUIRE: Dr. Gottlieb?

14 DR. GOTTLIEB: I can't agree with that statement.
15 Take somebody who has psoriasis on the palms and the soles.
16 Not very much body surface area, but that person can't walk,
17 they can't work, they can't do their daily tasks of living.
18 And I think that those--and those are the kinds of patients
19 that I put on methotrexate and cyclosporine because they
20 just can't go on with their life and they're crying in my
21 office, many of them. And so I would say that that person,
22 despite their limited body surface area, is definitely
23 moderate to severe.

24 DR. DiGIOVANNA: I would agree with you, and I
25 would treat them in the identical way. But my point still

1 stands that the involvement of the palms and the soles might
2 not be the best clinical definer of the efficacy of the
3 drug, according to the study. I'm just merely saying that
4 the reasons for the classification might be slightly
5 different and they might be slightly variable because of
6 that. I'm in no way suggesting that because it's limited in
7 extent it's a lower quality-of-life issue.

8 CHAIRMAN McGUIRE: Well, after looking at the NPF
9 definitions, you know, perhaps it needs a little more
10 attention from the committee. But I think they've done a
11 good job. This is a first read for me, and I think they've
12 done a good job for categorizing the patients. And, John, I
13 would start from here. I don't think we're going to get
14 much more definition out of talking about it. You know, the
15 percentages are somewhat arbitrary, but it's clear that
16 certain types of clinical involvement graduate a patient to
17 the next level, as was just mentioned. Hand involvement,
18 foot involvement, if you can't walk, you have severe
19 disease, even if you don't have psoriasis any place else.

20 You had a comment?

21 DR. WEISS: Dr. DiGiovanna said much of what I
22 wanted to say, which was when you're talking about the
23 purposes of defining groups for a clinical trial to try to
24 best show that something is effective, you know, we're not
25 trying to--it's a different issue than, you know, who are

1 the best patients out there in the real world to treat. And
2 I think that that was the point. It's somewhat a little bit
3 counter to, I guess, the way we certainly see trials being
4 developed to have some of the patient quality-of-life, if
5 you will, type of factors being those--we're more used to, I
6 think, more objective type of measures for the purposes of
7 defining clinical trials. That's the only comment I wanted
8 to make.

9 DR. GOTTLIEB: The end result of that reasoning is
10 that we have essentially no studies other than individual
11 investigators using usually marketed drugs already. What is
12 the efficacy for palmar/plantar psoriasis, for example?
13 It's a hard thing to treat, and because of that way of
14 looking at it--see, I initially understood that Dr.
15 DiGiovanna meant safety, and that's why I commented on it.
16 But let's talk about efficacy. By excluding those kinds of
17 patients, you will definitely get no data on those patients
18 at the time of NDA approval. And so we're treating patients
19 by the seat of our pants, basically, and I think those
20 patients deserve better than that.

21 DR. WEISS: Well, I think it's--you know, these
22 are issues with whether or not one in the efficacy trials
23 has a--casts a broad net in terms of the inclusion criteria,
24 but for important types of variables to stratify, for
25 instance--I mean, you don't--we're going to have--get a

1 little bit more into that, I think on the next page, when we
2 talk about being able to extrapolate from one type of
3 disease or one type of location to another and whether or
4 not you need to have specific data in those different groups
5 and whether or not you can extrapolate and how best to do
6 it. Should there be separate trials? Should they all be
7 included in the same trial? And if that's the case, you
8 know, how many strata can you have in the study? Those I
9 think all come out.

10 CHAIRMAN McGUIRE: Dr. Schwieterman?

11 DR. SCHWIETERMAN: If I may add just one or two
12 comments to Dr. Weiss's, I think the point is well taken
13 that we shouldn't be excluding patients from clinical
14 studies simply because they have a particular kind of
15 psoriasis. In fact, I would reiterate the point that Dr.
16 Weiss was making, that to the degree we can get those data
17 extrapolated from clinical trial data to all patient sub-
18 populations, that's great. But the question at hand
19 actually has to do with very early studies of--

20 CHAIRMAN McGUIRE: Right, these are Phase 1.

21 DR. SCHWIETERMAN: Phase 1 going in, and to that
22 degree, it's important that you have a handle not just on
23 the safety, but also on the bioactivity that the products
24 have. And you run the risk of not getting good information
25 if you include certain types of patients.

1 CHAIRMAN MCGUIRE: And you're justifying potential
2 toxicity by evaluating the severity of impairment. I'm
3 comfortable with where we are here.

4 Okay. Please discuss how to best define patients
5 who are refractory to or unresponsive to systemic therapies.

6 Dr. Miller? I think what we can do there is put a
7 time line on different modalities and say if not by a
8 certain time, then patient is refractory.

9 DR. MILLER: Yes, I think if the systemic therapy
10 has been used properly and for an appropriate period of
11 time, and that's what would have to be defined, well, then,
12 he or she would be declared refractory. I think that goes
13 for topicals and systemic therapy.

14 CHAIRMAN MCGUIRE: So it would be a dose times
15 time threshold for different modalities.

16 Dr. Duvic?

17 DR. DUVIC: You know, clinically what's more of a
18 problem is not that they're refractory or unresponsive, but
19 the fact that they've got cumulative toxicity. They've been
20 on methotrexate and now they have liver disease, or they
21 have hepatitis C virus so you can't put them on such-and-
22 such. And I think that's more--I mean, I think the
23 therapies---being refractory to therapy isn't as much of a
24 problem as--you can't just give it to them for another
25 health-related disease, issue.

1 CHAIRMAN MCGUIRE: That may drop into c).

2 DR. DUVIC: Sorry.

3 CHAIRMAN MCGUIRE: No, I'm not--I say it may drop
4 into c). I'm not sure. If the agency is satisfied with our
5 response to b), which is how best to define patients who are
6 refractory or unresponsive, that would be appropriate does
7 times an appropriate time for each of the modalities. It's
8 going to be different for cyclosporine, methotrexate,
9 etretinate, et cetera, and PUVA. And then if you accept
10 that, please discuss the criteria that should be used in
11 defining patients who have failed standard therapies. Well,
12 you can fail PUVA by beginning to get squamous carcinomas.
13 You can fail methotrexate by getting liver toxicity. You
14 can fail cyclosporine by having nephrotoxicity,
15 hypertension, and so those would all be drug-driven
16 failures.

17 DR. WEISS: Karen Weiss, Center for Biologics.
18 Should there be any kind of distinction made between failure
19 in the sense of the disease--having an adequate course of
20 treatment and the disease not responding the way it should,
21 one would hope, versus, I guess, the phrase intolerant to
22 existing therapies such as developing unacceptable
23 toxicities to methotrexate? Is that a distinction that is
24 worthy of being made?

25 CHAIRMAN MCGUIRE: I think they're different. I

1 mean, you know, some patients don't respond to etretinate.
2 But it's not because of the etretinate toxicity. It's
3 because their psoriasis just doesn't respond, or doesn't
4 respond very well.

5 DR. WEISS: I was just reacting to the fact that
6 you said, well, somebody could fail methotrexate because
7 they have liver toxicity, and I wasn't hearing they failed
8 methotrexate because their disease didn't respond, it's
9 because they have liver toxicity. And so that's, I guess,
10 the reason why I was expounding on that question to ask if
11 there's a difference.

12 CHAIRMAN MCGUIRE: If you initiate a therapy with
13 methotrexate and the patient responded to methotrexate and
14 four years later had liver toxicity, that would be another
15 way to fail. The first way to fail would be not to respond
16 to the methotrexate. But for methotrexate, read anything,
17 read cyclosporine.

18 Does the committee have different feelings? Dr.
19 Duvic and then Dr. Armstrong.

20 DR. DUVIC: I assume your purpose in this is to
21 set up entry criteria for clinical trials. I would urge you
22 not to micromanage entry criteria for clinical trials. Some
23 patients live on a mountain. They can't get to the PUVA box
24 three times a week because the nearest dermatologist in
25 Wyoming is 400 miles away. And yet some of these trials are

1 set up that you have to fail PUVA. Well, they can't get
2 PUVA because they don't have access to it, and some people
3 can never take methotrexate because they have chronic active
4 hepatitis.

5 So, I mean, I think that oftentimes entry criteria
6 are too strict for these clinical trials.

7 CHAIRMAN McGUIRE: Dr. Armstrong?

8 DR. ARMSTRONG: My name is Robert Armstrong. I
9 work for a pharmaceutical company which does not have a drug
10 pending in this area, and I'm speaking more from the
11 perspective of a practitioner with experience in treating
12 psoriatic patients.

13 I think Dr. Duvic's point is one to underscore.
14 This is a complicated disease that we don't know what the
15 cause is, we don't know what the mechanism is. We're
16 talking about severity in terms of is it the extent, is it
17 the ability to respond to therapy, is it the social or
18 psychological impact, is it the occupational impact. All of
19 these are different parameters, but they clearly have an
20 importance for how much impact it has on the patient's life.
21 And because it's different in all these different ways, we
22 don't have a simple formula that lets you calculate who is
23 severe and who is not severe.

24 In the same way, on the choice of therapy, this
25 seems to me to be an area that is also difficult and calls

1 on the clinician to make judgments for the particular
2 patient. A young patient I'm reluctant to use PUVA for. An
3 older patient I'm not. Same disease, different clinical
4 context in terms of the time for the adverse experiences to
5 play out.

6 So unless you try to weigh those things, I think
7 it's best done on an individual basis by the physician and
8 the patient. That's why I think it's more helpful to figure
9 out how does the drug work, how often does it work, what are
10 the side effects at the doses that it works, how long is the
11 remission and so on, and then leave it to the physician to
12 have the dialogue with the patient. We do have an informed
13 learned intermediary to have that discussion, and we have
14 the person who is going to benefit from the therapeutic
15 efficacy or suffer from the adverse experiences. Let that
16 be an individual discussion between those individuals once
17 they have the data in hand.

18 DR. WILKIN: Dr. McGuire?

19 CHAIRMAN MCGUIRE: Dr. Wilkin?

20 DR. WILKIN: Actually, I guess I can present it as
21 two fairly opposite ways of going with this. I think, you
22 know, there is a compelling need for new medications to be
23 available early on in the development process. And I think
24 that's what you're speaking to, that someone not be denied
25 access to a particular new product that's being developed.

1 But that can be done separately from, you know, the Phase 2
2 trial that the sponsor is working on. I mean, there's a
3 separate pathway for an IND to be obtained and a patient can
4 receive that kind of medication. So it's not like if they
5 can't get into the trial that might have fairly explicit
6 entry criteria, exclusion criteria, that they are closed out
7 of getting that particular product altogether.

8 DR. DUVIC: Do you know how much time that takes?

9 CHAIRMAN McGUIRE: Dr. DiGiovanna?

10 DR. DiGIOVANNA: I just wanted to pick up again on
11 a point that Karen Weiss mentioned about intolerant to other
12 therapies. I think the other issue, rather than the
13 development of a toxicity or the lack of efficacy, is the
14 inappropriateness of the therapy so it's never started. And
15 I think that's a distinct situation where someone is not a
16 candidate for methotrexate because of hepatitis C. There's
17 a medical reason, not a logistic reason, why that person
18 cannot be--and I think that often happens. There are a
19 variety of reasons. A female may not be an appropriate
20 candidate for Soriatane, a female of child-bearing
21 potential.

22 So for those individuals where those therapies are
23 not available, they may as well have failed them and
24 probably should be considered in the same situation. I
25 don't know if the right word is intolerant or inappropriate,

1 but it wouldn't just be refractory or unresponsive.

2 CHAIRMAN MCGUIRE: I think we're ready for d).
3 Please discuss the criteria to be used in determining
4 whether a patient is "stable" on phototherapy or other
5 therapies (e.g., duration on such therapy).

6 Well, that would have been a much easier question
7 if it had been confined to phototherapy, but you are
8 interested in all systemic therapies and topical therapies?

9 DR. WEISS: Probably we don't have enough time to
10 go through all of them. The reason--let me take a step back
11 and say why we're asking this, is that--I guess I bristled a
12 little bit with Dr. Duvic's comment about micromanaging
13 studies, and I hope we're not perceived as doing that. But
14 oftentimes entry criteria from studies that have come to us
15 have these types of criteria, and I think part of it is just
16 making sure that everybody is speaking the same language,
17 that we all--just like when we're talking about what does a
18 remission mean and does it mean different things to
19 different people. My sense is I want to make certain that
20 I'm clear and that everybody's clear when we talk about
21 somebody who's on stable doses, because many therapies
22 you're--part of the entry criteria is it's okay to be on
23 steroids, but you have to be on a stable dose of steroids.
24 Well, there's a lot of confusion about what that means, how
25 long that has to be, and what kind of dose you're talking

1 about. And that's the sense of these types of questions.
2 Given the fact there's such a variety of different types of
3 therapies that can be used, maybe the committee could just
4 limit it to the more--the larger areas of drugs that are
5 used, phototherapy, and one or two other types of treatments
6 that are more commonly used in people with severe disease,
7 for instance.

8 CHAIRMAN MCGUIRE: Well, Karen, these are criteria
9 for subjects who are going to be entering a Phase 1 trial?

10 DR. WEISS: Probably not in the phase--that's
11 probably more--maybe it's a little bit out of order, the
12 questions. It's probably more in the Phase 2 and
13 particularly the Phase 3 trial where people who enter on
14 trials can receive a new agent and they're on some type of
15 existing therapy, the stipulation is they have to be on
16 stable doses as opposed to having, you know, escalating
17 doses of some type of therapy.

18 CHAIRMAN MCGUIRE: Yes, I may have misunderstood
19 this, but my initial reading was that you wanted patients
20 with some degree of disability who were at risk from their
21 disease to enter into Phase 1 trials that might incur some
22 unknown toxicity.

23 DR. WEISS: That is correct. That's generally--
24 d), relooking at this more carefully, seems to be a little
25 bit out of order for this series of questions. But I think

1 it would still be helpful to hear if there's any--if people
2 can provide us with any commentary on what is meant by a
3 stable--

4 CHAIRMAN McGUIRE: Dr. Miller?

5 DR. MILLER: Stable to me means that the patient
6 has responded to therapy and the lesions are pretty much the
7 same and they're not waxing and waning to any large degree.
8 You know, they're maintaining the status quo. They've
9 responded and this is the level at which they're remaining.
10 There aren't big shifts in the disease or big swings in the
11 disease manifestations.

12 CHAIRMAN McGUIRE: And the treatment is not
13 escalating.

14 DR. MILLER: And the treatment is staying the
15 same, and from the clinician's standpoint, at that point
16 after they're stable for a period of time, you'd begin to
17 think about reducing therapy or even stopping, you know,
18 some of the systemic therapy.

19 CHAIRMAN McGUIRE: Dr. Duvic?

20 DR. DUVIC: I would say stable for a topical would
21 be two months, at least, minimum. And I think it would be
22 helpful for the ability to design criteria where patients
23 who were on stable but minimal therapy could actually enter
24 clinical trials to avoid that washout period that we talked
25 about this morning that's really very difficult for our

1 patients to put up with.

2 DR. WEISS: That leads right into e) as well.

3 DR. DUVIC: Right.

4 DR. WEISS: We should probably just move right
5 into there.

6 DR. DUVIC: Well, I think that's where you're
7 going with this, defining stable, is what's--what could we
8 call stable so that something could be added to it. So you
9 still have to have measurable disease and be on an agent
10 that's working somewhat, but not enough. Again, I think
11 it's arbitrary.

12 CHAIRMAN MCGUIRE: Well, e) is a tough one. Are
13 you satisfied with our definition of stability?

14 DR. WEISS: Yes. Thank you.

15 CHAIRMAN MCGUIRE: Okay. Now we have a difficult
16 question. For drugs ultimately intended as monotherapy,
17 patients enrolled in clinical studies are often taken off
18 existing therapies for a specified period of time (i.e., a
19 "washout" period). This may be a concern because patients
20 with more severe disease may experience difficulty during
21 the "washout" period. Should a "washout" period be utilized
22 In early safety studies? Please discuss appropriate
23 durations of "washout" for broad classes of psoriasis
24 therapies.

25 That one's tough. John, help.

1 DR. DiGIOVANNA: I don't know if it will be a
2 help, but I think the reason you get into trouble here is
3 because psoriasis allows us to make these studies a hybrid
4 of efficacy and safety. And if we were really talking about
5 a safety study, then there wouldn't be a problem, I think,
6 with allowing patients to continue some reasonable form of
7 therapy rather--considering we're going to select those
8 individuals with the most severe disease, as Dr. Gottlieb
9 has mentioned several times, and I do agree with here, these
10 individuals are often the ones with the most difficult
11 disease, which, when it does get out of hand, sometimes can
12 be difficult to get back in the box, and sometimes it just
13 makes them not very good candidates for this kind of a
14 study, even though they are the ones who we are specifically
15 selecting.

16 So I think there's a real role in the early
17 studies to in some cases maybe sacrifice some of the
18 efficacy with the understanding that we not only would be
19 able to do more justice to the patients but be able to get
20 the same safety data and maybe even actually do the studies
21 a lot more easily because we would have a much larger group
22 of patients who we're treating in a more equitable
23 situation.

24 CHAIRMAN McGUIRE: Yes, I haven't heard anyone say
25 the word ethics.

1 DR. DiGIOVANNA: I said equitable. I tried not to
2 get--

3 DR. DUVIC: Alice said it several times.

4 CHAIRMAN McGUIRE: Okay. Dr. Gottlieb?

5 DR. GOTTLIEB: In this case, you can have your
6 cake and eat it, because basically if you use a less--for
7 the first studies in Phase 1, the Phase 2(a), however you
8 call it, the first studies in a patient, you can actually
9 get both. Just don't do it in the 10 percent or more. Do
10 your first studies, which you know you're going to do with
11 very low doses to begin, probably single doses, do it in
12 that 2 to 10 percent range. It will give you proof of
13 concept and give you perfectly fine safety data, and you
14 won't get into some of the problems that you're getting into
15 now in the fact that you're now limiting it to 10 percent or
16 more. And these are the kind of patients who can't tolerate
17 those kinds of washouts and being on ineffective treatments.
18 So you can have your cake and eat it.

19 CHAIRMAN McGUIRE: Dr. Gerry Krueger?

20 DR. G. KRUEGER: I've struggled with this a lot.
21 Okay? And it's my suggestion that you make the statement
22 that if the patient is on stable therapy and meets the
23 entrance criteria and doesn't have any exclusion criteria,
24 they're on. So you have a patient who comes in, is on--I
25 don't know. Let's just for argument's sake say that they're

1 on 2.5 milligrams of prednisone, which sometimes they are
2 because they have arthritis. What are you going to do?
3 Well, they meet all the entrance criteria. They've got
4 enough induration, no scale, and everything else; they've
5 got enough body surface area involvement; but they're off
6 the study because they're on 2.5 milligrams of prednisone.

7 So I would just say, you know, stable chronic
8 disease and meet all other criteria. As long as there isn't
9 a conflict with exclusion, you know, that you're trying to
10 mix cyclosporine and PUVA and some therapies that are
11 extremely dangerous.

12 CHAIRMAN MCGUIRE: So, Gerry, before you leave the
13 microphone, you are comfortable leaving a potential subject
14 on a stable therapy if there's no reason to think that
15 there's going to be synergistic toxicity or other
16 complications?

17 DR. G. KRUEGER: Yes.

18 CHAIRMAN MCGUIRE: We'll have your twin, Jim
19 Krueger.

20 DR. J. KRUEGER: Like Gerry, I, too, have
21 struggled a lot with this particular issue because many of
22 the trial designs that we construct have required stopping
23 active therapy and washing people out. I'd like to say I
24 think there are only really two kinds of stable disease.
25 There are people who have been off therapy for so long, for

1 months, and have reached some kind of equilibrium state, so
2 they might have 20 or 30 percent body surface involved, say,
3 for instance, and they probably could stay that way for
4 another year or two without any active treatment. They're
5 pretty miserable, but they're stable.

6 I think for the moderate to severe group, when you
7 take them off methotrexate or some other highly active
8 agent--cyclosporine--it simply is a matter of the disease is
9 going to get worse over time, it's not stable, and it's a
10 matter of the rate of worsening. And that makes it very
11 difficult to many of the current studies that are
12 entertained because if they get bad really fast--and I think
13 that tends to be the case off cyclosporine--you're
14 introducing an agent where it may be only moderately
15 effective the way it's been introduced, and the disease may
16 get a lot worse. So it may obscure the potential of
17 measuring efficacy and at the same time put a patient in
18 crisis.

19 You've talked about the patient who gets out of
20 the box of therapy. Well, we get patients in crisis by this
21 type of clinical management in studies, and sometimes
22 they're very, very difficult to get back in the box. A
23 psoriatic patient in crisis is something that unless you
24 take care of people with this disease, it's hard to imagine.
25 They may end up in the hospital for weeks to even a month or

1 two at a time and be a disaster to take care of.

2 CHAIRMAN McGUIRE: Thanks, Jim.

3 Dr. Kilpatrick had a comment.

4 DR. KILPATRICK: Thank you. I'm wondering why we
5 need a washout period. I'm really going on from what's been
6 said earlier. I wonder why nobody has mentioned the
7 possibility of cross-over designs, presumably where the
8 standard treatment is alternated with an investigational
9 treatment. Indeed, if you get into more sophisticated
10 designs from agriculture, you can get balance squares where
11 you get combinations of three or four or five treatments.
12 Those may not be feasible given the complexity of working
13 with real individuals, but, again, I'd like to hear why we
14 can't use cross-over designs.

15 CHAIRMAN McGUIRE: Are you going to address that,
16 Bill?

17 DR. DUVIC: I am. I will.

18 CHAIRMAN McGUIRE: Let's stay with that question
19 for a minute. Dr. Duvic?

20 DR. DUVIC: If you're on cyclosporine and you stop
21 it, you'll be worse in a month. So if you start the other
22 therapy on day one, you'll show that the drug makes
23 psoriasis worse. If it doesn't have very much activity.

24 DR. KILPATRICK: No, the implication being is
25 that--and, again, all of this is based on certain

1 assumptions, but the analysis can tease out the synergistic
2 effect, if that's what you're talking about.

3 DR. DUVIC: I don't think it can. I think there
4 will be a rebound after coming off of certain drugs, like
5 prednisone or like cyclosporine. There will be a rebound
6 time. And if you've started the new drug on that day you
7 take them off the other one--

8 DR. KILPATRICK: Again, I think it depends on the
9 period that we're looking at and how many periods you're
10 going to do cross-over, as I say. I'm rather rusty in this.
11 It's been 20-plus years since I learned about designing an
12 experiment.

13 CHAIRMAN MCGUIRE: But my understanding is that
14 we're looking for toxicity in Phase 1, and so if there is no
15 evidence of synergistic toxicity or that the two compounds
16 are going to be working to the detriment of the patient,
17 then one could start the proposed drug and then eventually
18 discontinue the drug that was holding the disease under
19 control. And then you'd find out. You'd get your toxicity
20 data, is what I'm trying to say.

21 Dr. Rosenberg?

22 DR. ROSENBERG: Well, I disagree. It's so
23 important that we find out whether these things really work
24 or not and really are safe or not. And, of course, the
25 lawyers know that hard cases make bad law. And it's easy to

1 recruit patients from your own practice, and it makes the
2 studies easier. But that's really not the way to do it, in
3 my opinion. There are enough people with psoriasis out
4 there who are unhappy with previous treatments, who have
5 stopped going to doctors, who got all stages of psoriasis,
6 but read the newspaper, and if one wants to work hard
7 enough, one can find people who are on no medicine, who meet
8 the entry criteria, and who can give some clean data.

9 I think to try and fit these new studies in as, A,
10 a way of helping your hard patients, totally inappropriate;
11 or, B, using hard patients to try and learn things about, a
12 mistake. And I think the old-time way of doing it is the
13 best, and I don't think you should change your ordinary
14 criteria for evaluating drugs.

15 CHAIRMAN MCGUIRE: Okay. Well, you're hearing
16 more than one thing from the committee.

17 Now, you've not received much support from us for
18 a washout period.

19 DR. WEISS: Yes, we got the message.

20 CHAIRMAN MCGUIRE: Okay. I was sure you had.

21 Item f) Should Phase 1 studies of potentially
22 toxic agents be limited to those with more severe disease?
23 If it is acceptable to enroll patients with milder forms of
24 psoriasis, please discuss the criteria that should be used
25 to identify appropriate patients and the appropriate

1 monitoring for such patients.

2 That question is written to answer itself. I
3 mean, I think. Should Phase 1 studies of potentially toxic
4 agents be limited to those with more severe disease? I
5 think that we are told that if we're studying potentially
6 toxic material, then we restrict that to people who have
7 greater need. I mean, I think that's intrinsic in the
8 contract here.

9 John, what do you think?

10 DR. DiGIOVANNA: I have a number of years of
11 experience in a former life of being on the Institutional
12 Review Board of the National Cancer Institute where lots of
13 chemotherapeutic agents are studied in many novel and not
14 the safest ways, many dangerous sorts of situations. And I
15 think still the premise goes--and there are several--it's
16 reiterated from several codes of ethics that with the
17 earliest testing of drugs, we really don't know the scope of
18 what might happen and that in these early Phase 1 studies,
19 which usually are geared towards safety and a very small
20 number of patients, in the earliest of studies it would make
21 sense to use those patients who have the most severe disease
22 and have a small amount of potential for identifying benefit
23 rather than those patients who may be more common but suffer
24 a toxicity that's out of proportion to any potential benefit
25 that would weigh that.

1 Now, that's for early studies that are geared
2 towards predominantly safety. I think that certainly as one
3 gets out to studies involving larger numbers of patients, as
4 the degree of experience and comfort with the preparation
5 increase, then certainly milder degrees and forms of
6 psoriasis would certainly be appropriate candidates.

7 CHAIRMAN MCGUIRE: Dr. Duvic?

8 DR. DUVIC: I think you can argue the other side
9 as well, and that is, patients with severe psoriasis have
10 already been exposed to multiple toxic agents, and giving
11 them just another one will increase their risk more than
12 other people who haven't been exposed to these agents. And
13 so I don't have a problem with letting people with less of
14 their psoriasis into the Phase 1 studies as long as they're
15 adequately educated about the potential risk that they face,
16 because I think some of those people can see the benefit to
17 other patients or to their children and have altruistic
18 motives, and I don't have a problem with it.

19 CHAIRMAN MCGUIRE: Dr. Miller?

20 DR. MILLER: I think Mr. Barton said that this
21 morning, and as long as it's clearly defined what the agent
22 is, and if it's a topical agent, you certainly should have a
23 good grasp on what you're getting into. Then I think it can
24 be up to the patient. But it would seem to me to be very
25 reasonable to do Phase 1 studies on people with disease.

1 DR. WEISS: I'm sorry. I didn't hear the last
2 statement.

3 DR. MILLER: It would seem to me to be reasonable
4 to do the Phase 1 studies on psoriatics with less severe
5 disease.

6 CHAIRMAN MCGUIRE: Whatever is decided by the
7 agency, the final decision will be made by the IRB.

8 DR. WEISS: We're balancing--this is Karen Weiss,
9 again, from CBER. You never know exactly what the risks are
10 when something hasn't had a lot of experience. Sometimes we
11 have agents that have been studied first in other disease
12 settings where they have some data, even though, again, it's
13 comparing a different disease population and different type
14 of schedule usually that's administered to. But, you know,
15 it seems like there's a balance. You don't want people to--
16 you know, you try to minimize serious injury from occurring
17 in early studies, and that's not really something anybody
18 wants to see, and it also is quite damaging to drug
19 development. I mean, I think that's where the old algorithm
20 comes from, particularly in things like cancer studies or in
21 AIDS trials, where the newer agents are given to people that
22 have failed therapies, that have no other alternatives.

23 The converse--I think, Dr. Duvic, you said it very
24 well--is that these are also people that have had a lot of
25 systemic toxicities and may not be the most able to tolerate

1 the therapies. So it also doesn't necessarily give you the
2 best picture.

3 It's a difficult question, and it's a balance that
4 one has to wrestle with as you start early development.

5 CHAIRMAN McGUIRE: This is a good stopping place.
6 I would like to have a break for a few minutes and reconvene
7 at 3:15.

8 [Recess.]

9 CHAIRMAN McGUIRE: Let's reconvene the meeting.
10 Let's see. I'll start naming committee members by name.

11 Okay. Good afternoon. We are on the bottom of
12 page 6. Item 2, Issues relating to studies in and
13 extrapolation across subgroups.

14 Does everyone have this document? Or let me do it
15 the other way. Does anyone not have the document? The
16 agenda. Read the first paragraph, and then I will read the
17 questions. Begin reading at "At the time of a marketing
18 application, it is generally desirable..."

19 [Pause.]

20 CHAIRMAN McGUIRE: I'm looking at disease-related
21 subgroups. How generalizable are safety and efficacy data
22 across the various subsets of patients with plaque
23 psoriasis? If clinical studies show an agent to be safe and
24 effective in a subset of patients with psoriasis (as
25 defined, for example, by disease severity, locations such as

1 scalp, extent of skin involvement, duration), what safety
2 and effectiveness criteria should be used to determine if
3 the indicated population should be identical to the
4 population studies or if it is appropriate to label the
5 product for a broader patient application? And we've
6 discussed tangentially some of these issues earlier today
7 when we were talking about erythrodermic and pustular
8 psoriasis, which is in Item b). Disease variants such as
9 erythrodermic and pustular psoriasis are uncommon. What
10 kind of patient numbers would be needed for studies to
11 obtain such indications? Can such indications be obtained
12 by analyzing stratified populations within a study that
13 includes such psoriasis types, if the analysis is clearly
14 preplanned?

15 Well, let's look at the first part of the
16 question. How generalizable are safety and efficacy data
17 across the various subsets of patients with plaque
18 psoriasis? Dr. Duvic?

19 DR. DUVIC: I'll limit it to topical therapy here.
20 I think it depends on the agent. For instance, some agents
21 are used, and then if you combine them with light, they can
22 cause side effects that are undesirable. Others, like
23 strong steroids, might cause problems in the groin, like a
24 very strong steroid might be not safe in the groin. So I
25 think it depends on the agent.

1 CHAIRMAN MCGUIRE: Okay. Dr. Duvic, would you
2 like to say anything about various subsets of patients with
3 plaque psoriasis? Or maybe I could ask someone from the
4 agency, I'm not entirely clear what subsets of plaque
5 psoriasis you're talking about, if you're talking about
6 inveterate elbow and knee involvement.

7 DR. WEISS: This is Karen Weiss from Center for
8 Biologics. The parentheses I think give certain examples of
9 what we were meaning, subsets of specifically plaque
10 psoriasis. We talked a lot about severity of disease and
11 how you can quantify and identify various groups based on
12 severity. So that would be one. The location is another
13 one. The duration of disease or recent history of how the
14 disease has been behaving, those are all, you know,
15 potential--I mean, there's probably myriad numbers of
16 different covariates that can be considered, and it's always
17 an issue when you have a study population that is agreeing
18 to be in the clinical trial. How generalizable is that
19 population? I think this is just sort of one aspect of that
20 question.

21 CHAIRMAN MCGUIRE: Earlier today I think we
22 separated scalp out of general plaque psoriasis because of
23 the different types of preparations that are used for scalp
24 psoriasis.

25 Dr. Duvic?

1 DR. DUVIC: I think you know that by collecting
2 the data in your clinical trials, by having index lesions or
3 lesions from different areas, and then looking at how
4 effective they are in different areas. And I think that's
5 the only way you can get the data. And I think if the data
6 comes out as a subset that's significant, then you should
7 probably consider giving labeling for that indication. Does
8 that make sense?

9 CHAIRMAN MCGUIRE: Dr. DiGiovanna?

10 DR. DIGIOVANNA: With respect to the issue of
11 safety of topicals, there are some where one might consider
12 the extent of application. For example, with Dovonex or for
13 potent steroids, there may be an issue of absorption when
14 applied to a larger body surface area than the smaller body
15 surface area. So that would be one other.

16 CHAIRMAN MCGUIRE: Dr. Kilpatrick?

17 DR. KILPATRICK: Thank you, Joe, I think. I want
18 to come back to Madeleine and say that I think it depends
19 whether one randomizes index lesions or patients into
20 trials. We haven't heard about that. And I'm a little bit
21 concerned about confusion between what I call sampling units
22 and measurement units.

23 CHAIRMAN MCGUIRE: Jim, could you help me a little
24 bit with that? I don't understand your language.

25 DR. KILPATRICK: Sampling units are units that are

1 allocated, ideally at random, into different treatment arms.
2 And measurement units are different units that might be made
3 on a given patient who is randomized to a given treatment.
4 And here I'm concerned about the non-independence or the
5 lack of independence among different sites. This obviously
6 depends on the clinician's evaluation of the difference
7 between systemic and topical treatment and how independent
8 different sites might be if different agents were applied to
9 different sites.

10 CHAIRMAN MCGUIRE: Dr. DiGiovanna?

11 DR. DIGIOVANNA: I'm not sure I can answer your
12 question, but I'll give it a shot. I think usually when we
13 would do a topical study, it would be the patients that
14 would be randomized. You wouldn't randomize within one
15 patient different lesions because of cross-over and whatnot.
16 So if, for example, you had 100 patients and 50 had placebo
17 and 50 were using a topical, using the active agent, of
18 those 50 you'd have a spectrum of the different types of
19 psoriasis, and you would get by observation--if, once again,
20 you not only looked at the target lesion but the overall
21 patient, for example, that there was a good or bad effect of
22 the medication in an intertriginous area, that there was
23 more or less toxicity in those areas that the lower leg,
24 more resistant lesions cleared worse or didn't clear at all.
25 So one would get some of that observation, I think.

1 DR. KILPATRICK: May I come back on that? I'm
2 making a general comment which has undergirded most of the
3 discussion today. We keep hearing about classifications of
4 information at the various groupings. That might be
5 valuable for the definition of primary response variables
6 and for subsequent analyses. But I would hope that the raw
7 data comes to the FDA so that it would permit subgroup
8 analysis--this may anticipate what's coming up here--and not
9 necessarily restrict it to the mild, moderate, severe type
10 of classification because these things, as you're all
11 saying, are arbitrary classifications, and there may be
12 extreme examples where it would not be beneficial to use
13 those classifications, but, in fact, to go back to the raw
14 data and do some other evaluation.

15 CHAIRMAN MCGUIRE: Well, we might--oh, I'm sorry.
16 Dr. Ko?

17 DR. KO: In a sense, this question is the reverse
18 of an earlier question. If you recall, earlier we tried to
19 ask you, if you have a drug that is approved for general
20 indication like for plaque psoriasis, whether you need
21 specific studies for like scalp psoriasis. Now, here we may
22 be dealing with a situation where the sponsor studied a drug
23 for scalp psoriasis, and they want a claim for treating
24 psoriasis in general. So it's the reverse kind of situation
25 that we'd like your opinion on.

1 CHAIRMAN MCGUIRE: Let me take an extreme example.
2 If a sponsor had a product that was efficacious for chronic,
3 thick, scaly plaque psoriasis, it would certainly work for
4 intertriginous psoriasis, but it would work too well, and
5 you would damage the skin there long before you probably had
6 a clinical effect on the elbows and knees. And so you can't
7 run it that way.

8 It is conceivable that you would have a product
9 that was designed for scalp that turned out to be wonderful
10 for psoriasis--I don't mean wonderful; I mean terrible; it
11 would make the psoriasis go away--on the knees and elbows.
12 There wouldn't be a problem there with safety, I wouldn't
13 think. It would be more a question of efficacy.

14 Would anyone on the committee like to comment?
15 Does that mean you agree with what I said? John?

16 DR. DIGIOVANNA: I agree, but I just want to get a
17 little clarification. I'm not quite sure what the intent
18 is. Most of the time, when I look at the label of a product
19 for psoriasis, it doesn't specify knees or more difficult
20 areas. This is a new concept for me with respect to
21 labeling, so I don't know if that's something you intend to
22 introduce or whatever. I think that's something that the
23 dermatologist eventually gets an understanding of over time
24 and which preparations are best for many areas. There are
25 things that are specifically labeled for the scalp, and

1 they're not necessarily labeled for other areas, often
2 because they are not the vehicles that are the best for
3 there. I don't know--I would suppose if someone--I think we
4 agreed before--wanted an indication outside the scalp,
5 they'd probably have to go for that and actually try it and
6 see, because it's a different sort of toxicity balance that
7 you're talking about.

8 But I'm not quite sure--I mean, one of the
9 questions here relates to different body surface areas, not
10 scalp versus trunk. The other you're talking about more
11 resistant areas. So I think they're really different
12 issues. One is what would be a labeling issue. The other
13 is, you know, how do you really want to--do you want to tell
14 them to avoid the intertriginous areas or something like
15 that? That's something you might learn throughout the
16 study.

17 CHAIRMAN McGUIRE: Dr. Mindel?

18 DR. MINDEL: I was going to say that it really
19 doesn't matter because all that has to happen is the drug
20 has to be approved. And once it's approved, no matter what
21 the labeling says--let's say the drug isn't approved for
22 psoriasis. It's approved for seborrhea. If the physician
23 feels that it's useful for psoriasis, he's going to use it
24 for psoriasis. He has the legal right to do that and the
25 moral right to do that.

1 So I think it's in this sense unnecessary to have
2 to split all these different categories and worry about the
3 labeling.

4 CHAIRMAN MCGUIRE: Well, Joel, I don't know. I
5 think that simply because the physician can prescribe and
6 treat with a drug doesn't give the agency any freedom with
7 their labeling. I think they still need to--

8 DR. ROSENBERG: I agree.

9 CHAIRMAN MCGUIRE: --be rigorous with their
10 labeling.

11 DR. ROSENBERG: You think a zinc parathion spray
12 would be good for psoriasis, Joel?

13 CHAIRMAN MCGUIRE: That was Dr. Rosenberg. I'll
14 bet.

15 Dr. Wilkin? Then we'll go to you, Bill.

16 DR. WILKIN: Actually, the notion of off-label
17 use, that is a fact. I think it would be very difficult to
18 practice as a dermatologist and not use drugs in an off-
19 label manner. I mean, I--other people will no doubt hear
20 about this at the FDA, but, I mean, that's my view,
21 nonetheless, as a dermatologist. That may or may not be my
22 view at the FDA.

23 [Laughter.]

24 CHAIRMAN MCGUIRE: You might want to say that two
25 or three times.

1 DR. WILKIN: The truth is that the FDA is not
2 interested in interfering with the practice of medicine. I
3 think what we're after in this kind of a question is if the
4 sponsor--you know, there are actually two settings. One is:
5 Do you think we should ask the sponsor to be looking at
6 other areas, anatomic regions? And then, of course, the
7 second part is a lot easier, incredibly easier, and that's
8 if the sponsor comes in and says, you know, we would like
9 the palms--we would like to say it's not just treatment of
10 psoriasis in general, but also palmar/plantar psoriasis or
11 scalp psoriasis. We would like that in addition. That is
12 easy for us to work with. We can think about, you know, how
13 to get to that. It's do you want to go to other regions,
14 and I guess I'm not really hearing the urge to go to other
15 regions anatomically unless the sponsor desires that.

16 CHAIRMAN MCGUIRE: Dr. Schwieterman?

17 DR. SCHWIETERMAN: Dr. Schwieterman, CBER.
18 Actually, there's been two or three people who talked before
19 me who largely have said what I meant to say, but the FDA's
20 mission beyond approving products is to gather the most
21 information possible so that physicians and patients can use
22 these drugs in the safest and the best way that they're able
23 to. And I think Dr. Wilkin made a good point. It's never
24 our intention to interfere with the practice of medicine.
25 We understand, and even in some cases think it's necessary,

1 for obvious reasons--off-label use, that is, given that the
2 studies need to catch up and so forth. It really depends on
3 the patient.

4 But to the extent that we believe that the
5 clinical trial can provide maximal information with regard
6 to the safety and efficacy, is it this committee's opinion
7 that we should be encouraging a heterogeneous patient
8 population in these studies, and to what extent? In other
9 words, should we include X number of patients with knee
10 lesions or elbow lesions and so forth? Or is psoriasis
11 simply psoriasis and you don't have to worry about it that
12 much?

13 CHAIRMAN MCGUIRE: Okay. Well, that should split
14 the committee. Let's just go around. John, what's your
15 opinion?

16 DR. DiGIOVANNA: Not early, but late. So for
17 Phase 1 studies I don't think you'd want to do that. When
18 you get to talking about Phase 3, Phase 4 studies, I like
19 this idea of stratifying and including some patients with
20 pustular psoriasis. You're probably going to find that
21 they're not so easy to find, but if they're included, one
22 would be able to do an analysis of the subset.

23 Certainly I think if you're talking about studies
24 involving hundreds of people, you certainly wouldn't want to
25 confine all of those to the mildest form of psoriasis. You

1 would want to include patients, I think, that had a broad
2 range.

3 CHAIRMAN McGUIRE: I'm comfortable with that.
4 When you move into Phase 2, Phase 3, then the stratification
5 is essential because scalp is not palms and soles, palms and
6 soles is not intertriginous areas, intertriginous areas is
7 not plaque psoriasis elsewhere on the trunk, and facial
8 psoriasis is probably in a category by itself, as far as I'm
9 concerned.

10 Bill, how would you put it? Do you agree with
11 any--

12 DR. ROSENBERG: I agree with just what you said.

13 CHAIRMAN McGUIRE: Okay.

14 DR. WEISS: Just to follow up on something Dr.
15 Kilpatrick said earlier, the agency, certainly when we have
16 a marketing application, and particularly for a disease like
17 this, where I'd imagine it would be sizable study
18 populations, not only do we encourage our sponsors to look
19 at various subgroups to try to get a sense about whether or
20 not, at least in a crude sense, the product works across
21 different types of subgroups, but, you know, we ourselves
22 will also receive the raw data and can do some of these
23 analyses ourselves.

24 I guess the question of the committee, though, in
25 light of--and I'm very happy and satisfied with the answers

1 you've given us in this area, and the other areas as well,
2 but is it useful in a label--there's lots of questions that
3 come up about what to put into a label, how much to put in
4 there. It's not supposed to be a treatise on the disease
5 itself, but to put in the information that's important, and
6 that includes usually the primary efficacy endpoints and
7 important supportive secondary endpoints. And is it useful
8 for physicians and patients to see if there's a particular
9 product that was evaluated in a broad group of people and
10 there were various subgroups, to put in some statements
11 about how there didn't seem to be or there seemed to be
12 similar types of efficacy shown in people that had knee and
13 elbow lesions, because it's not going to be everybody in the
14 study.

15 Is that the kind of information--that's oftentimes
16 what we do in labeling, and I just want to know if that's a
17 helpful bit of information to have in the label,
18 descriptions of subgroups. And the next part of it, if that
19 is, then is it important that those groups then--these are
20 important groups that be stratified up front at the time of
21 randomization. I guess it's a question to Dr. Kilpatrick.

22 CHAIRMAN McGUIRE: John?

23 DR. DiGIOVANNA: I would think that some of that
24 information would be very helpful. I think it probably
25 would not be usually helpful to say that it was effective in

1 psoriasis of the knees or elbows or abdomen or lower legs,
2 because that is more of a situation that psoriasis is
3 psoriasis is psoriasis.

4 However, with respect to pustular psoriasis or
5 erythrodermic psoriasis, or palmar/plantar psoriasis, I
6 think those are diseases that are often very difficult to
7 treat and may be flared by many medications. And I think it
8 would be very useful to know in those patients. That could
9 be sub-stratified from the beginning whether there was some
10 sense of efficacy, because that maybe is the place where the
11 dermatologist would have a little more trepidation about a
12 new drug or would use it more if there was some evidence
13 that it was more helpful. But personally, I don't think
14 that if it said it was effective for psoriasis of the knees
15 that that would make much difference.

16 CHAIRMAN MCGUIRE: Dr. Duvic?

17 DR. DUVIC: I kind of partly disagree with what
18 you said because knees and elbows are more difficult to
19 treat, and it takes more to get rid of them. So I think in
20 setting patients' expectations, I think sometimes it is
21 helpful.

22 I think it should be done by including the
23 necessity for one of those type of lesions in your index
24 lesions for topicals. I think another indication that
25 would--a body surface area indication would be a groin where

1 there's a lot of potential irritation that deals with
2 safety, and I think to know that an agent could be used and
3 is an effective agent but doesn't cause side effects in that
4 area would be helpful to patients in setting expectations.

5 I think it's important to collect as much data as
6 you can. Something that hasn't been mentioned is the
7 difference potentially between Type 1 and Type 2 psoriasis
8 where people may--it may be a little bit of a different
9 disease, the early onset versus the late onset. And that
10 could be another way of sub-categorizing data.

11 And I think these trials are opportunities for us
12 to learn about the disease and the different subsets, and I
13 think collecting the information is helpful if it can be
14 done in a reasonable way.

15 CHAIRMAN MCGUIRE: Dr. Mindel?

16 DR. MINDEL: This is just a basic philosophy that
17 I'm speaking from, but I think that you want to do a simple,
18 inexpensive, quick, and thorough study of any drug, get it
19 out on the market, and then you're not going to be able to
20 tell about all the drug interactions in a study. You're not
21 going to be able to tell about all these different forms of
22 psoriasis without making it immensely expensive. I think
23 whatever the drug you are talking about, you want a simple
24 study for drug approval, and then you have to open it up.
25 You're not going to be able to guarantee safety or efficacy

1 across a spectrum of disease like I'm learning about.

2 CHAIRMAN McGUIRE: Yes

3 DR. KILPATRICK: I'd like to climb on my friend
4 John Mindel's back as usual because I have, frankly, not
5 known how to answer this question. I have seen arguments
6 for and against this, but I'm very conscious of the fact
7 that subgroup analysis will not have the power to detect
8 differences like the primary response, the design for the
9 primary response would have. Therefore, I'm seconding Dr.
10 Mindel's suggestion of a focused study with the realization
11 that maybe this will require a meta analysis of subsequent
12 clinical trials as they appear in the literature where
13 subgroup analyses then would have more power because they
14 would be aggregating hopefully different types of psoriasis
15 and coming to conclusions.

16 This is an ideal because we haven't the control
17 over the various clinical trials that go on, and we can't
18 certainly require the sponsor to do that.

19 CHAIRMAN McGUIRE: I think that takes care of a).
20 I'd like to go on to b), which is: Disease variants such as
21 erythrodermic and pustular psoriasis are uncommon. What
22 kind of patient numbers would be needed for studies to
23 obtain such indications? Can such indications be obtained
24 by analyzing stratified populations within a study that
25 includes such psoriasis types, if the analysis is clearly

1 preplanned?

2 I think that without a national health plan or
3 some organized statewide or nationwide or regional provider
4 system, I don't think there are enough patients to do a
5 stratified study with these disorders. At least in the two
6 places where I have spent most of my career, Connecticut and
7 California, which are dissimilar geographically and
8 climatically, there are not enough patients to do a study.

9 DR. DUVIC: Agree.

10 CHAIRMAN MCGUIRE: Madeleine agrees. John, how do
11 things look in Rhode Island?

12 DR. DiGIOVANNA: I think I alluded to that before.
13 I think they're very uncommon. I still think it sometimes
14 would be interesting to get some of those patients treated
15 because those are the first patients--for the systemic agent
16 that's effective that once it's available that they're going
17 to want to treat because they're the most difficult ones,
18 the most recalcitrant ones. So while you may not be able to
19 get statistical--I hate to argue with the statistician
20 again, but you may not be able to get statistically
21 significant numbers to analyze the subset. You will get a
22 useful clinical experience if the drug is very powerful, and
23 the only example I have from that is with--I guess
24 etretinate was approved for--I'm not sure of the wording,
25 but it was severe, recalcitrant psoriasis. I don't believe

1 pustular or erythrodermic was in there, nor do I believe it
2 was studied during the time of the clinical trials. But
3 afterwards, it was observed that it was extraordinarily
4 effective for pustular psoriasis, and it would have been
5 helpful to have known that. It would have been easily
6 observed with a few patients had they been included.

7 CHAIRMAN MCGUIRE: Dr. Miller, do you have
8 anything to add?

9 DR. MILLER: No. I would agree. I think that if
10 the patients are available, they could be enrolled, and
11 you're not going to get maybe statistical significance, but
12 you'll certainly see anecdotally what happens. These are
13 people who are desperate.

14 CHAIRMAN MCGUIRE: Okay. High need. These are
15 the patients who die, the elderly erythrodermic patients.
16 And one ordinarily doesn't think of psoriasis as being a
17 fatal illness, but the deaths that we have are usually in
18 that elderly erythrodermic group.

19 DR. DUVIC: I would just make the observation that
20 many of the erythrodermics have staph bacteremia if you look
21 for it. They die of sepsis often.

22 CHAIRMAN MCGUIRE: So the need is there. The
23 numbers aren't.

24 Subgroups defined by geographic region. Given the
25 known variability in disease manifestations in different

1 climates, should sponsors be required to enroll patients
2 from different geographic regions?

3 I don't know much about that.

4 DR. MILLER: Is there a difference among regions
5 of the United States with psoriasis?

6 DR. WILKIN: That's our question. And someone
7 knows.

8 [Laughter.]

9 DR. GOTTLIEB: The kind of obvious one is that
10 when you have the Sun Belt, when you're studying a response
11 to treatment, the Sun Belt regions you're going to have much
12 more of a contribution of natural UVB/UVA light, and that
13 has been demonstrated to have an effect, certainly a
14 confounding variable in studying response to therapy. So in
15 that sense, there's a very significant regional difference.

16 DR. DUVIC: There was a difference in humidity in
17 Houston versus Utah's dryness. I think in some of the
18 studies that were done, the dryness kind of interfered with
19 the therapy. Right, Gerry?

20 DR. GOTTLIEB: Or the therapy wasn't adequate.

21 DR. WILKIN: Actually, I think that was one of the
22 points we were thinking about, was the humidity aspect, and
23 I passed through several centers on the way finally to make
24 it to Rockville, and one was Houston, Texas. And,
25 Madeleine, actually what I thought I saw in Houston was the

1 patients who got worse at a specific time of year tended to
2 be July August, and they worked in banks or grocery stores
3 where they kept it as cold as a refrigerator and fairly dry.
4 And the rest of the time of the year, their psoriasis, you
5 know, sort of bumped along on its usual course. And as one
6 proceeds northward, winter is a more harsh time for
7 psoriatics. That's been my general impression.

8 CHAIRMAN MCGUIRE: The question implies that you
9 know something about climatic effect that I don't know, and
10 that could be. But what I'm not finding here is anything
11 about ethnicity. For instance, in California, northern
12 California, we have a large Vietnamese population, and some
13 of the worst psoriasis I have seen has been in that
14 population. In northern California, there is not an
15 enormous Afro-American population. There is in Connecticut,
16 and much of the clinical psoriasis in that population was
17 quite severe.

18 So there's probably some important information
19 that could be had by some sort of ethnic correlation that I
20 don't see in your proposal here.

21 DR. WILKIN: We look for a demographic balance
22 whenever we receive the studies. That's discussed.

23 DR. WEISS: And if there's an expectation that
24 there might be differences, I think we'd like to hear and
25 see whether or not we need to, you know, encourage people

1 when they come up with their designs of their Phase 3
2 efficacy trials, to just make certain that they're--these
3 are multi-center trials, anyway--that they include broad
4 representation of the population that may be getting the
5 drug when it's approved.

6 CHAIRMAN MCGUIRE: My point was that the ethnic
7 considerations could be considerably greater than climatic,
8 and I don't see any indication that you're headed down--or
9 you're doing that.

10 To my left is Jacqueline Goldberg, who is our
11 consumer.

12 DR. GOLDBERG: I'm new to this board and I wasn't
13 here for the March meeting, but one of the things I
14 discussed with Karen at the break was building on the
15 question you just raised about ethnicity and also women's
16 health. I haven't heard anything all day today about
17 women's health or minority health. And since I wasn't at
18 the March meeting, I don't know if any of this was
19 discussed. I would like a short--my short question is, you
20 know, what's already known about psoriasis in women and
21 minority populations, and does the disease play out
22 differently? And, you know, are these subgroups that we
23 need to address in here? And you already said yes to one
24 thing, so that was my concern, to whoever wants to answer
25 it.

1 DR. DUVIC: Women get it the same as men. Blacks
2 get it the same as whites. The blacks may be a little bit
3 more difficult to treat with sunlight, PUVA. You have to
4 give them more to get them clear. But other than that, I
5 don't think this is a disease that has racial or sexual
6 predilections.

7 DR. GOLDBERG: Unlike, I gather, that AIDS does--I
8 mean, the AIDS profile in women played out differently,
9 apparently, also, so--

10 DR. DUVIC: I don't feel that it's that way in
11 psoriasis. Pretty much the same.

12 DR. GOLDBERG: All right. Thank you.

13 CHAIRMAN McGUIRE: John, do you have any comments?

14 DR. DiGIOVANNA: I had a comment that was a half-
15 step back with respect to geographic and climatic
16 influences. And I think that it would be very important to
17 use a broad geographic area.

18 One of the things that patients with psoriasis
19 intrinsically know is that in a large subgroup, if not most
20 of them, the disease varies with the climate and also that
21 sunlight helps. So those individuals who have been trained
22 all their life in the South to get sunlight will be getting
23 probably more exposure than those in the more northern
24 areas. And that may affect either the therapy or
25 photosensitivity of some particular products more so. So I

1 think that it would--that was just one additional reason I
2 think that's important.

3 DR. WEISS: Just to follow up on that, what about--
4 -would that also apply then to studies not just across a
5 broad region of the United States, but when we have
6 international trials? I don't know how many trials for
7 psoriasis--you know, what the incidences are in Europe and
8 other types of populations. But that's just another--
9 clearly, there's large, you know, climatic differences. You
10 can imagine the Scandinavian countries versus southern Italy
11 or something. Is that also?

12 DR. DiGIOVANNA: I think that point is extremely
13 important, and the reason I do is because of an anecdote of
14 my own, where I wasn't aware of the climatic importance of
15 topical preparations, and I was on a trip to Cairo seeing
16 patients who had ichthyosis, and I was trying to show the
17 application of Vaseline to a kid in a 109-degree clinic, and
18 I stuck my hand into the Vaseline, and it was liquid. So
19 topical products in particular in certain climates where
20 refrigeration may not be commonly available will not be
21 stable for very long. The consistency may be
22 extraordinarily different than what one expects in temperate
23 climates, and also, I would assume, in the colder climates.
24 I was lucky to escape the field trip to Alaska, so I don't
25 know what would have happened on that one.

1 CHAIRMAN MCGUIRE: Dr. Mindel?

2 DR. MINDEL: I don't believe you mean to say
3 climactic.

4 CHAIRMAN MCGUIRE: They meant climatic.

5 DR. MINDEL: They meant climatic.

6 CHAIRMAN MCGUIRE: Dr. Kilpatrick?

7 DR. KILPATRICK: This is a question for the
8 committee and, indeed, for the audience generally. We're
9 interested here in the potential of treatments. Does
10 anybody have any idea of the potential interaction of
11 treatments with various ethnic, climatic, or other
12 variations? I'm thinking here of side effects. We on the
13 committee have been reminded very recently about
14 Thalidomide, but is there any contraindications of treatment
15 of psoriasis in any of these subgroups of patients?

16 CHAIRMAN MCGUIRE: I don't think so. And I
17 believe we're on pediatrics now, unless the agency wants--
18 we're out of this.

19 In settings where the course of the disease and
20 the effects of the drug--oh, let me interrupt at this point.
21 Dr. Gerry Krueger has a couple of slides that he would like
22 to show and I would like to see, and so if we get through,
23 then we can all share in that. Consider that an inducement.

24 Pediatrics. In settings where the course of the
25 disease and the effects of the drug, both beneficial and

1 adverse, are sufficiently similar in pediatric and adult
2 populations, extrapolation of adult efficacy data to
3 pediatric patients is permissible. Ordinarily, additional
4 information obtained in pediatric patients, including
5 pharmacokinetic (+/- pharmacodynamic) data and safety data,
6 would be necessary.

7 d) Is psoriasis in pediatric patients sufficiently
8 similar to that in adults so that efficacy in adults can be
9 extrapolated to pediatric populations without the need for
10 separate efficacy trials? If so, does this hold for
11 pediatric patients at all age ranges, or just certain age
12 groups (adolescents) or just for certain forms of psoriasis?

13 Let me make a couple of comments, and then I'll
14 turn it over to the committee. Fortunately, psoriasis in
15 pediatric age range is not common. It does occur. In my
16 experience, it's a much more labile disease than in adults.
17 It gets better quicker and it gets worse quicker. And if a
18 child has so-called guttate psoriasis, often they have a
19 very good outcome with intensive therapy.

20 The concern in children is the toxicity of the
21 therapeutic modality, and I think the agency has taken a
22 position on topical steroids and there is at least one
23 topical steroid of moderate potency that has had pediatric
24 studies on adrenal suppression. It was done about three
25 years ago. It was Nomedisone (ph).

1 We use the same therapy. Clinically, we use very
2 similar therapy on children as we do in adults with the
3 exception of PUVA and etretinate and methotrexate. So the
4 systemic therapies are not included in that group, but the
5 topical therapies are rather similar. The concern is for
6 atrophy and thinning of the skin, damage to the skin with
7 the potent steroids.

8 Those are just general introductory remarks about
9 children. I'd be happy to hear what the Advisory Committee
10 has to say. Dr. Duvic?

11 DR. DUVIC: I agree it's mainly safety in children
12 rather than efficacy. And children with psoriasis have a
13 genetic disease that's HLA-mediated. They're going to have
14 it for the rest of their lives, and that has to be taken
15 into consideration.

16 CHAIRMAN MCGUIRE: John, do you have any comment?

17 DR. DiGIOVANNA: I agree. I think it's mostly a
18 safety issue. I think there's probably absorption issues
19 that are more profound than with adults, and I think those
20 need to be assessed with respect to steroids, possibly with
21 respect to drugs like calcifotryan (ph) and other drugs that
22 can have more profound effects, local atrophy and systemic
23 effects. I don't believe it's an efficacy issue.

24 CHAIRMAN MCGUIRE: Geriatrics. An existing
25 guidance addresses studies in the geriatric population. The

1 guidance suggests assessments of age-related differences in
2 response rates, adverse events, and underlying interactions
3 (e.g., concomitant medications; presence of hepatic or renal
4 impairment) in clinical studies of drugs "that are likely to
5 have significant use in the elderly, either because the
6 disease intended to be treated is characteristically a
7 disease of the aging or because the population to be treated
8 is known to include substantial numbers of geriatric
9 patients." The guidance states that "for drugs used in
10 diseases not unique to, but present in, the elderly, a
11 minimum of 100 patients would usually allow detection of
12 clinically important differences." Should efficacy trials
13 for psoriasis be designed to include a minimum number of
14 patients of age greater than 65?

15 John?

16 DR. DiGIOVANNA: Yes.

17 CHAIRMAN McGUIRE: Great. I like those crisp--
18 Bill?

19 DR. ROSENBERG: I don't think so. I think it's
20 the same disease. I think the safety concerns are the only
21 ones.

22 CHAIRMAN McGUIRE: And we were talking earlier
23 about the aging kidney, which you might want--

24 DR. ROSENBERG: Oh, yes, that's something special,
25 I think. I'll be glad to talk about it. I hope to talk

1 about that when we get to long-term safety.

2 CHAIRMAN McGUIRE: Okay. Dr. Miller?

3 DR. MILLER: I think with the topical preparations
4 there's no issue. I don't know that it's a different
5 disease in the older people. Certainly in the systemic
6 diseases, you have a whole new set of rules or, you know,
7 you have criteria before you put them on it.

8 CHAIRMAN McGUIRE: Dr. Duvic?

9 DR. DUVIC: I don't feel strongly about it.

10 CHAIRMAN McGUIRE: Okay.

11 DR. WEISS: Can I just ask one other additional
12 question? I'm sorry. Does it make a difference--and this
13 is not necessarily people just over 65, but the duration
14 that they've had their disease. Is that more of an issue
15 with respect to either one, but I guess more in particular
16 efficacy? In some diseases, if you've had it, if you're an
17 elderly person and you've had the disease that long, the
18 characteristics of the disease are different and you have
19 maybe burned-out disease and it's not--or not? That was
20 just a question, I guess, to add on to this for the
21 committee.

22 DR. DiGIOVANNA: I don't know that I have an
23 answer to that, but I think that people who have had the
24 disease longer have been exposed to a lot more in the way of
25 treatments and often develop tachyphylaxis to a lot of those

1 treatments. So I don't know that it's something that's been
2 characterized well, but the likelihood exists they would be
3 a little bit more resistant.

4 DR. WEISS: Just also--this is Karen Weiss again.
5 There are new requirements that when we go through labeling,
6 we're required to put in specific statements on labels with
7 respect to pediatric experience and now to geriatric use.
8 And there are specific phrases that are suggested in our
9 regulations to use. Some of them will say things like X
10 number of patients age 65 and older have been studied, and
11 the disease--you know, the efficacy and safety appear
12 similar, or if there are differences, important
13 pharmacokinetic differences, we're supposed to describe as
14 well in the labeling. There's a lot of guidance that has
15 now been given to us that addresses some of these important
16 sub-populations, which is why we brought the question up
17 here whether or not there are important differences and
18 whether or not we need to encourage, you know, sufficient
19 numbers of these different types of groups of patients into
20 studies.

21 DR. DUVIC: Who does this? Who makes you do this?

22 DR. DiGIOVANNA: Congress.

23 DR. DUVIC: I mean, you run the danger of going to
24 the nursing homes to find people to put in trials. I mean,
25 come on.

1 Who makes you do this? Yourselves?

2 DR. WEISS: No. These are actually--these are the
3 law, which means they come down to us from Congress.

4 DR. DUVIC: From Congress?

5 DR. WEISS: They ultimately go back to the
6 Constitution, but we don't need to go back that far.

7 [Laughter.]

8 DR. DUVIC: I think we're overregulated as a
9 society, actually.

10 CHAIRMAN MCGUIRE: Okay. Wait a minute. Wait a
11 minute.

12 [Laughter.]

13 CHAIRMAN MCGUIRE: Let's see. You have two weeks--
14 -I've already voted my ballot. I can't understand the
15 ballot in California, so I have to vote it at home and read
16 all the propositions.

17 John, you had a comment.

18 DR. WILKIN: Actually, it was--I heard several
19 different comments, and I just wanted to play back what I
20 thought I might have heard. So this is not necessarily my
21 point of view.

22 I think what I heard was that in the elderly that
23 it's the same disease, and so that one can extrapolate
24 efficacy from the under-65 population. One can infer
25 efficacy over age 65. I think I heard something to that

1 effect. But that safety may be the more significant
2 concern, and that it should perhaps be directed--that is, if
3 during Phase 2 one learns that, you know, there is some
4 important pharmacokinetic issue, like there's important
5 first pass hepatic extraction, these sorts of things, then--
6 or, you know, kidney degradation of the drug, then one would
7 want to look specifically at those kinds of issues.

8 CHAIRMAN MCGUIRE: We're going to get into that in
9 just a minute, John. Dr. Rosenberg has some information
10 from Zachariah's (ph) recent study on renal aging and renal
11 toxicity.

12 DR. WILKIN: But how that plays into this question
13 is I guess I didn't hear that there was a specific issue
14 with aging per se, with the over-65 group per se. If their
15 kidneys are in good shape, their live is in good shape, that
16 their disease is the same.

17 CHAIRMAN MCGUIRE: If you can wait until Item 2,
18 we're going to talk about that.

19 DR. WILKIN: Okay.

20 CHAIRMAN MCGUIRE: Safety assessments. Extent of
21 population exposure. An International Conference on
22 Harmonization guideline entitled "Guideline on Extent of
23 Population Exposure Required to Assess Clinical Safety for
24 Drugs" specifically addresses long-term treatment (chronic
25 of repeated intermitted use for longer than 6 months) for

1 non-life-threatening conditions. This guidance states that
2 there is general agreement that 300 to 600 subjects treated
3 at dosage levels intended for clinical use for at least 6
4 months would be adequate; 100 subjects treated for at least
5 1 year would be acceptable; and a total safety database of
6 1,500 patients treated (including all drug exposures) would
7 be anticipated. Where specific concerns exist, more
8 patients may be necessary.

9 Are these recommendations appropriate for products
10 intended for psoriasis?

11 Bill, is this a good place for you to--

12 DR. KILPATRICK: Mr. Chairman?

13 CHAIRMAN McGUIRE: Yes, Dr. Kilpatrick?

14 DR. KILPATRICK: Is that a misprint, 100 subjects,
15 going from 300 to 600 for 6 months, 100 for at least a year,
16 and then up to 1,500? Should that 100 read 1,000?

17 DR. SCHWIETERMAN: No, it's a year--it's 100 for a
18 year. One hundred patients is the minimum for treatment.
19 The 1,500 patients refers to total exposure regardless of
20 indication. These are the ICH guidelines.

21 DR. KILPATRICK: I'm just simply saying that it
22 doesn't progress step-wise, and that caught my attention.

23 DR. SCHWIETERMAN: Yes, it is a little bit
24 confusing, but it is 300 for 6 months, 100 for a year, and
25 1,500 overall suggested.

1 CHAIRMAN MCGUIRE: Dr. Wilkin?

2 DR. WILKIN: Yes, I don't want to digress too much
3 and take a lot of time on this issue, but it is I think well
4 discussed in ICH E(1)(a). This is a document one can
5 download from the Internet. It talks about the amount of
6 safety, amount of exposure, duration of exposure one would
7 like to see in clinical development of a drug for agents
8 that are for non-life-threatening or severely debilitating
9 diseases. And the thought is that 300 to 600--and, again,
10 this is for chronic types of treatments--that 300 to 600 for
11 6 months will rule out most of the kinds of things that one
12 would see, and that 100 would be typical for going up to a
13 year, but it does allow, if you're thinking about some kind
14 of safety issue that might not be detected until later that
15 you could up the number. I mean, it's a guidance. One can
16 go up with the numbers and down with the numbers depending
17 on, you know, what logic, structure, and evidence one has
18 from Phase 2.

19 CHAIRMAN MCGUIRE: Okay. Bill, I think this might
20 be a good place for you to talk about the Zachariah study.

21 DR. ROSENBERG: I do want to talk about the
22 Zachariah study as a specific one, and then I wanted to talk
23 about the studies from Toronto of expected mortality of
24 patients with psoriatic arthritis, the two that I brought
25 along. This is by Hugh Zachariah. I'm sorry. I just saw

1 it two days ago in an off-print from the National Library of
2 Medicine, but an article from the July issue of--in Danish,
3 from Denmark. The English abstract, summary abstract is all
4 I have, but Zachariah and Cragwell (ph), these are leading--
5 Zachariah, for those who don't know, really wrote the best
6 paper showing that one-third of methotrexate, people can
7 expect some fibrosis if they use it. Here he is now, the
8 title is "Renal Biopsy in Connection with Long-Term
9 Treatment of Psoriasis with Cyclosporine." I'll read the
10 whole thing, the whole abstract:

11 Renal biopsies were performed in 30 psoriatics
12 during long-term, low-dose cyclosporine therapy range 2.5 to
13 6 milligrams per kilo per day from 6 months to 8 years. The
14 study included pretreatment biopsies in 25 of the patients.
15 After two years, all biopsies shared features consistent
16 with cyclosporine nephropathy despite completely normal
17 pretreatment morphology in 18 of the 25. The severity of
18 the findings, which consisted of arteriolar hyalinosis,
19 focal interstitial fibrosis, and sclerotic glomeruli,
20 increased with length of therapy. Mild renal lesions were
21 seen during the first 2 years. After 4 years, all but one
22 had arteriolar hyalinosis with interstitial fibrosis
23 pronounced in five and moderate in six of 11 patients. At
24 the same time, glomerular sclerosis had become significant.
25 A decrease in glomerular filtration rate, GFR, correlated

1 with the severity of the fibrosis. GFR studied in 14
2 patients 6 months to 7 years after discontinuation of
3 cyclosporine was still significantly decreased in relation
4 to baseline prior to therapy. The data from our study
5 together with experiences from cardiac transplant patients
6 indicate patients with psoriasis after 2 years therapy with
7 cyclosporine should be rotated to other treatments or be
8 followed carefully by glomerular filtration rates and
9 sequential renal biopsies.

10 So the point I was going to make in general is
11 that treatments like this which are affecting important
12 parts of the body need to be followed. You can't require an
13 8-year study prior to release. Nobody would ever get drugs
14 in time who wants them. And yet how to figure out how to
15 keep up with patients once drugs are out is a vexing one.
16 Certainly, you know, I would wonder if you knew this then,
17 you know, how the vote would have gone on cyclosporine for
18 psoriasis. Certainly my suggestion would be that doctors
19 who are thinking about prescribing it ought to be aware of
20 this.

21 In relation to aging, we all lose nephrons as we
22 get older, all of us, and if we're lucky, it comes out even.
23 But we need more than the functional requirements of our
24 body when we're young in order to have some left when we get
25 old. So I think this type of nephron loss in early life,

1 you know, might not be recognized until later.

2 Cyclosporine might be something special, but the
3 other point I wanted to make--and I brought these along,
4 too, and they're in the packets of the committee members.
5 Two papers from the Canadian Center for Prognosis Studies in
6 Rheumatic diseases at the Toronto Hospital, a group of
7 Gladman and some others, and it's "Mortality Studies in
8 Psoriatic Arthritis," published in 1997, 1998, in Arthritis
9 & Rheumatism.

10 Essentially, the standardized mortality rate for
11 females was 1.59, and for the men it was 1.65, indicating,
12 of course, 59 and 60--a 5 percent increase in the death
13 rate, respectively, over expected.

14 And in a table in the second paper where they
15 analyzed factors about the patients, that the relative rate
16 went up with the number of previous medicines used, so
17 rotation--I don't know what rotation means in this--prior
18 medicine use, if they hadn't used any, they were given an
19 index of 1. Those who had five prior medicines, no matter
20 what the medicine was, had a 4 relative risk of dying.
21 This, of course, is methotrexate era at the Arthritis
22 Clinic. You know, we have been taught and teach that
23 psoriasis is a disease of healthy people.

24 And again, just to get back to what I was harping
25 on before, this American Journal of Medicine Sciences for

1 October, you know, raises questions about the essential
2 nature about this group of diseases and suggests that there
3 may be microbial antigens at play all the time, and then the
4 risk of suppressing the body's immune system chronically
5 comes up.

6 I think I've said enough.

7 CHAIRMAN MCGUIRE: Well, Bill, I really appreciate
8 your finding these two reports, and I think to my knowledge
9 the Zachariah report is the only longitudinal study, and
10 although the abstract doesn't give the age of the
11 individuals, a couple of the key words are male, middle-age,
12 female, and the point you made is a very important one. We
13 lose nephrons all the time, and the kidney ages along with
14 the rest of our body. We just can't see it as it gets old
15 and wrinkled. And if you poison it late, you poison it much
16 worse than if you poison it young. You don't have the
17 leeway. So I think that needs to be taken into
18 consideration. Cyclosporine is a hazard, and as you're
19 compromised by age, it's more of a hazard.

20 Let's see. Theoretical risks exist with the
21 administration of systemic therapies and certain topicals
22 (primarily those that result in a high degree of systemic
23 absorption). Immunomodulators and antimetabolites may, in
24 the short term, result in serious infections or, in the
25 longer term, development of new autoimmune diseases or

1 malignancy.

2 I don't know how the agency plans to deal with
3 this. It would seem to me that with the important and, in
4 quotation marks, "potentially toxic" systemic therapies that
5 postmarketing studies will be very important, because there
6 is no way that you can do a premarketing analysis of
7 toxicity if it's going to be something that occurs at 3
8 years, 5 years, 7 years.

9 DR. SCHWIETERMAN: Yes, I think that's helpful.
10 We brought this to the committee's attention for a couple of
11 reasons, the most important of which is to get a feel for
12 the Phase 4 studies, but also just to bring this to your
13 attention in general, that as immunomodulatory agents get
14 into these patients with chronic diseases, the long-term
15 risks need to be defined. In other indications, for
16 example, in rheumatoid arthritis, there's consideration for
17 registries being established. There's active discussion
18 about that. Just FYI.

19 CHAIRMAN MCGUIRE: Are there other issues of
20 toxicity you'd like for us to deal with?

21 DR. SCHWIETERMAN: Just to clarify your earlier
22 comment, when you say Phase 4 studies, you were thinking of
23 registry data of some sort or some sort of follow-up to the
24 patients that had been treated?

25 CHAIRMAN MCGUIRE: Yes.

1 DR. SCHWIETERMAN: Could you clarify that?

2 CHAIRMAN MCGUIRE: Bill, I don't know what methods
3 you have at hand. I don't know what--I mean, obviously the
4 registry is very restrictive, very expensive, and requires a
5 lot of work from everyone. And I don't know if there is an
6 easier way. But I think the data have to be collected.

7 DR. SCHWIETERMAN: Yes, it's a very difficult
8 issue, I acknowledge. I'm not sure I know the answer
9 either, but--

10 CHAIRMAN MCGUIRE: Well, obviously, I didn't.

11 If there is no more discussion on toxicity, Dr.
12 Krueger has some data that he would like to share with us
13 that is germane to today's work.

14 DR. G. KRUEGER: What I would like to do is to
15 share with you a study that we did some 8 or 9 years ago and
16 it never was published, and the reason it wasn't published
17 is because the person working with me went into practice,
18 and so it hasn't seen the light of day, although it was
19 prepared as a presentation. So this is the first time that,
20 to my knowledge, it's been given.

21 What this study was was a comparison of twice
22 daily versus once daily administration at 4 mg/kg based on
23 ideal weight for severe psoriasis. And the sub-plot was to
24 assess psoriasis using various measurement parameters:
25 PASI, target lesions, body surface area, transepidermal

1 water loss, and color change using a colorimeter.

2 All we did was to take ten patients with severe
3 psoriasis and then blinded them to get either twice a day or
4 once a day therapy. Phase 1 was a 12-week study or
5 treatment until clear. Phase 2 was a cross-over to other
6 dosage regimens after recurrence of disease was at 75
7 percent severity of initial evaluation, and then we again
8 treated for 12 weeks until clear. And one of the things
9 that we've been talking a little bit about today is when do
10 you retreat and all of that, and these were just some
11 arbitrary numbers that we chose so that we'd get the study
12 done in a reasonable amount of time.

13 The purpose I've already gone through, and the
14 things that you've heard about today are global evaluation.
15 We used a 1 to clear, 6 to worse. One of the nice things
16 about global evaluations is that it's simple. It has a
17 limited scale, and the other one that's very simple is a
18 body surface, and there we used the palm of the patient.

19 One of the reasons that pediatrics is much more
20 difficult is you're an adult, you're looking at this little
21 kid, and he has tiny hands. So it's not easy.

22 The feature with that is that it's simple, but a
23 problem with it is that it doesn't easily accommodate for
24 non-uniform changes, that is, changes occurring on the trunk
25 and other places versus, let's say, the arms or elbows.

1 The target lesions score, what we did was to take
2 three target lesions, one from the arm, one from the trunk,
3 one from the legs, and then we ranked each one in severity,
4 erythema, induration, scale, and we used two kinds of
5 scales, either 0 to 4 or 0 to 3. Don't ask me why we did it
6 other than at the time we were doing clinical trials; some
7 had a 0 to 4 scale, some had a 0 to 3 scale.

8 I really like target lesions because we can bring
9 definition to both erythema--to all three, erythema, scale,
10 and induration. It's easy to use. However, it does not
11 easily accommodate non-uniform changes, again, does not
12 evaluate size, the overall--the lesion itself or the entire
13 body. However, as we've heard, a photo can be used to
14 confirm evaluation, and here you have a limited value.
15 People will tell you they have robust--to be able to detect
16 robust changes, you need to have a score that goes from 0 to
17 100, that actually operates through all elements of that 0
18 to 100 range, not just down the lower registry, as you'll
19 see in just a moment for PASI.

20 PASI measures severity, erythema, induration,
21 scale. You've been through this. The total PASI score
22 can't be higher than 72, and because of the limitations of
23 it, most everyone who's in a clinical trial has PASI scores
24 that are in the neighborhood of less than 20 and frequently
25 less than 15. So that the robustness that would be

1 suggested by the maximum score does not work out in clinical
2 usage.

3 I've already gone through this.

4 There was another idea that we had, and I'll share
5 it with you, and that was to take a total of the target
6 lesions and simply add to that the body surface area. And
7 you'll see in a moment another approach on that is to just
8 multiply the total erythema, induration, and scaling score
9 times the body surface area and sort of get what Madeleine
10 was talking about, a combination score, so that you get one
11 score, your target lesions, which is a picture of your
12 psoriasis, and you get total body surface at the same time.

13 One of the other things that you haven't been
14 introduced to, and I'll just introduce it because it works,
15 and it works very nicely, but it's not easy to use, and
16 that's the system that Irv Katz from Minneapolis has
17 advocated, and that's a total lesion area severity score.
18 He has noted, as have all of the rest of us who have treated
19 psoriasis, that psoriasis doesn't go generally from this
20 involved to clearing. It frequently takes this tour through
21 this little diagram down here where you have areas that are
22 fairly severe. And when you're doing target lesion
23 assessments, you're asking your investigators, well, you've
24 got to put on your magic computer and you've got to kind of
25 tell me what that is.

1 So you look at it, and you say, well, 90 percent
2 of it is clear, so you give it a score of 1 for induration.
3 Well, in truth, you give it a 1 only because you can't give
4 it a 0. If you gave it a 0, it would be all gone. And 1 is
5 a big lie as well. So what Irv said is, well, what you need
6 to do is to have two; when you do your target lesions, you
7 do the area and then you subtract out these worse areas, and
8 come up with a total lesion area severity score. Not a
9 popular one. This just goes through it. I told you I
10 wouldn't take you through it.

11 But let me just take you through--I think I put in
12 three patients. I've got all ten of them in here, but I'm
13 just going to put in--this is a patient, LCC, who was
14 treated once a day with cyclosporine for psoriasis. And
15 what you have listed here are her PASI score, the total
16 targets plus the area, so this is erythema, induration, and
17 scaling for all three, plus the body surface involved, and
18 then this is a multiplication of those. And what you
19 appreciate, what I'd like for you to appreciate is that this
20 gives you a bit more robust scale, and it spreads it over 0
21 to 100. The PASI score takes you from--most everyone in
22 this room appreciates you don't get PASIs that generally are
23 much more than 25. And with time, there's a nice decrease,
24 as you might imagine.

25 This is transepidermal water loss and is a mean of

1 the three target lesions, and this is the--am I getting too
2 close to the speaker? I can stay over here, but then I need
3 a pointer. Thank you.

4 This is the involved skin coming right through
5 here, the orange line, and this is the uninvolved skin. And
6 while there are changes that occur fairly early on, the
7 differences after that are simply not very dramatic. The
8 Minolta chronometer--and I'm sorry this box got overlaid--
9 gave us a fairly good estimate--or gave a nice
10 representation of change in color over background. And this
11 works really well if there isn't much scale. However, I can
12 assure you that if there's much scale, this doesn't work.

13 This is another patient--the same patient, rather,
14 in the twice daily phase. Again, there's a nice decrease.
15 This time her disease, using the target times area,
16 decreased a little more dramatically than did the target of
17 the area plus the area. And, again, there was a nice change
18 in transepidermal water loss, a nice change in color.

19 This is another patient taking it every day. This
20 patient was very interesting in that there wasn't much
21 change until right at the end. This patient had really
22 tenacious scale that just simply wouldn't come off. But
23 once it came off, we were able to appreciate a dramatic
24 change in the target times area. The target plus area
25 follows this particular format, and then the PASI takes a

1 much less robust change.

2 But look at what happens with the transepidermal
3 water loss. We actually had less water loss through his
4 lesions than we did through his normal skin. A tremendous
5 amount of variability, and, likewise, the color was
6 diminished, trying to get through all of this scale.

7 And the final patient is a patient that had to be
8 taken off the study. This patient was very, very large, and
9 we weren't able to get the patient on enough cyclosporine to
10 really cause improvement. And the only parameter that
11 really showed this was the transepidermal water loss
12 increasing as well as the target times area. This one
13 didn't show much change, but curiously enough, there was
14 actually an improvement in the PASI all the way through
15 therapy.

16 I guess I would summarize by saying that in this
17 small trial, the PASI is not very robust, and in one case,
18 where we had to take the patient off, he was actually
19 getting better by that score than he was--he was getting
20 better by PASI than he actually was in the clinic, and
21 because of that we had to take him off, as I just said.

22 With that, I think I'll stop. If there are some
23 questions I can answer, I'll take them, but I will thank you
24 for your attention.

25 CHAIRMAN McGUIRE: Thanks, Dr. Krueger, for

1 showing us those data. I think I asked you earlier, but for
2 the record, you need to tell us whose flag you're flying
3 under and what you're doing here.

4 DR. G. KRUEGER: I was invited to come and talk to
5 the Advisory Committee about the immunobiology of psoriasis.
6 I'm going to do that tomorrow. I am the Chairman of the
7 Medical Advisory Board of the National Psoriasis Foundation.
8 And I have participated in 60-some different clinical
9 trials, treatment of psoriasis, over the last 20 years.
10 This particular trial was funded by then Sandoz, now
11 Novartis. They did not pay me, and he didn't even know
12 about this.

13 CHAIRMAN MCGUIRE: Are there questions from the
14 committee? John DiGiovanna?

15 DR. DiGIOVANNA: In your experience, in your best
16 estimate or hypothesis, what would the optimal psoriasis
17 grading scale be for plaque-type psoriasis?

18 DR. G. KRUEGER: Well, for me, it's some
19 combination of target lesions, and at least two target
20 lesions--I wouldn't object to three--and erythema,
21 induration score. If you want to summate all three of them,
22 that's fine. I don't have a problem with that to give you
23 some kind of a larger number to begin to work with. If you
24 want to take a mean, that's fine. If you want to separate
25 out elbows, knees, that's fine. But I really like target

1 lesions because we can give very accurate word descriptions
2 that talk about how much scale is 4 and how much is 3, et
3 cetera. And you're looking at that same lesion every time.
4 You can take pictures of it. I don't have a problem.

5 And I like body surface area, especially for
6 systemic disease. And this just puts it together. I don't
7 think it's going to be very helpful to the clinician,
8 though, because it's a combination number, just like the
9 PASI score is. But it does give robustness. If you're
10 looking for numbers spread over a large range, this is the
11 way to do it.

12 CHAIRMAN McGUIRE; Are there other questions from
13 the agency or from the committee?

14 [No response.]

15 CHAIRMAN McGUIRE: Dr. Krueger, thanks--

16 DR. G. KRUEGER: You don't want to do the multiple
17 parameters, measuring them all out, and subtracting out.

18 CHAIRMAN McGUIRE: John, you have a question?

19 DR. WILKIN: Yes. It probably is an excellent use
20 of the word robustness. I guess I just haven't thought of
21 it in that way. I mean, robustness does have some other
22 meanings like a technique that, you know, works under a
23 variety of conditions. So maybe it actually applies.

24 I was thinking of it more as a scaling phenomenon,
25 and I guess I was thinking somewhat of--my sons are 26 and

1 24 now, but as they grew up, we would periodically, you
2 know, have them in the kitchen and they would back up
3 against the door, and we would put the ruler over the head
4 and mark the little mark, and so that there would be a
5 difference between the two. You know, they would always
6 look to see whether the younger one was closing in on the
7 older one. And I think the older one would have preferred
8 that we used a scale that was in angstrom units, and the
9 younger son would have chosen something, you know, on the
10 order of meters.

11 But the idea here is it's not so much whether--how
12 precise one can get because we can actually have more
13 precision; then at the end of the day we have useful
14 information. One of the things that we're after is we would
15 like to know what is a clinically meaningful difference, if
16 there is such a minimal clinically meaningful difference.
17 And if you're comfortable with your 9-point or 12-point
18 scale--I mean, can you select out a number on that scale
19 where you would say if patients finally get down--their
20 target lesions, if the target lesion actually gets down to
21 that level, that you would feel very comfortable that they
22 would not require, for example, additional therapy?

23 DR. G. KRUEGER: You know, I'd be foolish enough
24 to try and answer that. I guess I am foolish enough to try
25 to answer that.

1 In our experience, with the super-potent
2 corticosteroids, if we got patients down to a score of 1 or
3 less--and 0 was no lesions--if they get to 1 or less, all of
4 them--because we did a patient survey on them--they all were
5 very happy. That was good enough. In their mind they were
6 clear. That's 90 percent improvement, which is something
7 that has been kicked around here before. I would say that
8 90 percent or more improvement in most patients' minds is
9 clear.

10 DR. WILKIN: Okay. I think, you know, that was
11 generally--actually, this is sort of an awkward situation.
12 Normally the agency is viewed as rather parsimonious, and I
13 find myself in the position of suggesting that actually, you
14 know, maybe that--you're saying that the total score at the
15 end is going to be 0 or 1? That's what you're saying?

16 DR. G. KRUEGER: Yes. If you can get your target
17 lesions to a 0 to 1--

18 DR. WILKIN: This is a group of patients that are
19 starting out around 9?

20 DR. G. KRUEGER: This is patients who are starting
21 out at day zero with mild to moderate disease--

22 DR. WILKIN: With a score of approximately?

23 DR. G. KRUEGER: With a score of 6 or more.

24 DR. WILKIN: Of 6 or more.

25 DR. G. KRUEGER: Minimum of 6, and 30 days later,

1 twice daily applications of a potent corticosteroid
2 ointment, 75 percent of them were at a 1 or lower.

3 DR. WILKIN: I guess I'd be interested if you
4 thought there was some advantage to getting to a score that
5 might be above 1, like 2 or 3.

6 DR. G. KRUEGER: I don't know where comfort sets
7 in because that's something I've never been challenged to
8 do. At what point are you comfortable? For the patient who
9 is a 9 or a 10, getting them down to a 5 I can believe must
10 be useful; otherwise, we would have some real difficulty
11 using--or getting patients to continue to use agents that we
12 routinely prescribe.

13 CHAIRMAN McGUIRE: John?

14 DR. DiGIOVANNA: That's a very difficult question,
15 and I don't know that this type of scale can answer the
16 question that Jonathan Wilkin is asking. One question is:
17 Can the scale detect an improvement? And it can't really
18 address whether that improvement is clinically efficacious
19 or satisfactory. Is the question whether it's satisfactory
20 to the dermatologist and he feels this is a substantial
21 improvement, or whether it's a substantial improvement to
22 the patient, that they're happy, they would buy this at this
23 particular point in time?

24 Maybe that question needs to be asked at some
25 point in the study, maybe at each visit. Is the improvement

1 that you have today worth all the effort you've put into the
2 study? Would it be worth it if it cost you \$10 a visit? I
3 don't know how to assess that, but from all I've seen of all
4 of these scales and all I've used them, I think they're so
5 difficult and convoluted, and they can be misconstrued and
6 misapplied so easily, that I think they're trying to detect
7 efficacy and not satisfactory efficacy. They're trying to
8 detect difference.

9 DR. G. KRUEGER: It's something that you've
10 struggled with before. What is a successful treatment
11 outcome? Twenty-five percent improvement? Fifty percent
12 improvement? Seventy-five? Ninety? A hundred? It depends
13 on where you're coming from.

14 CHAIRMAN MCGUIRE: I'd like to thank the committee
15 and the agency and Alice Gottlieb from Robert Wood Johnson,
16 Beatrice Abrams from Novartis, Don Barton from Palo Alto,
17 Tara Rolstad from NPF, Todd Plott from Schering-Plough, Jim
18 Krueger from Rockefeller, and Gerry Krueger from Utah.
19 Thanks for your contributions.

20 Yes, I have a question from the audience.

21 MS. OTT: I'd just like to make some observations
22 about today's meeting. Is that appropriate at this time?
23 Or do you prefer that the public sign up to make comments?

24 CHAIRMAN MCGUIRE: It's the wrong time for it, but
25 we have time, so take a few minutes and make comments.

1 Extensive comments or brief comments?

2 MS. OTT: It's just brief.

3 CHAIRMAN MCGUIRE: Sure.

4 MS. OTT: I think this meeting is very exciting
5 for many different reasons.

6 CHAIRMAN MCGUIRE: Can you tell people who you
7 are?

8 MS. OTT: My name is Ms. Amy Ott. I've had
9 psoriasis for over 30 years. I'm not a government official.
10 I'm not a professor. I used to call myself a patient. Then
11 I called myself a consumer. Now I call myself a survivor.

12 I've had it up to about 75 percent of my body.
13 I've had to stop working because of it. I've gone back to
14 work. But it's been wonderful to be here today because I
15 learned some information. But I also feel that the people
16 that are working on the topic are smart, and they're
17 invested in it, which is very reinforcing. It's really nice
18 to sit in a room all day and hear the word psoriasis over
19 and over and over, because it's such a hidden, ill-defined,
20 mysterious, and, to the public, lots of times a joke
21 disease.

22 I would make one recommendation to the panel, and
23 that is that you bring at least three to five consumers to
24 sit in this room and have equal footing with you. Lots of
25 stuff that you guys asked I could answer before they could.

1 And I'm not a clinician. I'm a consumer more than anything.

2 Somebody asked the question about women, is there
3 anything different? Sure. Get five women in a room who've
4 gone through menopause and ask them about what changed, and
5 you'll get significant reports about what happened during
6 menopause.

7 I think that most groups are at a stage in their
8 development where they recognize that the experts are the
9 people that walk around with it and deal with it over time
10 and can tell what's happening to them because of it and
11 because of their families, whatever.

12 So I'm not in any way trying to in any way reduce
13 the significance of what you do. I think it's fabulous and
14 I learned a lot of stuff. But I think if you put consumers
15 together with you, the power of that kind of an interaction
16 and observations and the ability to use their history would
17 be great. And there's so many people who would die to do
18 that. They would just love it if you would just ask them.

19 So I thank you, and if that's helpful to you, I
20 appreciate it.

21 CHAIRMAN MCGUIRE: Thanks for saying what you did.
22 The power of the National Psoriasis Foundation is that it
23 was patient-based, and those of us who were in the hierarchy
24 of the various committees always made sure that the patients
25 ran the NPF, and the patients still do.

1 Jackie, you wanted to make a remark?

2 DR. GOLDBERG: Yes, just a quick remark. As I
3 said before, I'm new to this committee, and I see my role as
4 being a conduit for consumer voices. But I don't think
5 that's the same thing as replacing consumer voices, and I
6 think it's very important for every disease state that we
7 end up dealing with on this committee to have some
8 representation over and above me. So thank you for your
9 comments.

10 CHAIRMAN MCGUIRE: The closed session will begin
11 in this room at 8 o'clock tomorrow morning, and the open
12 session will begin about--when, 10:30? 9:30, or whenever
13 the closed session is over.

14 We're adjourned. I'll see you in the morning.
15 Thank you.

16 [Whereupon, at 4:45 p.m., the meeting was
17 adjourned, to reconvene in closed session at 8:00 a.m.,
18 Thursday, October 22, 1998.]

C E R T I F I C A T E

I, **THOMAS C. BITSKO**, 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.

A handwritten signature in black ink, appearing to read 'T.C. Bitsko', is written over a horizontal line.

THOMAS C. BITSKO